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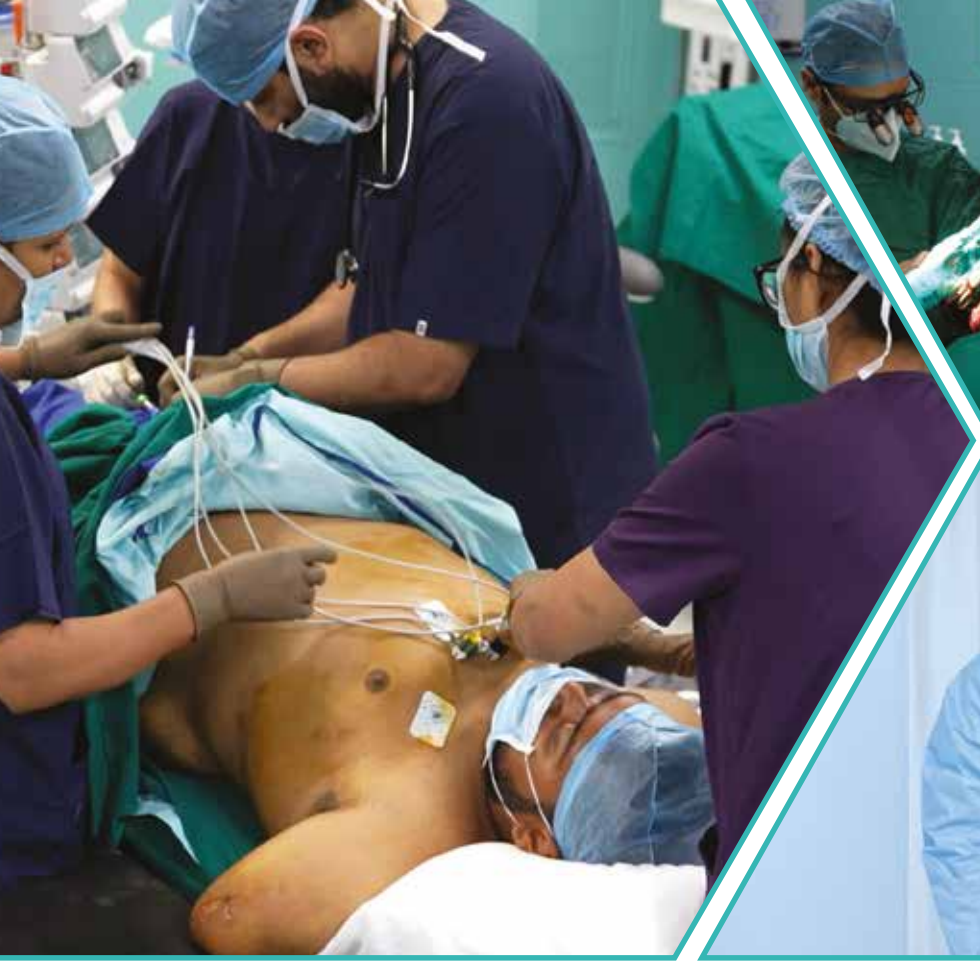

Bilateral Hand Transplantation from Female Donor to Male Recipient: Advancing the Boundaries of Vascularised Composite Allotransplantation

An 18-year-old male presented with bilateral traumatic hand amputations. He sustained a non-salvageable crush injury in a farm equipment accident in January 2024. The tissue damage required amputation of both hands and resulted in profound functional loss. After a comprehensive medical, psychological, and immunological evaluation, he was considered suitable for bilateral hand transplantation. Due to the rarity of appropriate donors and strict compatibility requirements, he remained on the transplant waitlist for 13 months.

In January 2026, a suitable cadaveric donor became available, a 50-year-old deceased female whose family consented to organ donation. Her upper limbs were allocated for transplantation, and her lungs, liver, and corneas were retrieved and transplanted across hospitals in Mumbai and Surat. The bilateral hand transplant was performed at Nanavati Max Super Speciality Hospital in Mumbai with the objective of restoring upper-limb continuity and functional potential in the young recipient.

Following the donor family's consent, the limbs were retrieved in Surat and transported to Mumbai within a short window through coordinated efforts of teams and authorities in Maharashtra and Gujarat.

The transplant procedure was performed overnight on 9th–10th January 2026, under the direction of Dr. Nilesh Satbhai, Director of Plastic, Reconstructive Microsurgery and Hand Transplantation. Over 13 hours, the team completed skeletal fixation, arterial and venous anastomoses, tendon repairs, nerve coaptation, and soft-tissue reconstruction. Intraoperative planning focused on minimising warm ischaemia time and ensuring vascular patency. Immediate graft perfusion confirmed successful revascularisation.

Postoperatively, the patient was managed according to a structured, multidisciplinary protocol encompassing immunosuppression, vascular surveillance, infection prophylaxis, and early rehabilitation planning. Vigilant monitoring for vascular compromise and acute rejection was critical during the early postoperative period.

Unlike organ transplantation, vascularised composite allotransplantation (VCA) transfers tissues like skin, muscle, tendon, bone, vessels, and nerves, creating immune challenges because skin is highly antigenic. Yet when successful, hand transplantation can restore feeling, position sense, and coordinated movement beyond what prosthetics can offer.

This case underscores the extraordinary complexity of VCA and the immense team effort required to execute such a procedure successfully. Representing the pinnacle of surgical precision, meticulous planning, and sustained team effort, the procedure demanded seamless multidisciplinary coordination, endurance, and clinical judgement at every stage. It sets a new benchmark for collaborative surgical achievement and advances the frontier of functional restoration in complex reconstructive transplantation.

Contents

WHEN THE DAUGHTER FROM CALIFORNIA ARRIVES

> "We are not just adding years to life, but more importantly, adding life to years."
>
> — Dr. Monica Mahajan

Yes, we've all met her. The 'Daughter from California' was described by David Molloy in 1991 in an article in the Journal of the American Geriatrics Society. The case vignette involved an 83-year-old dementia patient residing in a nursing home. She had a hip fracture. Her daughter suddenly arrived from California and demanded irrational, aggressive treatment for her mother, who was on palliative care. She was abusive and accused the medical staff of negligence. This was quite contrary to the other daughter's wishes, despite the fact that she had been the long-term caregiver and had seen the cognitive decline and terminal condition of her mother. The behaviour of the daughter visiting from California is attributed to the feeling of guilt stemming from neglecting her mother's health needs and the denial of accepting her current condition. There is a clash of egos and conflict between the family members in decision-making for a mentally incompetent patient at this critical juncture. I am sure all of us have met these uninvolved sons and daughters from California, New York, Ontario, or Timbuktu, making sudden appearances during the family meetings and counselling sessions for terminally ill intensive care, neurology, and oncology patients. Why is it that 'code violet' is becoming more common in this day and age?

There are very pertinent questions that arise during the family meetings on our daily rounds. We need to figure out the family dynamics, understand their emotional state and feelings of guilt and self-reproach, address their queries clearly and prognosticate. It is quite a challenge to draw out a rational care plan, keeping in mind the patient's dignity and quality of life. At the same time, it is a challenge to keep our cool and not be frustrated if the family cannot reach a consensus.

The Supreme Court of India passed a landmark judgement in 2018 (Non-Governmental Organisation [NGO] Common Cause v. Union of India), which recognised the 'right to die with dignity' as a 'fundamental right' under Article 21 of the Constitution. America had laid down provisions for a 'living will' way back in 1998. A 'Living Will', in layman's terms, is called an 'Advance Medical Directive' in legal parlance. This permits an individual to specify what treatment he is willing to receive or whether to refuse life-saving interventions in case he becomes terminally ill in the future or is not in a condition to communicate his explicit wishes. A living will can be the basis for passive euthanasia in the court of law. A newer, simplified version for executing a living will has been released by the Supreme Court in 2023. An adult with a sound mind can execute a living will, signed by two independent witnesses, and notarised. He needs to nominate a surrogate authorised to give consent for withdrawal of care in case the individual becomes incapacitated. A copy needs to be submitted to the Municipal Corporation office. There are quite a few challenges. Firstly, with our fast-paced lives and lack of meticulous planning, how many of us are going to spend time and effort on planning our death? Secondly, the implementation process is cumbersome, with a primary medical board formed by the hospital, a secondary board to concur with the findings and judicial magistrate oversight before the treatment can be withdrawn. 'Living Will Clinics' have been set up to create awareness and to assist people. With the stark rich–poor divide, this may be a tool

for only a handful of citizens. In a country where money makes the mare go, this paper can definitely be misused by unscrupulous relatives. Also, patients may have misconceptions that may hinder their decisions while writing a living will. Surrogates may extrapolate or misinterpret the will.

There is also a question of dying peacefully with dignity. Active euthanasia or mercy killing involves administering lethal drugs or life-ending interventions. Some of the countries that allow active euthanasia include the Netherlands, Belgium, Canada, Luxembourg, Spain, New Zealand, Colombia, and Portugal. In the case of 'Physician-Assisted Suicide' (PAS), the patient self-administers the lethal substance. Switzerland permits PAS. Under the Bharatiya Nyaya Sanhita, active euthanasia is illegal and considered a culpable homicide.

In 2011, the Supreme Court of India laid down guidelines for 'passive' euthanasia while debating the Aruna Shanbaug case. This involves withholding life-saving treatment in exceptional cases involving terminally ill patients, where a medical board reviews the case and gets approval from the High Court. Euthanasia is a hotly debated topic with both schools of thought — those in favour and those against it. The Jain community believes in 'Santhara' or embracing death voluntarily by fasting. The Hindus also opine that we cannot defy fate and disrupt the cycle of reincarnation. Others are apprehensive that the guidelines can be misused for financial or property gains. Do doctors and the law have the right to play God? Yet, there is an increasing focus on end-of-life care, palliative medicine and dignity in death. The '3 Wishes Program' is a palliative care programme initiated in many hospitals around the world to make the process of dying more compassionate for the dying patient, their families and the clinician by fulfilling three meaningful, personal wishes of the patient during their final days of life. There may be soothing music, room decorations, a home blanket, birthday celebrations or favourite food, a prayer ceremony — the little efforts matter in humanising the dying process and creating positive memories. As per the American Medical Association, only 5 out of 126 medical schools in the United States of America (USA) offer a course to students on the care of dying.

Who decides if the patient is incompetent to decide? What happens when there is no living will? Aruna Shanbaug, a nurse at King Edward Memorial Hospital (KEM), Mumbai, was a sexual assault victim who spent 42 years of her life in a vegetative state. She was the eighth among six brothers and three sisters and the only one in her family to complete higher education. Her colleagues at KEM looked after her after this incident with utmost love and care, and attempts by the Municipal Corporation of Greater Mumbai (BMC) to vacate the hospital bed she occupied failed. Her family abandoned her and stopped visiting her in the hospital. The accused was only charged with attempted murder and never charged with rape. He was released after a jail sentence of six years. In 2011, activist Pinki Virani filed a plea in the Supreme Court of India for a medical panel to examine her and permit euthanasia. The petition was rejected by the court but paved the way for permitting 'passive euthanasia' in India. Shanbaug died of pneumonia four years later.

In the case of Aruna Shanbaug v. Union of India (2011), the Supreme Court gave a landmark judgement and legalised 'passive euthanasia' in India. The guidelines allowed withdrawal of treatment, nutrition or water, but the decision-making power for discontinuing life support was in the hands of parents, spouse, close relatives or a 'next friend', with court approval. In the Shanbaug case, the KEM nurses looking after her like a child were designated as 'next friend' and decided not to withdraw her life support. The same was communicated to the court, and it allowed them the option to change their mind at a later date if they desired. However, the nurses continued looking after her until she finally died. Her funeral rites were performed by the nurses.

So, the challenge remains whether you resuscitate a terminally ill patient, especially if it is a stalemate and the relatives cannot form a consensus opinion. Documents and directives may be used or misused. The smartly dressed, ChatGPT-educated, articulate daughter is always going to be the angriest and the most unreasonable relative to deal with. You have to be smarter so that you don't end up in a legal soup. If you are too aggressive in your treatment approach, you are labelled 'unethical and money-minded'. If you are more into palliative comfort care, some smart colleague may tell the family that you are 'outdated' and that there are newer treatments available. So, decision-making and end-of-life care for the incompetent elderly patient who has lost decision-making capacity is a tough situation where the doctor and the daughter need to be playing for the same team. You need to respect the spiritual, cultural and religious beliefs. After all, we are not just adding years to life but, more importantly, adding life to years. So brace up, stay cool and reasonable, and go meet the daughter who has just arrived from California. You have to find a common ground while remaining within the realms of medical ethics.

Dr. Monica Mahajan

Editor-in-chief,
The Max Medical Journal

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ORIGINAL ARTICLES

Analysis of Laboratory Quality Control Performance: A Six-Month Six-Sigma Metric Study

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Abstract:

The Sigma Metric is a crucial tool for evaluating laboratory quality control (QC) performance, providing a standardised measure of analytical process capability. This manuscript presents a comparative analysis of sigma values for routine chemistry parameters (29 analytes) between January and July at our laboratory using two levels of controls. The objective was to assess changes in analytical performance over a six-month period. Data were analysed for January and June, followed by July, with sigma values calculated based on internal QC and proficiency testing data. The findings clearly highlight the laboratory's strong analytical capability, with the majority of analytes (25 analytes) achieving Six-Sigma performance — reflecting excellent precision, accuracy, and process stability. A few parameters (4 analytes) showed sigma values in the 3–5 range, which served as constructive indicators for fine-tuning existing processes. We took additional measures for these selected parameters by consistently following maintenance guidelines and improving QC storage and water quality, which led to an upward trend in sigma values for these analytes in July. These findings underscore the dynamic nature of laboratory performance and the importance of maintaining high-quality patient care.

Key words: Six-Sigma, Quality Controls, Quality Performance, TIQCon.

Introduction

Quality control (QC) is an essential component of clinical laboratory operations, ensuring the accuracy and reliability of patient test results.[1] The Sigma Metric provides a quantitative framework for assessing the effectiveness of a QC system by relating the analytical process to its defined quality requirements. A higher sigma value indicates a more capable and robust process, with a widely accepted benchmark of Six-Sigma representing world-class performance.[2] By analysing changes in the Sigma Metric over time, laboratories can identify trends, troubleshoot issues, and implement corrective actions to improve analytical quality.[3] This study aims to compare the sigma values of common analytes at distinct time points — January and June, followed by July — to evaluate changes in analytical performance over a six-month period using two levels of controls.

Methods

The dataset for this analysis consisted of sigma values for all 29 analytes, collected from PreciControl Clinical Chemistry (PCCC1 and PCCC2) controls running on Cobas Pro (Roche) at our laboratory (Max Lab). Data

was provided for two time points: January and June, followed by July after taking necessary measures. The sigma values were calculated using TIQCon Quality Performance (TIQCon QP) software,[4] which applies the standard formula:

$$\sigma = (TEa - Bias\%)/CV\%$$

Where:

TEa = Total allowable error (from Clinical Laboratory Improvement Amendments [CLIA], European Federation of Clinical Chemistry and Laboratory Medicine [EFLM], National Accreditation Board for Testing and Calibration Laboratories [NABL], etc.)

Bias = Difference between lab mean and target mean (%)

CV = Coefficient of variation (%)

For this study, the sigma values were treated as the primary data points for comparison. A simple descriptive statistical analysis was performed to identify the change in sigma values for each analyte between January and June, followed by July. An increase in the sigma value was considered an improvement in performance.

Results

The comparative analysis revealed a strong and encouraging performance trend across all analytes, with 25 parameters (Figure 1) consistently achieving Six-Sigma from January to June, followed by July (Figure 2), reflecting exceptional analytical capability and a highly robust testing process.

Figure 1: : Analytes achieving Six-Sigma or more.

Abbreviations: ALB: Albumin; ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AMYL: Amylase; AST: Aspartate Transferase; BIL: Bilirubin; BILD: Direct Bilirubin; CA: Calcium; CHOL: Cholesterol; CK: Creatine Kinase; CREA: Creatinine; CRP: C-Reactive Protein; FE: Iron; GGT: Gamma-Glutamyl Transferase; GLUC: Glucose; HDL-C: High-Density Lipoprotein Cholesterol; LDH: Lactate Dehydrogenase; LDL-C: Low-Density Lipoprotein Cholesterol; LIP: Lipase; MG: Magnesium; PHOS: Phosphorus; TP: Total Protein; TRIG: Triglycerides; UA: Uric Acid.

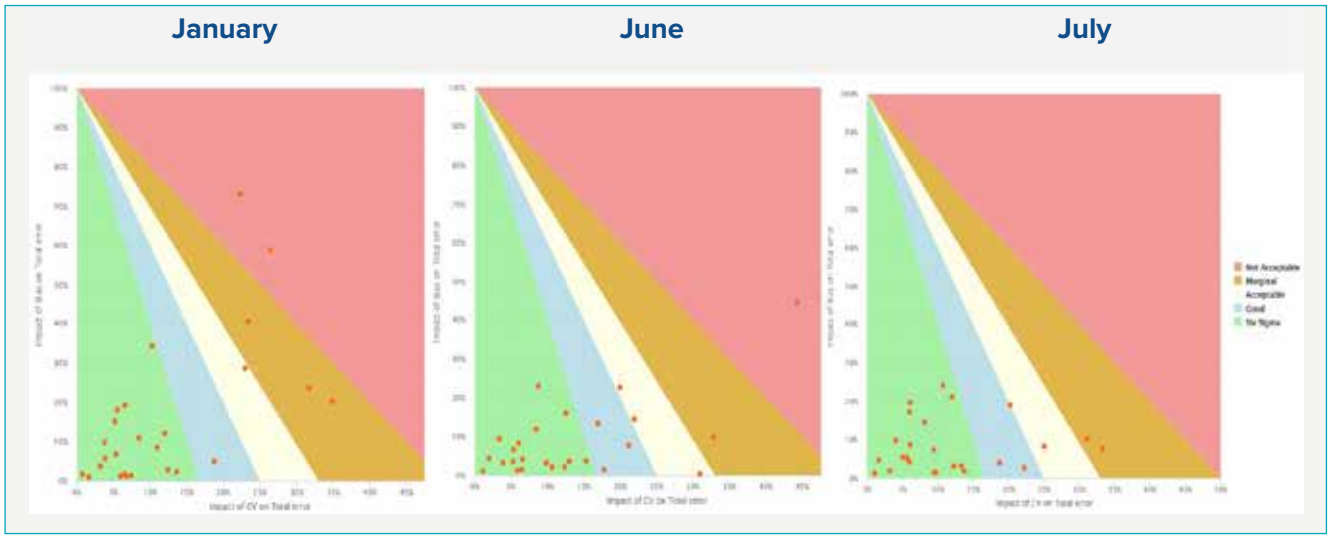

Figure 2: Sigma Matrix (Operational performance specifications [OPS] chart) of all the analytes across the months using PreciControl Clinical Chemistry (PCCC1) in Cobas Pro with TIQCon Quality Performance software.[5]
Abbreviation: CV: Coefficient of Variation.

While most analytes demonstrated strong and stable performance — particularly enzymatic and endpoint assays such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) — reaching and sustaining Six-Sigma capability, a few parameters reflected sigma values in the 3–5 range. Rather than indicating concern, these findings highlight valuable opportunities for further optimisation. Electrolytes such as chloride, sodium, and magnesium remained only marginally below the Six-Sigma threshold, suggesting that with minor refinements — such as focused maintenance, verification of QC storage practices, and routine lot assessment — their sigma performance can be enhanced. This positive trend underscores the system's robustness and shows that continuous quality improvement measures are already guiding these analytes toward Six-Sigma capability.

These focused actions led to measurable improvement in sigma values for these analytes, as demonstrated in Figures 1, 2 and 3. This positive trend underscores the system's robustness and reflects the effectiveness of ongoing quality improvement efforts.

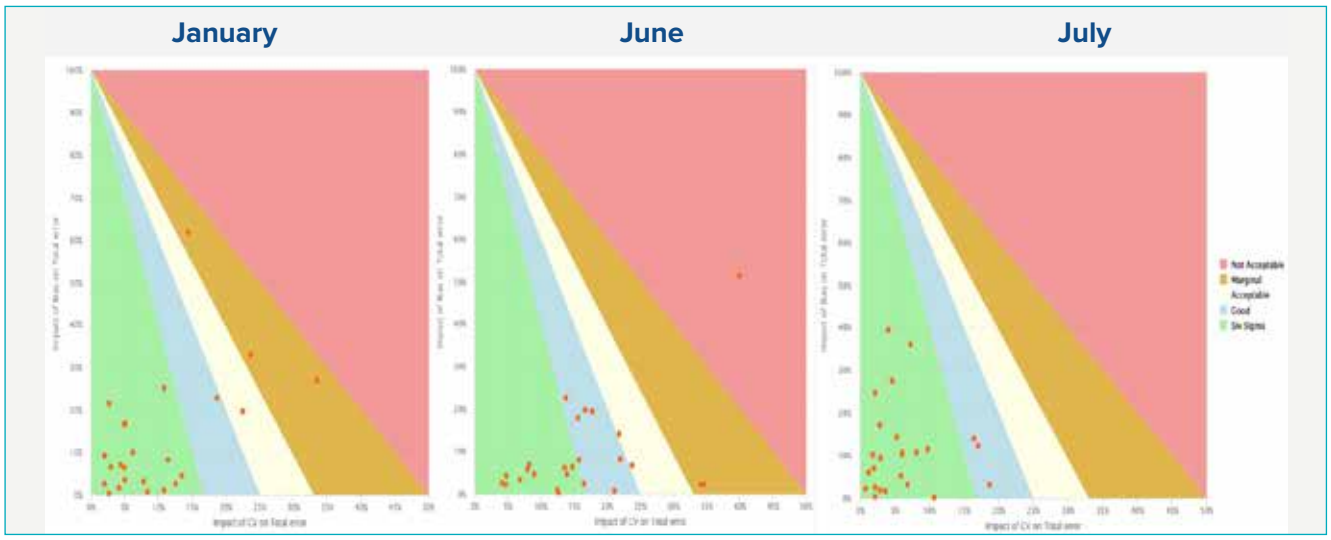

Figure 3: Sigma Matrix (Operational performance specifications [OPS] chart) of all the analytes across the months using PreciControl Clinical Chemistry (PCCC2) in Cobas Pro with TIQCon Quality Performance software.[5]
Abbreviation: CV: Coefficient of Variation.

Discussion

The overall Six-Sigma assessment demonstrates that the majority of analytes are performing exceptionally well within desirable quality specifications, with several achieving Six-Sigma capability — an indicator of strong analytical robustness and effective quality management. This consistent performance affirms that the laboratory's calibration practices, reagent management, and QC procedures are operating at an optimal and stable level.[6] The few analytes reflecting sigma values in the 3–5 sigma range should be viewed positively, as they highlight natural operational variability and offer meaningful opportunities for refinement.[7] Importantly, the notable improvements observed in parameters such as chloride, sodium, and magnesium reflect the effectiveness of timely interventions, including proactive maintenance, calibration, reagent lot verification, and optimisation of QC storage and maintenance workflows. These actions successfully improved precision, reinforcing the system's capability for rapid performance recovery. Operational factors — such as reagent lot transitions, scheduled maintenance activities, and environmental or storage conditions — can influence sigma values, and addressing them through routine preventive maintenance and strengthened QC handling ensures sustained high-quality output. Overall, this assessment validates the strong analytical performance of the Roche Cobas Pro platform while also demonstrating the laboratory's commitment to continuous improvement. Although based on a short evaluation period, the trends provide valuable insights and clearly support ongoing strategies for maintaining and further enhancing Six-Sigma-level capability.

Declaration of Conflicting Interests

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Author(s) also declare no use of artificial intelligence (AI) in generating images and writing the article.

Conclusion

The comparative analysis of sigma values from January to July highlights the strength of Six-Sigma as a proactive and dynamic tool for monitoring analytical performance. It is encouraging that most analytes consistently achieved sigma values within the desirable Six-Sigma range, reaffirming the laboratory's strong analytical capability. In July, the impact of focused quality interventions — such as scheduled maintenance, optimised QC storage, and seamless lot-to-lot verification — resulted in a clear upward shift in sigma performance. Although the data are based on a limited evaluation duration, the positive trends clearly illustrate the laboratory's commitment to quality excellence and further strengthen overall patient safety.

Mohini Bhargava, Prabhat Maurya. Analysis of Laboratory Quality Control Performance: A Six-Month Six-Sigma Metric Study. MMJ. 2026, March. Vol 3 (1).

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Pudendal Neuralgia: What Does a Gynaecologist Need to Know?

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Abstract:

Pudendal neuralgia is a rare, chronic and debilitating pain syndrome affecting the sensitive areas of the body innervated by pudendal nerve. However, due to lack of awareness, most patients are frequently misdiagnosed or underdiagnosed by healthcare providers, including gynaecologists. Patients often go through multiple consultations with physicians of various disciplines, undergo multiple evaluations, and experience years of delay in diagnosis, resulting in significant delays in appropriate treatment. Consequently, those affected have a severely compromised quality of life and often develop mental health problems. They may suffer from depression or anxiety, accompanied by feelings of frustration, loneliness, and shame, and some may resort to suicide. Therefore, there is an urgent need for approaches towards growing awareness of the seriousness of this disease among gynaecologists.

Key words: Pudendal Neuralgia, Pudendal Nerve Entrapment Syndrome, Alcock Canal Syndrome, Neuropathy, Chronic Pelvic Pain, Nantes' Criteria, Pudendal Nerve Block, Pudendal Decompression.

Introduction

Pudendal neuralgia is a chronic neuropathic pelvic and perineal pain syndrome that originates from injury, inflammation, or irritation of the pudendal nerve. It is also called the Alcock canal syndrome or pudendal nerve entrapment syndrome. As estimated by the International Pudendal Neuropathy Foundation, the incidence of this condition is 1 per 100,000, but the actual prevalence is believed to be substantially higher than reported.[1] Pudendal nerve entrapment syndrome may affect 1% of the general population and accounts for about 4% of all patient consultations for pain control in chronic pelvic pain, with women affected more than twice as often as men.[2] Primary symptoms of pudendal neuralgia include pelvic pain, sexual dysfunction and difficulty with urination or defaecation.[3]

Pelvic pain:

There is pain or an altered sensation in the dermatomal distribution of the pudendal nerve, including the vulva, clitoris, perineum and rectum. The pain typically occurs with sitting, especially on a hard surface, and improves on standing or in a lying-down position.[4] The pain is typically unilateral and rarely occurs on both sides. Patients often describe the pain as a shooting, burning, pricking or tingling sensation.

Sexual dysfunction:

Women with pudendal neuralgia may experience decreased sensation in the genitals, perineum, or rectum. It may be difficult or impossible for the woman to achieve orgasm. At times, the patient may also present with painful nocturnal orgasms and persistent sexual arousal.[5]

Difficulty with urination/defaecation:

Patients may experience urinary hesitancy, urgency and/or frequency. They may feel that they have to 'strain' to have a bowel movement and might have pain or discomfort after a bowel movement. Constipation is also common among these patients. In severe cases, complete or partial urinary and/or faecal incontinence may result.[5,6]

The sensation of a foreign object:

Some patients feel as though there is a foreign object sitting inside the vagina or the rectum. Some describe it as "sitting on a marble" or "having something stuck inside."[7]

Aetiology

The cause of pudendal neuralgia lies in its peculiar anatomy, which makes it susceptible to compression and entrapment, leading to nerve dysfunction and consequent symptoms. Other causes of pudendal neuralgia have also been described in the literature, like compression by a malignant or benign tumour, trauma at the sacral or nerve root level, stretching and lengthening of the nerve, followed by inflammation in situations like childbirth, repetitive straining during defaecation in case of constipation, squatting with heavy weights, etc.[1,3]

Anatomy of the Pudendal Nerve

The pudendal nerve is a mixed nerve carrying motor and sensory fibres from the ventral nerve roots of S2, S3, and S4. The nerve travels anterior to the piriformis muscle, squeezing between it and the coccygeus muscle through the greater sciatic foramen and between the sacrotuberous and sacrospinous ligaments. The net effect is analogous to a "clamp" or "lobster claw," pinching or impinging on the nerve.[8] Upon leaving this site, the nerve travels through Alcock's canal (also known as the pudendal canal). It divides into the deep and superficial perineal nerves, the dorsal nerve of the penis or clitoris, and the inferior rectal nerve (Figures 1–3).[6,8,9]

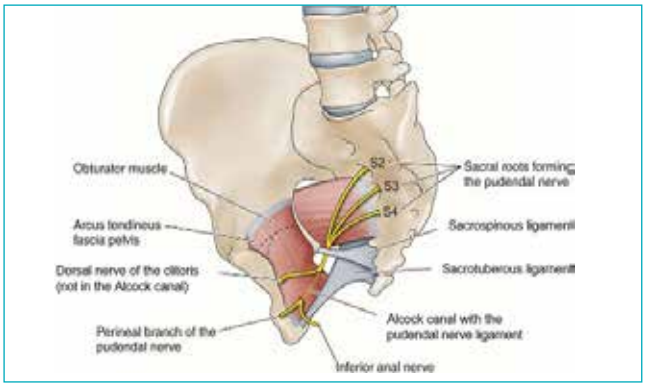

Figure 1: Course of the pudendal nerve. The nerve has a unique path in which it quickly exits the pelvis through the greater sciatic foramen inferior to the piriformis muscle. It then passes medially through the lesser sciatic foramen, enters the perineal region, and travels along the lateral wall of the ischioanal fossa in the pudendal canal (Alcock's canal).

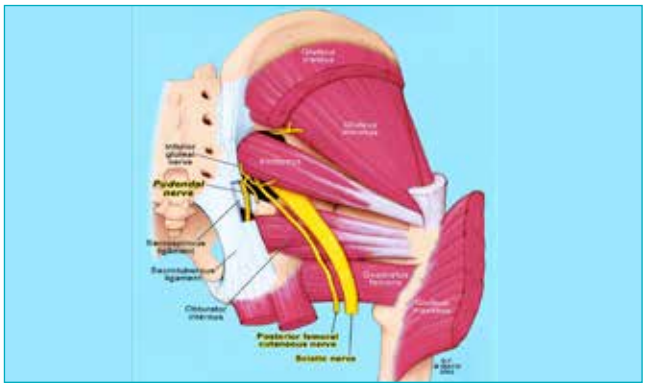

Figure 2: Pudendal nerve enters the gluteal region medial to the sciatic nerve, superficial to the sacrospinous ligament and deep to the sacrotuberous ligament. After coursing around the sacrospinous ligament, the pudendal nerve re-enters the pelvis through the lesser sciatic foramen.

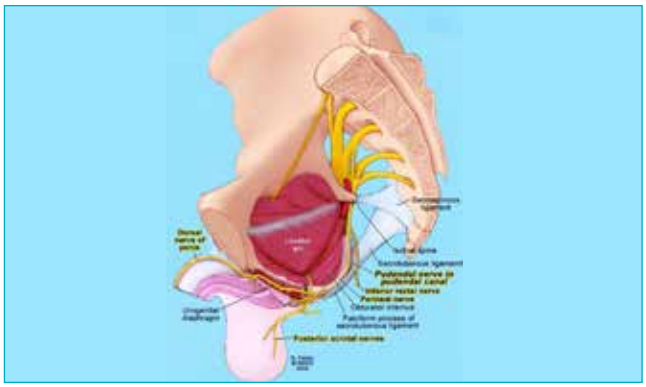

Figure 3: Pudendal nerve through the pudendal canal. Within the canal, the nerve splits into its 3 terminal branches, i.e. the inferior rectal nerve, the perineal nerve, and the dorsal nerve of the clitoris/penis. The inferior rectal nerve provides motor innervation to the external anal sphincter and surrounding levator ani muscles. It also provides sensory innervation to the skin of the anal triangle. The perineal nerve provides motor innervation to the transverse perinei muscle, the bulbospongiosus muscle, and the ischiocavernosus muscle, as well as to the external urethral sphincter. Finally, the dorsal nerve of the clitoris/penis travels parallel to the ischiocavernosus muscle and enters the clitoris/penis, providing innervation to the glans of each structure.

Pudendal neuralgia is caused by various mechanisms, which can be separated into three basic categories:[4]

1. As described, the pudendal nerve is anatomically vulnerable to compression and entrapment along its course (Figure 1). Patients with anatomical predispositions (i.e. smaller canals, a narrow window between ligaments, etc.) or biomechanical abnormalities are more susceptible to compression injuries. Patients may have a silent or asymptomatic compression for an extended period until an

exacerbating and inflaming factor, such as surgery, haematoma, cycling, prolonged sitting, stress and tension-holding patterns, horseback riding, etc., causes entrapment, nerve dysfunction and symptoms.

Four common sites of pudendal nerve entrapment are described below:[9]

- Type I: Entrapment below the piriformis muscle as the pudendal nerve exits the greater sciatic notch
- Type II: Entrapment between sacrospinous and sacrotuberous ligaments (this is the most common cause of pudendal nerve entrapment)
- Type III: Entrapment within Alcock's canal
- Type IV: Entrapment of terminal branches only (inferior rectal nerves, superficial and deep perineal nerves, and the dorsal nerve of the penis/clitoris)

2. Sacral or radicular type: Factors such as benign or malignant tumours and trauma to the area may cause nerve compression or inflammation at the sacral or nerve root level.[3,11]
3. The pudendal nerve is also vulnerable to tension injuries. A variety of factors including vaginal childbirth, constipation with repetitive straining to defaecate, and squatting with heavy weights, can put undue tension on the nerve, causing it to lengthen beyond its normal limits and resulting in neural inflammation.[13]

Diagnosis

The diagnosis of pudendal neuralgia by pudendal nerve entrapment syndrome is essentially clinical. A clinical diagnostic criterion was discussed and published by a multidisciplinary working party in Nantes, France, in 2006.[10] The "Nantes" inclusion criteria are shown in Table 1.

1. Pain correlates with the anatomical distribution of the pudendal nerve
2. Pain is predominantly in the sitting position
3. The patient does not get up at night due to pain
4. There is no identifiable sensory loss
5. Relief of pain occurs with a pudendal nerve block

Diagnostic Criteria for Pudendal Neuralgia by Pudendal Nerve Entrapment Nantes criteria
Essential criteria (must all be present) • Pain in the territory of the pudendal nerve: from the anus to the penis or clitoris • Pain is predominantly experienced while sitting • The pain does not wake the patient at night • Pain with no objective sensory impairment • Pain relieved by diagnostic pudendal nerve block
Complementary diagnostic criteria • Burning, shooting, stabbing pain, numbness • Allodynia or hyperpathia • Rectal or vaginal foreign body sensation (sympathalgia) • Worsening of pain during the day • Predominantly unilateral pain • Pain triggered by defaecation • Presence of exquisite tenderness on palpation of the ischial spine • Clinical neurophysiology findings in men or nulliparous women
Exclusion criteria • Exclusively coccygeal, gluteal, pubic or hypogastric pain • Pruritus • Exclusively paroxysmal pain • Imaging abnormalities able to account for the pain
Associated signs not excluding the diagnosis • Buttock pain on sitting • Referred sciatic pain • Pain referred to the medial aspect of the thigh • Suprapubic pain • Urinary frequency and/or pain on a full bladder • Pain occurring after ejaculation • Dyspareunia and/or pain after sexual intercourse • Erectile dysfunction • Normal clinical neurophysiology

Table 1: Nantes criteria for diagnosis of pudendal neuralgia.
Source: Labat J-J, *et al. Neurourol Urodyn.* 2008;27(4):306–10.[10]

When pudendal neuralgia due to pudendal nerve entrapment is diagnosed according to the Nantes criteria, no further investigation is required, and medical or surgical treatment can be proposed. Nevertheless, a number of other possible causes of pudendal neuralgia, like benign or malignant pelvic tumours, endometriosis, neuroma, pelvic floor dysfunction, genital prolapse, etc., must not be overlooked.[11] However, a study conducted by Indraccolo *et al.* showed that atypical presentation of pudendal neuralgia (i.e. other than pudendal nerve entrapment) in females is low when clinical criteria for pudendal entrapment syndrome are applied. Hence, pudendal neuralgia has come to be used interchangeably with pudendal nerve entrapment and Alcock canal syndrome.

Management

Conservative: Avoidance of painful stimuli is one of the most important components of treatment. For instance, if cycling causes pain, the patient should use proper padding or cease the activity. Other activities to avoid might be hip flexion exercises, jogging, rowing and gymnastics. Roughly 20%–30% of patients see relief from conservative measures alone.[7]

Physical therapy: Pelvic floor physical therapy works best for patients in whom pain results from muscle spasms. Physical therapy releases spasms and relaxes pelvic floor muscles, thereby causing muscle lengthening. A course of 6–12 weeks is commonly recommended. Adding transcutaneous electrical nerve stimulation (TENS) to physical therapy appears to be helpful.[12]

Pharmacologic therapy: There are no randomised trials to study and evaluate the efficacy of these drugs or which combinations might be most effective. Often, several medications from different drug classes are used. A typical combination would be a tricyclic antidepressant (amitriptyline), a serotonin–norepinephrine reuptake inhibitor (duloxetine), and a neurotransmitter analogue (gabapentin and/or pregabalin).[7,13]

Pudendal nerve block: Infiltration with a local anaesthetic or steroid in an area encircling the pudendal nerve is the mainstay of pudendal nerve pain management. The block can be given unguided or with the aid of ultrasonography, fluoroscopy, or computed tomography (CT). While no standard medication or combination is used, one frequently used mixture includes 1% lidocaine, 0.25% bupivacaine, and a corticosteroid such as triamcinolone. About 25% of patients report pain relief lasting more than one month following pudendal nerve blocks.[7] While this can be effective, there is evidence that ongoing therapeutic pudendal blocks may lose efficacy after two years.[13]

Surgical decompression: Surgery to directly free the pudendal nerve in Alcock's canal is considered the most effective long-term treatment and potential cure for pudendal nerve entrapment. The four different approaches are transperineal, transgluteal, transischiorectal, and laparoscopic.[14] Overall success with surgical decompression is about 70% (60%–80%).[15] The goal of decompressive surgery is to completely free the nerve from entrapment and compression while allowing it complete mobility. Laparoscopy has the advantage of a better visual surgical field with built-in magnification. It allows for the option of leaving a neuromodulation electrode in place as a backup.[15]

Sacral neuromodulation: This minimally invasive treatment includes using a peripheral nerve stimulator, which causes neural regulation of the pudendal nerve in the ischioanal fossa. It has often been used as a treatment of last resort when patients have failed all other treatments, including surgical decompression.[2]

Pulsed radiofrequency ablation, cryotherapy and lipofilling are relatively newer experimental methods of treatment of pudendal neuralgia.[2]

Declarations

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Conclusion

Lack of awareness on the part of physicians, including gynaecologists, about pudendal neuralgia has a severe negative impact on the quality of life of those suffering from it. Approaches like conducting workshops with the aim to impart extensive training on the anatomy of pelvic nerves and the ways to perform examinations specifically designed to evaluate the pudendal nerve may help in the diagnosis and management of this neuropathic pain. A multidisciplinary approach involving gynaecologists, urologists, colorectal surgeons, physical therapists and pain management specialists for the management of pudendal neuralgia should be encouraged to improve outcomes for the patients. Resources like the Health Organization for Pudendal Education (HOPE) and the International Pelvic Pain Society (IPPS) aim to provide information and support to both patients and healthcare providers to bridge the knowledge gap.

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Revisiting Radiotherapy: Low-Dose Radiation Therapy for Refractory Osteoarthritis

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Abstract:

Osteoarthritis (OA) is a highly prevalent musculoskeletal disorder causing chronic pain and disability. As many patients fail conservative therapy or are unsuitable for surgery, effective non-invasive options are needed. Low-dose radiation therapy (LDRT) has re-emerged as a treatment targeting OA-related inflammation and providing symptom relief. This narrative review summarises the epidemiology and pathophysiology of OA, the radiobiological rationale for LDRT, patient selection criteria, clinical outcomes, and safety considerations. Evidence from randomised controlled trials, observational studies, and international guidelines — particularly German Society for Radiation Oncology (DEGRO) — was also reviewed. At low doses (0.5–1.0 Gy per fraction; total 3 Gy), LDRT exerts anti-inflammatory effects that translate into significant pain relief and functional improvement in OA of affected joints. Evidence from randomised and observational studies showed good tolerance, mild to no toxicity, and an extremely low theoretical risk of secondary malignancy. DEGRO guidelines endorse LDRT as an adjunctive treatment for selected patients with painful OA who have failed conservative therapy or are unsuitable for surgery. LDRT is a safe, evidence-based, non-invasive option that provides effective pain relief and functional improvement in selected patients with osteoarthritis. By addressing chronic joint inflammation, it offers a practical therapeutic "middle ground" between conservative management and surgery. Further research is warranted to optimise patient selection, timing, and predictive biomarkers of response.

Key words: Osteoarthritis, Low-Dose Radiation Therapy, Pain Relief.

Introduction

Osteoarthritis (OA) affects nearly 595 million people globally and is a leading cause of pain and disability. By 2050, OA prevalence is projected to increase by 74.9% for the knee, 48.6% for the hand, 78.6% for the hips, and 95.1% for other joints.[1] In India, symptomatic OA cases rose 2.66-fold, from 23.46 million in 1990 to 62.3 million in 2019.[2]

OA is no longer viewed as a simple "wear-and-tear" disorder but as a disease of joint failure, involving cartilage degeneration and chronic low-grade inflammation.[3] OA risk increases with age and is influenced by female sex, obesity, prior injury, and genetic factors. While management ranges from lifestyle measures and pharmacotherapy to surgery, a subset of patients remains refractory to conservative treatment, yet unsuitable or unwilling for surgical intervention. For such patients, low-dose radiation therapy (LDRT) offers a non-invasive, effective therapeutic option, addressing the inflammatory component of OA.[3]

Historical Perspective

The use of radiation for non-malignant diseases dates back nearly a century. Following the discovery of X-rays by Wilhelm Conrad Röntgen in 1895 and radioactivity by Henri Becquerel and Marie Curie, radiotherapy was rapidly adopted for a wide range of benign conditions, often without robust evidence or long-term safety data.[4] As early as 1898, X-rays were reported to provide effective pain relief in patients with arthritis.[5] However, growing recognition of the risk of radiation-induced secondary malignancies led to fear and uncertainty, resulting in a gradual global decline in the use of radiotherapy for benign diseases.

Radiobiological Rationale for LDRT

LDRT exerts anti-inflammatory and immunomodulatory effects that result in pain relief (Figure 1). At doses used for OA (0.3–1.0 Gy),[6] LDRT downregulates pro-inflammatory cytokines (tumour necrosis factor-α [TNF-α], interleukin-1β [IL-1β], interleukin-6 [IL-6]), upregulates anti-inflammatory mediators (transforming growth factor-β [TGF-β]), reduces endothelial activation and leukocyte recruitment, and promotes macrophage polarisation towards an anti-inflammatory (M2) phenotype.[7] These combined effects suppress chronic synovial inflammation and nociceptive signalling, leading to improved pain and joint function without significant structural damage.[8]

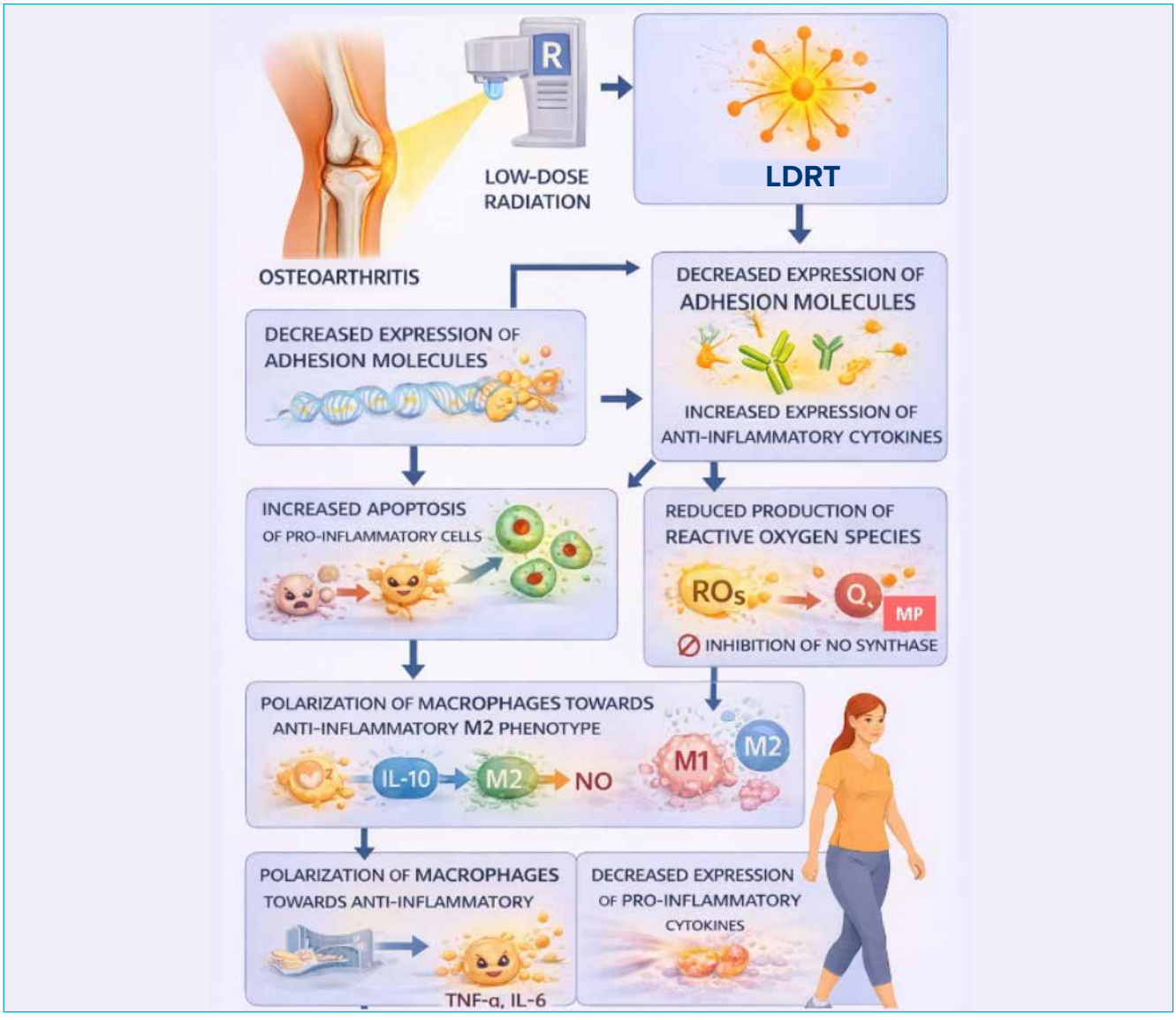

Figure 1: Radiobiological mechanisms of the anti-inflammatory effect of low-dose radiation therapy. **Abbreviations:** DNA: Deoxyribonucleic Acid; IL-6: Interleukin-6; IL-10: Interleukin-10; LDRT: Low-Dose Radiation Therapy; M1: Classically Activated Macrophages; M2: Alternatively Activated Macrophages; MP: Metalloproteinases; NO: Nitric Oxide; O_4: Tetraoxygen; ROS: Reactive Oxygen Species; TNF-α: Tumour Necrosis Factor-α.

Indications and Contraindications for LDRT in OA

Appropriate patient selection for LDRT in OA is essential, as it plays a key role in determining the treatment outcomes shown in Table 1.

Indications	Contraindications
Age > 40 years	Spine osteoarthritis
Sites - Upper and lower limbs	Active pregnancy
Kellgren-Lawrence (KL) stage ≤ 3	Kellgren-Lawrence stage 4
Pain score of at least ≥ 4 on Visual Analog Scale (VAS)	Active infection of the joint (e.g. septic arthritis)
History of chronic pain > 3 months, refractory to conservative line of treatment	Active infection of the affected joint
Surgical options contraindicated or opted against by the patient	Active cancer or undergoing cancer treatment

Table 1: Indications and contraindications of low-dose radiation therapy for osteoarthritis.

Treatment Planning

LDRT planning involves patient consent, computed tomography (CT) simulation with immobilisation, and target volume delineation, with careful shielding of adjacent critical structures (Figures 2, 3A and 3B). Based on clinical studies and international guidelines, the standard dose for OA is 3 Gy in 6 fractions (0.5 Gy each) over 2 weeks.[9] Treatment response is assessed at 6–8 weeks using the Visual Analogue Scale (VAS), Numeric Rating Scale (NRS), or Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores.[10,11] In cases of partial or no response, a second LDRT course may be delivered 8–12 weeks after the initial treatment.[12,13]

Risk-Benefit Profile

Benefits of LDRT for OA:

- Reduction in pain, improvement in joint function and improved quality of life
- Non-invasive treatment option
- Minimal to no acute toxicity and good overall tolerance
- Potential benefit in patients with refractory OA who have failed conservative therapies
- Long-term effect

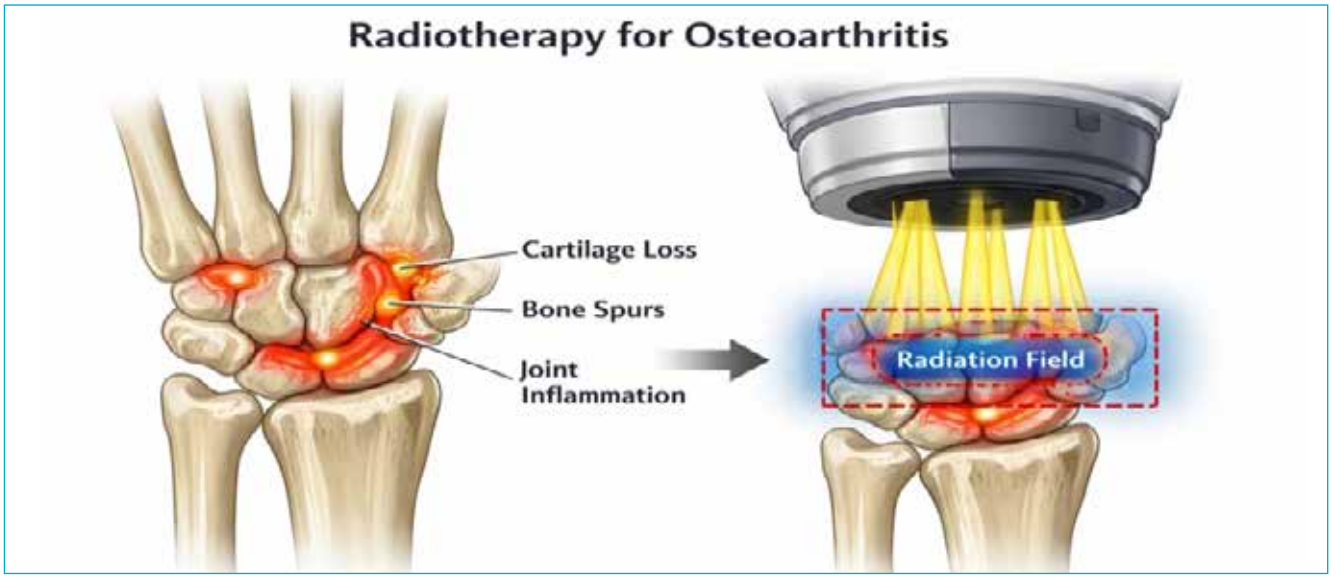

Figure 2: Graphic representation of a wrist joint showing changes of osteoarthritis. Only the affected area is targeted as per guidelines and treated with low-dose radiation therapy.

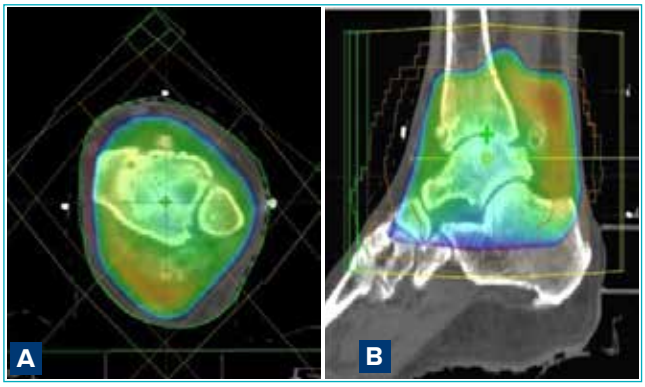

Figure 3A and B: Computed tomography-based target delineation and dose distribution for ankle osteoarthritis.

Risks of LDRT for OA:

- Acute (early) toxicities (< 1%). A small but non-negligible theoretical risk of radiation-induced malignancy has been described; however, contemporary evidence suggests this risk is extremely low when low-dose regimens and appropriate patient selection are employed.[13]

LDRT for OA in Randomised Trials and Guidelines

Some randomised trials exist in the literature, highlighting the promising role of LDRT for OA, as shown in Table 2.

Trial	Patients	Randomised arms	Results
Kim *et al.*[11]	114 patients with hip or knee OA	3.0 Gy in 0.5 Gy treatments versus 0.3 Gy in 0.05 Gy treatments versus sham	Significant pain relief at 4 months
Niewald *et al.*[14]	229 patients with hand/ finger or knee OA	3.0 Gy in 0.5 Gy given bi-weekly versus 0.3 Gy in 0.05 Gy given bi-weekly	Favourable pain relief in both arms
Fazilat-Panah *et al.*[15]	60 patients with knee OA	3.0 Gy in 0.5 Gy treatments versus sham	VAS pain score, Lysholm scale, PS, and analgesic consumption were improved from the 1st month to the end of assessment

Table 2: Randomised trials highlighting the successful role of low-dose radiation therapy in osteoarthritis.
Abbreviations: Gy: Gray; OA: Osteoarthritis; PS: Pain Score; VAS: Visual Analogue Scale.

Few case series and observational studies are mentioned in Table 3.

Trials	Study design	Patients	Follow-up (months)	Response
Koneru *et al.*[16]	Retrospective	69	3 and 12	12 m = 80%
Alvarez *et al.*[17]	Prospective	100	10.5 (median)	3–12 m = 70%–94%
Donabauer *et al.*[18]	Retrospective	483	3 and 6	3 m = 70% 6 m = 70%

Table 3: Case series and observational studies highlighting the role of low-dose radiation therapy in osteoarthritis.

DEGRO guidelines:

These comprehensive guidelines by the German Society for Radiation Oncology (DEGRO) support the use of LDRT as a non-invasive, adjunctive option for painful OA, and are summarised below (Table 4).[9]

Category	Recommendation
Indications	Painful knee OA (Kellgren stage 2–3): Recommended when conservative treatment fails or is contraindicated
	Painful hip OA
	OA of small joints (e.g. hand, foot)
Patient selection	LDRT is typically considered only after conservative therapies fail (e.g., medications, physical therapy)
	Patients > 40 years
Dose and fractionation	Single fraction dose: 0.5 Gy
	Total dose per series: 3.0 Gy
	Schedule: 2–3 fractions per week
Target volume/ technique	Entire affected joint, including adjacent bone, synovium, muscles/connective tissue
Response assessment	Evaluate clinical benefit with pain scores/functional scales at the end of radiation and then at 3, 6, 12 months post-therapy and so on (as per department protocol)
Safety/radiation considerations	Mild to no acute toxicity
	The risk of secondary malignancy is very rare
General recommendation	LDRT can be performed for selected patients of OA if, after other conservative treatments have failed or are not suitable, and if surgery is contraindicated

Table 4: Summary of the German Society for Radiation Oncology (DEGRO) guidelines for use of LDRT in OA.
Abbreviations: LDRT: Low-Dose Radiation Therapy; Gy: Gray; OA: Osteoarthritis.

A summary of common queries and their evidence-based responses are mentioned in Table 5.

Future Directions

Given the rising global burden of OA, LDRT offers a valuable non-surgical option for pain relief, supported by four randomised trials and multiple case series showing significant benefits. Future research should refine timing, predictive inflammatory markers, concurrent therapies, and site-specific efficacy.

Query	What does the evidence say?
Issue of secondary malignancies with the use of LDRT?	Based on current evidence and long-standing clinical experience, the risk of secondary malignancy from LDRT in osteoarthritis is theoretical and extremely low, and when appropriately delivered, LDRT is a safe and effective option for pain relief
What are the acute and late side effects of LDRT?	Available evidence indicates minimal to no acute or late toxicity with LDRT, with only rare, mild, and transient skin erythema reported, and no significant long-term risks such as secondary malignancy or joint damage
Will LDRT replace surgery for knee OA?	No, LDRT does not replace surgery; it is a complementary, evidence-based non-surgical therapy that provides symptomatic relief and may delay surgery in selected patients
Is surgery possible if LDRT has been given previously?	Yes, surgery after LDRT is feasible. The low dose (3 Gy) targets inflammation without harming healthy tissue, and post-RT fibrosis or negative surgical outcomes have not been reported

Table 5: Queries and concerns about LDRT.
Abbreviations: LDRT: Low-Dose Radiation Therapy; Gy: Gray; OA: Osteoarthritis; RT: Radiotherapy.

Conclusion

As evidence continues to evolve, LDRT could emerge as a practical "middle-ground" treatment for osteoarthritis, offering an effective bridge between conservative management and surgical intervention.

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A Mini Review on Stage-Specific Autophagy Dynamics and Immune Regulation in the Reproductive System

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Abstract:

Autophagy is a conserved intracellular degradation mechanism critical for cellular homeostasis, differentiation, and adaptation to stress. Within the reproductive system, autophagy plays a dynamic, stage-specific role in gametogenesis, implantation, placentation, and parturition, aligning cellular metabolism and immune regulation to reproductive demands. Dysregulation of autophagic pathways contributes to reproductive pathology, including infertility, pre-eclampsia, and polycystic ovary syndrome (PCOS), underscoring its significance in reproductive health. This review aims to synthesise current understanding of stage-specific autophagy regulation in reproductive tissues, with a focus on its intersection with immune dynamics at the maternal–foetal interface. It highlights mechanistic pathways, immune cell modulation, and pathological outcomes associated with altered autophagy. Data were drawn from recent peer-reviewed publications indexed in PubMed, Frontiers, and ScienceDirect, focusing on studies published between 2018 and 2025 that investigated autophagy-related gene expression, signalling pathways, and immune modulation in reproductive tissues. Comparative analyses integrated molecular, cellular, and physiological findings across mammalian models and human studies. Autophagy acts as an integrative regulatory mechanism bridging cellular metabolism and immune adaptation in the reproductive system. Understanding its temporal and spatial regulation provides essential insight into fertility, pregnancy maintenance, and the pathogenesis of gestational disorders. Future research should explore therapeutic strategies that target autophagy to restore immune homeostasis and improve reproductive outcomes.

Key words: Autophagy, Reproductive Immunology, Maternal–Foetal Interface, Pregnancy, Reproductive Ageing.

Introduction

Autophagy, a highly conserved catabolic process, orchestrates intracellular degradation and recycling of proteins and organelles to preserve cellular homeostasis.[1,2] First characterised in yeast and later defined across eukaryotic organisms, autophagy ensures cell survival under conditions of nutrient deprivation, oxidative stress, or infection by mobilising lysosomal degradation pathways.[1,2] In mammalian reproduction, autophagy performs roles that extend far beyond basic metabolic housekeeping — it serves as a critical determinant of cellular fate, tissue remodelling, and immune equilibrium across multiple reproductive stages.

The reproductive system presents a unique biological environment characterised by cyclic tissue remodelling, immune modulation, and cellular differentiation. From gametogenesis to parturition, reproductive success relies on the precise coordination of cellular turnover and immune adaptation. Autophagy acts at

the core of this coordination, integrating metabolic cues with immune and endocrine signalling to ensure functional competence of germ cells, embryos, and maternal tissues.[1] Dysregulation of autophagy has been implicated in infertility, implantation failure, pre-eclampsia, recurrent pregnancy loss, and other gynaecological disorders.[3]

Historical and conceptual framework

The conceptual link between autophagy and reproduction has evolved significantly over the past two decades. Early studies identified autophagic vacuoles in ovarian follicles and preimplantation embryos, suggesting a role in developmental remodelling. Subsequent molecular investigations revealed the involvement of autophagy-related genes (ATG family), Unc-51-like kinase (ULK) complexes, and mammalian target of rapamycin complex 1 (mTORC1) signalling in regulating these processes.[2] Modern approaches, including conditional gene knockout models, live-cell imaging, and omics-based profiling, have deepened understanding of how autophagy coordinates reproductive function in a temporally and spatially specific manner.

Autophagy's physiological importance extends to the maternal–foetal interface, a site where the immune system must balance tolerance and defence. Decidual cells, trophoblasts, and infiltrating immune populations rely on autophagy to adapt to hypoxic, oxidative, and inflammatory microenvironments characteristic of early pregnancy.[1] Autophagic regulation determines trophoblast invasion depth, uterine natural killer (uNK) cell cytotoxicity, macrophage polarisation, and T-cell tolerance, thereby collectively shaping pregnancy outcomes.

Mechanistic overview of autophagy in reproductive biology

Macroautophagy, the most extensively studied subtype, involves sequestration of cytoplasmic components into double-membraned autophagosomes, which subsequently fuse with lysosomes for degradation. Key molecular mediators include the ULK1 complex (ULK1, ATG13, FIP200, and ATG101), the class III phosphatidylinositol 3-kinase (PI3P) complex (Beclin-1, vacuolar protein sorting 34 [VPS34], VPS15, and ATG14), and the ATG5–ATG12–ATG16L1 conjugation system.[1] mTORC1 serves as a master regulator, inhibiting autophagy under nutrient-rich conditions and relieving repression during energy stress or hypoxia—states frequently encountered in reproductive tissues, especially during implantation and placentation.

In reproductive contexts, autophagy provides energy substrates during oocyte maturation, prevents accumulation of damaged organelles in embryos, and enables trophoblast differentiation under limited oxygen supply.[2] Conversely, excessive or insufficient autophagy disturbs these finely tuned processes, leading to embryonic lethality or developmental arrest.

Integration of autophagy and immune function

Pregnancy imposes an immunological paradox—the maternal immune system must tolerate the semi-allogeneic foetus while maintaining defence against pathogens. Autophagy plays a pivotal role in maintaining this balance. In immune cells such as uNK cells and macrophages, autophagy regulates metabolic fitness and survival, modulates cytokine release, and determines the degree of cytotoxicity toward trophoblasts.[1] Autophagic flux within trophoblasts, in turn, shapes local immune responses by altering antigen presentation, cytokine secretion, and apoptotic signalling.

Recent studies have identified reciprocal signalling between autophagy-related transcription factors, such as transcription factor EB (TFEB), microphthalmia-associated transcription factor (MITF), and forkhead box O3 (FOXO3), and immune regulators, including tumour necrosis factor receptor superfamily member 14 (TNFRSF14), also known as herpesvirus entry mediator (HVEM), and nuclear factor kappa B (NF-κB).[2] These molecular circuits contribute to the maintenance of decidual homeostasis[2] and ensure stage-specific immune adaptation during implantation, gestation, and parturition.

Scope of this review

This review synthesises recent findings on stage-specific autophagy dynamics and their immunological implications across reproductive stages. By integrating evidence from molecular, cellular, and clinical studies, it delineates how autophagy governs immune tolerance, stress adaptation, and reproductive success. Emphasis is placed on:

1. Mechanistic regulation of autophagy in reproductive cells and tissues
2. Immunomodulatory effects of autophagy at the maternal–foetal interface

3. Consequences of autophagy dysregulation in pregnancy complications and reproductive disorders
4. Environmental, endocrine, and metabolic influences on autophagic function

Through this synthesis, the review aims to clarify the multifaceted roles of autophagy in reproductive immunology and identify emerging therapeutic opportunities for enhancing fertility and maternal health.

Literature Review — Mechanistic Basis of Autophagy in Reproductive Tissues

Overview of autophagic pathways in reproductive physiology

Autophagy is not a static process but a tightly modulated, multistep cascade comprising initiation, nucleation, elongation, fusion, and degradation. In reproductive tissues, the activation of autophagy reflects a dynamic adaptation to fluctuating hormonal, metabolic, and immune environments. Macroautophagy — mediated through autophagosomes — serves as the principal form of autophagy, with its regulation centred on nutrient-sensing pathways and stress-response kinases.[1,2]

At the molecular level, autophagy initiation is governed by the ULK1 complex (ULK1–ATG13–focal adhesion kinase family-interacting protein of 200 kDa [FIP200]–ATG101), which integrates upstream signals from mTORC1 and adenosine monophosphate-activated protein kinase (AMPK). Under nutrient sufficiency, active mTORC1 phosphorylates ULK1 and ATG13, preventing autophagosome formation. Conversely, energy depletion or oxidative stress activates AMPK, which inhibits mTORC1 and directly phosphorylates ULK1 to trigger autophagy.[1] Once initiated, membrane nucleation proceeds via the Beclin-1–VPS34–ATG14 complex, generating PI3P to recruit additional ATG proteins. Autophagosome elongation depends on two ubiquitin-like conjugation systems involving ATG12–ATG5–ATG16L1 and microtubule-associated protein 1 light chain 3 (LC3, also known as ATG8), which facilitate membrane curvature and cargo sequestration. Finally, autophagosomes fuse with lysosomes to form autolysosomes, enabling the degradation and recycling of macromolecules.[2]

In reproductive physiology, these pathways are not merely cytoprotective but fundamentally developmental. Autophagy mediates follicular atresia, oocyte maturation, sperm capacitation, and implantation[3] — all processes requiring coordinated turnover of cellular components. For instance, autophagic activation ensures removal of defective mitochondria and endoplasmic reticulum in gametes, maintaining genomic integrity and energy efficiency essential for fertilisation.[4]

Autophagy during gametogenesis

Oogenesis and follicular development

Autophagy contributes to both survival and quality control of oocytes. In primordial follicles, basal autophagy maintains quiescence by balancing nutrient supply and oxidative stress. During follicular recruitment, increased autophagic flux supports cytoplasmic remodelling and organelle biogenesis. Studies in murine models have shown that deletion of Atg7 or Beclin-1 within oocytes leads to premature ovarian insufficiency (POI), characterised by accelerated follicular loss and impaired meiotic progression.[1]

Moreover, autophagy interacts with hormonal signalling cascades. Follicle-stimulating hormone (FSH) and luteinising hormone (LH) stimulation upregulate autophagy-related gene expression, while oestrogen suppresses excessive autophagic activity, thereby maintaining optimal oocyte viability.[3] The mTOR–AMPK balance serves as a metabolic switch: activation of mTORC1 inhibits autophagy to support oocyte growth, while its inhibition promotes autophagic clearance during atresia.

In granulosa cells, autophagy prevents apoptosis by regulating mitochondrial function and lipid turnover. However, excessive autophagy under oxidative stress leads to granulosa cell death, contributing to follicular atresia. This dual role underlines the importance of fine-tuned autophagic regulation in ovarian physiology.[1]

Spermatogenesis and male reproductive function

While female reproductive autophagy has been extensively characterised, evidence also supports essential functions in spermatogenesis and sperm maturation. Autophagy facilitates the removal of cytoplasmic droplets and defective organelles during spermiogenesis, ensuring the streamlined morphology of mature spermatozoa.[5]

Autophagy-related gene expression is particularly high in spermatogonia and spermatocytes, with ATG5, ATG7, and LC3B localised to developing germ cells.

Conditional deletion of ATG7 in Sertoli cells results in abnormal sperm morphology, reduced motility, and subfertility, indicating that somatic cell autophagy indirectly supports germ cell maturation.[5]

Moreover, autophagy interacts with androgen receptor (AR) signalling, which is critical for spermatogenic progression. Inhibition of AR signalling downregulates autophagic gene expression and disrupts spermatid differentiation, linking hormonal control to cellular quality assurance mechanisms. Emerging evidence also implicates autophagy in protection against oxidative damage in spermatozoa, a factor crucial for maintaining deoxyribonucleic acid (DNA) integrity and fertilisation capacity.[2]

Autophagy in early embryogenesis and implantation

Zygotic activation and embryonic development

Immediately following fertilisation, the embryo transitions from maternal to zygotic control of gene expression — a process accompanied by extensive cytoplasmic remodelling. Autophagy eliminates residual maternal proteins and damaged mitochondria, ensuring developmental competence. Mouse embryos lacking Atg5 or Atg7 fail to progress beyond the 4- to 8-cell stage, underscoring autophagy's indispensable role in preimplantation development.[2]

During compaction and blastocyst formation, autophagy maintains energy homeostasis under fluctuating oxygen and nutrient conditions. The mTOR–TFEB axis governs this adaptive response, promoting lysosomal biogenesis and degradation of cytoplasmic components to meet bioenergetic demands.[1]

Implantation and decidualisation

Implantation represents one of the most metabolically demanding events in reproduction. Endometrial stromal cells undergo decidualisation, transforming into specialised secretory cells that support embryo implantation. Autophagy modulates this transformation by regulating intracellular lipid metabolism, endoplasmic reticulum (ER) stress, and cytokine release.

Inhibition of autophagy through mTORC1 activation impairs decidualisation, while pharmacological activation of autophagy via rapamycin enhances endometrial receptivity.[1] At the molecular level, ATG5 and ATG16L1 facilitate progesterone-induced differentiation, linking autophagy to hormonal signalling networks. In addition, autophagic degradation of lipid droplets provides fatty acids for prostaglandin synthesis, which is essential for implantation and vascular remodelling.[3]

Autophagy in placentation and trophoblast function

The placenta is a unique organ requiring precise cellular turnover and immune regulation. Trophoblast cells, which mediate maternal–foetal exchange, rely on autophagy for survival under hypoxia and nutrient limitation. Hypoxia-inducible factors (HIF1α) and AMPK upregulate autophagy in early placental development, promoting trophoblast invasion and vascularisation.[1]

Autophagy also mitigates ER stress during syncytiotrophoblast formation. Dysregulated autophagy, particularly reduced Beclin-1 or ATG16L1 expression, leads to excessive ER stress, contributing to pre-eclampsia pathogenesis.[2] Furthermore, autophagy influences trophoblast–immune cell interactions by modulating the secretion of interleukin-10 (IL-10) and transforming growth factor beta (TGF-β), cytokines essential for maintaining immune tolerance.

Interestingly, trophoblast autophagy exhibits temporal specificity: high during early invasion phases to support cellular migration and attenuated during mid-gestation when placental architecture stabilises. Late in pregnancy, autophagic reactivation accompanies parturition-associated inflammation, illustrating cyclic regulation across gestation.[1]

Molecular crosstalk with endocrine and metabolic pathways

Autophagy in reproductive tissues is closely intertwined with hormonal and metabolic cues. Oestrogen and progesterone exert differential effects — oestrogen generally suppresses autophagic activity, whereas progesterone enhances autophagic readiness, consistent with their roles in tissue proliferation and differentiation, respectively.[3]

Metabolic regulators such as AMPK, sirtuin 1 (SIRT1), and peroxisome proliferator-activated receptor gamma (PPARγ) link nutrient sensing with reproductive signalling. SIRT1 activation promotes autophagy through deacetylation of ATG proteins and transcriptional regulation of forkhead box O3 (FOXO3) and TFEB, thereby ensuring adequate metabolic adaptation during pregnancy.[2] Dysregulation of these pathways in metabolic syndromes like obesity or diabetes reduces autophagic flux, predisposing to implantation failure and placental insufficiency.

Summary

Autophagy's mechanistic framework in reproductive physiology is multifactorial, encompassing nutrient-sensing networks, hormonal regulation, and immune modulation. Across gametogenesis, embryogenesis, and placentation, autophagy acts as a molecular switch that maintains cellular quality, metabolic equilibrium, and immune readiness. Stage-specific fluctuations in autophagic flux ensure appropriate transitions between proliferation, differentiation, and degeneration — core processes underpinning reproductive success.

The next section will explore how these autophagic mechanisms intersect with immune regulation at the maternal–foetal interface, highlighting the bidirectional signalling between autophagy and immune cells in sustaining pregnancy.

Immune Regulation and the Maternal–Foetal Interface

Immunological paradox of pregnancy

Pregnancy presents a unique immunological paradox: the maternal immune system must tolerate the semi-allogeneic foetus derived from paternal antigens while simultaneously maintaining robust antimicrobial defence. This equilibrium is achieved through precise temporal modulation of immune activation and suppression across gestation. The maternal–foetal interface — comprising decidual stromal cells, trophoblasts, and infiltrating immune populations — functions as a dynamic immunological hub.[1]

Autophagy has emerged as a key regulator of this immunological balance. Acting as both a metabolic and immunological switch, autophagy modulates cytokine production, antigen presentation, and cell survival in the uterine microenvironment.[2] Dysregulation of autophagic signalling disrupts this equilibrium, predisposing to implantation failure, recurrent miscarriage, or pre-eclampsia.[2]

Immune cell composition of the decidua

The decidua, the modified endometrium during pregnancy, harbours a specialised population of immune cells distinct from peripheral immune compartments. The main cell types include:

- uNK cells (40%–70% of decidual leukocytes)
- Macrophages (10%–20%)
- T lymphocytes, including $CD4^+$, $CD8^+$, and regulatory T cells (Tregs) (~10%–20%)
- Dendritic cells (DCs), along with smaller subsets of B lymphocytes and innate lymphoid cells[1]

Each population performs stage-specific functions. In early pregnancy, immune cells promote controlled inflammation to support implantation and vascular remodelling; during mid-gestation, tolerance mechanisms dominate; and near parturition, inflammatory pathways reactivate to facilitate labour.[3]

Autophagy orchestrates these phase transitions by regulating immune cell metabolism, survival, and effector functions. For instance, ATG5-dependent autophagy maintains mitochondrial integrity in immune cells, preventing excessive reactive oxygen species (ROS) production and apoptosis.[2]

Uterine natural killer cells

Development and function

uNK cells, the predominant immune population in the decidua, differ functionally from peripheral natural killer (NK) cells. Rather than exerting cytotoxic effects, they contribute to vascular remodelling, trophoblast invasion, and cytokine-mediated tolerance. Their activity depends heavily on autophagic regulation.

Loss of Atg5 in NK cells results in mitochondrial dysfunction, ROS accumulation, and premature cell death, leading to reduced uNK cell numbers and impaired spiral artery remodelling.[1] Experimental enhancement of autophagy through rapamycin or other activators promotes uNK cell survival and functional maturation, while pharmacological inhibition increases cytotoxicity and embryonic resorption in murine models.[2]

Molecular signalling mechanisms

The MITF–TNFRSF14, also known as HVEM, signalling axis has been identified as a critical pathway through which autophagy in decidual stromal cells (DSCs) promotes uNK cell retention.[1] MITF, a transcription factor responsive to autophagic activity, induces expression of TNFRSF14, which mediates stromal–NK cell adhesion and immune crosstalk.

Additionally, autophagic control of mTORC1 activity in uNK cells influences cytokine production. Suppressed autophagy elevates interferon gamma (IFN-γ) and tumour necrosis factor alpha (TNF-α), driving a

pro-inflammatory phenotype associated with implantation failure, whereas enhanced autophagy supports anti-inflammatory cytokines such as IL-10 and vascular endothelial growth factor A (VEGF-A), promoting vascular stability and foetal tolerance.[2]

Macrophages

Autophagy-dependent polarisation

Decidual macrophages exhibit remarkable plasticity, capable of adopting M1 (pro-inflammatory) or M2 (anti-inflammatory) phenotypes depending on gestational stage. Autophagy modulates this polarisation through metabolic and signalling control.

Activation of Beclin-1 and LC3B facilitates transition toward an M2-like phenotype, characterised by high IL-10 and TGF-β secretion, essential for tissue remodelling and immune tolerance.[1] Conversely, inhibition of autophagy or excessive mTORC1 activation skews macrophages toward an M1-like profile, elevating pro-inflammatory cytokines such as IL-6 and TNF-α, which can lead to placental inflammation and foetal growth restriction.[2]

Autophagy in phagocytic clearance and tissue remodelling

Autophagy also supports macrophage-mediated clearance of apoptotic cells (efferocytosis) at the maternal–foetal interface. Efficient removal of apoptotic trophoblasts prevents release of damage-associated molecular patterns (DAMPs), maintaining immune quiescence. Impaired autophagic flux in macrophages leads to the accumulation of cellular debris and chronic inflammation.[2]

Furthermore, autophagy-dependent lysosomal degradation provides amino acids and lipids that fuel macrophage biosynthesis during placental vascular remodelling, linking cellular metabolism with immune function.[1]

Dendritic cells and antigen presentation

Dendritic cells bridge innate and adaptive immunity, shaping T-cell responses through antigen presentation. In the decidua, DCs exhibit a tolerogenic phenotype characterised by low expression of co-stimulatory molecules and high IL-10 production.

Autophagy enhances antigen presentation via major histocompatibility complex (MHC) class II loading but paradoxically contributes to immune tolerance during pregnancy. Studies demonstrate that autophagic degradation of endosomal content reduces surface presentation of paternal antigens, limiting maternal T-cell activation.[2]

Additionally, TFEB and FOXO3 — key transcription factors regulating lysosomal biogenesis and autophagy — are upregulated in decidual DCs, promoting cellular adaptation to hypoxia and nutrient stress. This autophagic conditioning maintains DC viability and prevents inflammatory activation.[1]

T lymphocytes and regulatory networks

Effector and Tregs

Autophagy is indispensable for the homeostasis and function of both effector T cells (Teffs) and Tregs.

In $CD4^+$ and $CD8^+$ T cells, autophagy maintains mitochondrial quality control, preventing excessive ROS and apoptosis. Loss of Atg7 or Atg5 in T cells leads to metabolic exhaustion and reduced proliferative capacity.[2]

In Tregs, autophagy sustains FOXP3 expression and suppressive function by modulating intracellular acetyl-CoA levels and mTORC1 signalling.[1] Impaired autophagy reduces Treg frequency in the decidua, resulting in breakdown of maternal–foetal tolerance and increased risk of miscarriage.

Cytokine crosstalk

Autophagy influences the cytokine milieu that shapes T-cell differentiation. By regulating IL-2, TGF-β, and IL-10 signalling pathways, autophagy promotes expansion of tolerogenic Tregs and restrains T helper 1 (Th1) and T helper 17 (Th17) polarisation. Conversely, defective autophagy elevates IL-6 and IFN-γ, reinforcing pro-inflammatory loops detrimental to implantation.[3]

At the molecular level, autophagy interacts with NF-κB, a key inflammatory transcription factor. Under physiological conditions, autophagy restrains NF-κB activation through degradation of IκB kinase (IKK) complexes. Under pathological stress, autophagic suppression leads to uncontrolled NF-κB activation, amplifying cytokine release and tissue inflammation.[1]

Trophoblast–immune cell interactions

Trophoblast cells, which form the foetal component of the placenta, directly communicate with maternal immune cells to establish tolerance. Autophagy within

trophoblasts modulates secretion of chemokines and cytokines that guide immune recruitment.

Enhanced autophagic activity in trophoblasts promotes the secretion of C-X-C motif chemokine ligand 12 (CXCL12) and IL-10, thereby recruiting Tregs and suppressing cytotoxic T-cell activity.[2] In contrast, inhibition of autophagy increases C-X-C motif chemokine ligands 9 and 10 (CXCL9/CXCL10) and IFN-γ expression, fostering a pro-inflammatory environment.

Autophagic flux also regulates expression of programmed death-ligand 1 (PD-L1), a critical immune checkpoint molecule that suppresses T-cell activation. Reduced autophagy diminishes PD-L1 expression, impairing local tolerance and increasing the risk of immune-mediated pregnancy loss.[1]

Temporal regulation of immune autophagy across gestation

Autophagic activity and immune responses vary dynamically throughout pregnancy:

- **Peri-implantation (Day 1–Day 7):** Pro-inflammatory autophagy supports tissue remodelling and trophoblast invasion.
- **Mid-gestation:** Anti-inflammatory autophagy predominates, maintaining immune quiescence and tolerance.
- **Late gestation and parturition:** Re-activation of autophagy accompanies sterile inflammation and labour.[1]

This cyclical modulation reflects a coordinated adaptation to developmental cues and metabolic demands. Misalignment of autophagic timing — either excessive activation or inadequate suppression — disrupts immune balance, contributing to pregnancy disorders such as pre-eclampsia and preterm birth.[3]

Summary

Autophagy serves as a central homeostatic mechanism governing immune equilibrium at the maternal–foetal interface.[6] By orchestrating immune cell survival, differentiation, and cytokine production, autophagy ensures appropriate transitions between inflammatory and tolerant states necessary for successful pregnancy.

Key insights from current research highlight that:

1. Autophagy sustains uNK and macrophage viability while modulating their effector functions.
2. It preserves tolerogenic profiles of DCs and Tregs, maintaining maternal–foetal immune harmony.
3. Autophagic flux within trophoblasts integrates metabolic stress signalling with immune checkpoint regulation.
4. Temporal shifts in autophagy mirror evolving immunological demands across gestation.

Collectively, these mechanisms underscore autophagy's role as a molecular integrator of reproductive immunology, coordinating cellular metabolism, immune adaptation, and foetal tolerance.[1,2]

Autophagy Dysregulation in Pregnancy Complications and Reproductive Disorders

Overview: From homeostasis to pathology

Autophagy is fundamentally a homeostatic process; when appropriately regulated, it supports cellular quality control, metabolic flexibility, and immune adaptation. Conversely, failure to maintain appropriate autophagic flux — whether due to genetic perturbation, metabolic stress, endocrine disruption, or environmental toxicants — can precipitate maladaptive inflammation, defective tissue remodelling, and impaired cellular survival at the maternal–foetal interface. A growing body of preclinical and clinical evidence implicates autophagic dysregulation in major pregnancy complications, including spontaneous abortion, pre-eclampsia, preterm birth, as well as in chronic reproductive disorders such as polycystic ovary syndrome (PCOS), POI, and endometriosis.[1,2,3]

Below, we review mechanistic links between defective autophagy and pathology, summarise relevant experimental and clinical findings, and evaluate therapeutic implications and remaining knowledge gaps.

Spontaneous abortion and recurrent pregnancy loss

Mechanistic links

Spontaneous abortion (miscarriage) and recurrent pregnancy loss (RPL) frequently arise from failures in implantation, trophoblast invasion, or immune tolerance. Several mechanistic pathways connect autophagic insufficiency to these failures. Loss-of-function in core autophagy genes (e.g., Atg5, Atg7) compromises

trophoblast survival and differentiation, increases oxidative stress and mitochondrial dysfunction, and amplifies pro-inflammatory signalling through NF-κB activation.[2] At the immune level, defective autophagy reduces the numbers and tolerance-promoting capacity of decidual Tregs and uNK cells, increasing cytotoxic responses against trophoblasts.[1]

Autophagy also participates in controlled apoptotic cell clearance (efferocytosis) by decidual macrophages; impaired flux results in accumulation of apoptotic debris and DAMP release, which propagate local inflammation and may trigger foetal rejection.[3]

Evidence

Animal models provide compelling causal evidence: conditional knockout of Atg5 or Atg7 in trophoblast or immune compartments leads to increased embryonic resorption and miscarriage-like phenotypes in mice.[2] Human studies of RPL patients report alterations in autophagy markers (reduced LC3-II/LC3-I ratio, altered Beclin-1, and variable ATG16L1 expression) in endometrial and placental tissues, though human data remain more associative than definitively causal.[1,3]

Pre-eclampsia and placental insufficiency

Pathophysiology and autophagy

Pre-eclampsia is characterised by defective trophoblast invasion, inadequate spiral artery remodelling, placental hypoxia, and a maternal systemic inflammatory state. Autophagy is tightly implicated at multiple nodes of this pathophysiology:

- **Hypoxia response and trophoblast survival:** Early placental hypoxia would ordinarily induce protective autophagy (HIF-1α/AMPK-mediated) to permit trophoblast invasion. Blunted autophagic responses compromise trophoblast adaptation to low-oxygen microenvironments, promoting cell death and limiting invasion.[1]
- **ER stress and unfolded protein response (UPR):** Reduced autophagy exacerbates ER stress in syncytiotrophoblasts; unresolved UPR contributes to the release of anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1), which drive maternal endothelial dysfunction.[2]
- **Inflammation amplification:** Autophagic failure augments NF-κB signalling and cyclooxygenase-2 (COX-2) expression, escalating pro-inflammatory cytokine production and systemic inflammation implicated in maternal hypertension and endothelial injury.[2,3]

Experimental and clinical observations

Human placentas from pre-eclamptic pregnancies often show altered autophagy marker patterns (variable Beclin-1, decreased ATG16L1, dysregulated LC3 processing) and evidence of heightened ER stress and oxidative damage.[2] Mouse models in which autophagy is impaired in trophoblast lineages recapitulate features of pre-eclampsia, including poor spiral artery remodelling and foetal growth restriction.[1] While human studies are complicated by heterogeneity in disease severity and sampling timing, the convergence of mechanistic and model evidence supports a contributory role for autophagy dysfunction in pre-eclampsia pathogenesis.

Preterm birth and inflammatory premature labour

Preterm birth (PTB) frequently follows intrauterine inflammation, infection, or sterile inflammatory triggers. Autophagy influences the inflammatory tone of decidual and placental tissues through regulation of cytokine release, inflammasome activation, and leukocyte survival.

Inflammasome regulation: Autophagy restrains the nucleotide-binding oligomerisation domain (NOD)-, leucine-rich repeat (LRR)-, and pyrin domain-containing protein 3 (NLRP3) inflammasome activation by degrading damaged mitochondria and cytosolic DAMPs. Autophagic insufficiency increases IL-1β maturation and release, favouring preterm labour cascades.[3]

Susceptibility to infection: Reduced ATG16L1 activity has been linked to increased susceptibility to intrauterine infection and accelerated labour progression in both human tissues and knockout mouse models, suggesting a dual role in antimicrobial defence and inflammatory regulation.[1]

Clinically, increased markers of inflammasome activation and decreased autophagy-related protein expression have been observed in placentas from PTB cases; experimental restoration of autophagy in murine models attenuates inflammation and lowers rates of preterm delivery.[2]

Polycystic ovary syndrome, premature ovarian insufficiency and endometriosis

Polycystic ovary syndrome

PCOS is a metabolic–endocrine disorder marked by hyperandrogenism, anovulation, and insulin resistance. Autophagy intersects with PCOS pathogenesis at several points:

- **Metabolic dysfunction:** Insulin resistance and chronic low-grade inflammation seen in PCOS modulate AMPK/mTOR signalling, often yielding altered autophagic flux. Reduced autophagy in ovarian granulosa cells is linked to impaired follicular development and anovulation.[3]
- **Steroidogenic dysregulation:** Autophagy influences lipid droplet turnover and cholesterol availability for steroidogenesis; dysregulated autophagy can therefore perturb androgen biosynthesis.[1]

Human studies report variable autophagy marker expression in ovarian tissue from PCOS patients. Mechanistic studies implicate high-mobility group box 1 (HMGB1) and Wnt family member 5A (Wnt5a) signalling as modulators linking autophagy to local inflammation and aberrant folliculogenesis.[3]

Premature ovarian insufficiency

POI involves early depletion of ovarian reserve. Genetic and environmental insults that impair autophagy in oocytes (e.g., defective Atg gene expression or chronic oxidative stress) accelerate follicular atresia via mitochondrial dysfunction and apoptosis.[1] Murine oocyte-specific deletion of autophagy genes results in POI phenotypes, supporting a causal role. In humans, associations between decreased autophagy markers and diminished ovarian reserve are reported but require larger, longitudinal studies to establish causality.[2]

Endometriosis

Endometriosis is characterised by ectopic growth of endometrial tissue, chronic inflammation, and altered immune surveillance. Autophagy appears to be dysregulated in ectopic lesions, with conflicting reports of both increased and decreased autophagic activity depending on lesion site and disease stage. Mechanistically, aberrant autophagy may promote survival of ectopic endometrial cells under oxidative and hypoxic stress, contribute to altered antigen presentation, and modulate macrophage polarisation in peritoneal fluid.[3] Molecules such as HMGB1 and Wnt5a have been implicated in linking autophagy to lesion survival and inflammation.[3]

Molecular mediators and genetic contributors to pathology

Several specific molecular factors have been directly associated with adverse outcomes when autophagy is dysregulated:

- **ATG16L1:** Reduced ATG16L1 expression associates with labour progression anomalies and heightened infection susceptibility; animal models with deficient ATG16L1 demonstrate exacerbated inflammation during gestation.[1]
- **mTORC1 hyperactivation:** Persistent mTORC1 signalling inhibits adaptive autophagy responses, promoting inflammatory signalling (NF-κB), impaired decidualisation, and defective trophoblast function.[2]
- **COX2 and NF-κB upregulation:** Autophagy deficiency often accompanies elevated COX2 and NF-κB signalling, shifting tissues toward pro-labour and pro-inflammatory states linked to preterm birth.[2]
- **HMGB1 and Wnt5a:** These mediators are reported in PCOS and endometriosis contexts, where they may sustain inflammation and aberrant autophagy that support disease progression.[3]

Genetic polymorphisms in autophagy genes and transcriptional regulators (e.g., TFEB, FOXO3) are plausible contributors to individual susceptibility, though human genetic data are still sparse and require rigorous association studies.

Environmental, metabolic, and endocrine triggers of dysregulation

External and systemic factors compound genetic vulnerability to autophagy dysfunction:

- **Obesity and diabetes:** Nutrient excess and insulin resistance disrupt AMPK/mTOR signalling, often suppressing beneficial autophagic responses in reproductive tissues. These metabolic states

are associated clinically with higher rates of miscarriage, pre-eclampsia, and embryopathy.[1,3]

- **Endocrine disruptors:** Environmental chemicals (phthalates, bisphenols) alter hormonal signalling and can disrupt autophagy-related gene expression in reproductive cells, potentially contributing to infertility and placental dysfunction.[2]
- **Ageing:** Age-associated decline in autophagic capacity promotes accumulation of mitochondrial damage and genomic instability in gametes and placenta, aligning with increased reproductive pathology in older individuals.[2]

Therapeutic perspectives and challenges

Given autophagy's centrality to reproductive homeostasis, modulating autophagy is an attractive therapeutic avenue. Potential strategies include:

- **mTOR inhibitors (e.g., rapamycin analogues):** These agents can enhance autophagic flux and have shown efficacy in experimental models to improve decidualisation and reduce inflammation. However, systemic mTOR inhibition carries risks (immunosuppression, metabolic effects) and may adversely affect foetal growth if not targeted precisely.
- **AMPK activators and SIRT1 modulators:** Agents that restore metabolic sensing and autophagic competence (e.g., metformin) may confer reproductive benefit, as suggested by clinical improvements in PCOS patients treated with metformin; mechanistic links to autophagy warrant further study.
- **Antioxidants and mitochondrial protectants:** By reducing mitochondrial damage and ROS, these agents can indirectly restore autophagic balance and reduce inflammasome activation.
- **Targeted delivery systems:** Nanoparticle-based or tissue-specific delivery of autophagy modulators to the decidua or placenta would theoretically minimise systemic side effects but remains largely experimental.

Crucially, the dualistic nature of autophagy — protective at physiological levels but potentially deleterious when excessive — necessitates precision in any interventional approach. Timing is critical: enhancing autophagy during early implantation may be beneficial, whereas late-gestation modulation could precipitate adverse inflammatory responses.

Outstanding questions and research directions

Several key gaps remain:

1. **Causality in humans:** Most mechanistic evidence derives from animal knockouts and in vitro models; longitudinal human studies linking autophagy markers to pregnancy outcomes are needed.
2. **Biomarkers of functional flux:** Reliable, non-invasive biomarkers that reflect autophagic flux in reproductive tissues (rather than static protein levels) are lacking.
3. **Temporal specificity:** Greater resolution is required to define when and where to modulate autophagy for therapeutic benefit.
4. **Interplay with microbiome and infection:** The influence of systemic and local microbiota on autophagy–immune interactions at the maternal–foetal interface remains an emerging research area.
5. **Individual genetic susceptibility:** Large-scale genomic and epigenomic studies could identify polymorphisms in autophagy pathways that predispose to reproductive disorders.

Summary

Dysregulation of autophagy represents a convergent mechanism in several pregnancy complications and chronic reproductive disorders. Experimental models provide strong mechanistic links — loss of core Atg genes leads to trophoblast dysfunction, impaired immune tolerance, and pregnancy loss — while human tissue studies support associations between altered autophagy markers and clinical pathology. Therapeutic modulation of autophagy is promising but requires nuanced, stage-specific strategies and improved biomarkers to ensure efficacy and safety.

Autophagy, Immune Regulation, and Female Reproductive Ageing

Transition from reproductive homeostasis to senescence

Reproductive ageing marks a progressive decline in ovarian reserve, oocyte quality, and uterine receptivity, culminating in menopause. At the cellular level, this transition reflects cumulative oxidative damage, mitochondrial dysfunction, genomic instability, and

altered hormonal signalling — all processes under tight autophagic control. With advancing age, the efficiency of autophagic flux diminishes across ovarian and uterine tissues, impairing clearance of damaged organelles and macromolecules).[5] This decline disturbs the metabolic and immune equilibrium necessary for fertility and healthy gestation.

Autophagy's role in maintaining gamete integrity and tissue remodelling situates it at the nexus between cellular ageing and reproductive capacity. Age-related attenuation of autophagy in oocytes, granulosa cells, and endometrial stromal cells fosters a pro-inflammatory microenvironment and heightens susceptibility to oxidative stress, leading to poor oocyte competence, implantation failure, and pregnancy complications.[2]

Molecular mechanisms of autophagy decline with age

Mitochondrial quality control

Mitochondrial autophagy (mitophagy) declines with age, resulting in accumulation of dysfunctional mitochondria and ROS in ovarian cells. The phosphatase and tensin homolog-induced kinase 1 (PINK1)–Parkin pathway, critical for recognising and recycling depolarised mitochondria, exhibits reduced activity in aged oocytes and granulosa cells.[1] Excess ROS not only damages mitochondrial DNA but also oxidises lipids and proteins, further impairing energy production and signalling. Diminished mitophagy limits adenosine triphosphate (ATP) availability for meiotic spindle formation and chromosomal segregation, contributing to the aneuploidy and embryonic loss frequently observed in advanced maternal age.

Lysosomal inefficiency and proteostasis imbalance

Lysosomal acidity and enzymatic capacity wane with age, reducing the degradation efficiency of autophagosomes. This results in the accumulation of lipofuscin and misfolded proteins in ovarian and uterine tissues.[2] The impairment feeds forward to suppress new autophagosome formation, aggravating proteostasis imbalance. In decidual and placental cells, lysosomal dysfunction impairs antigen processing and cytokine turnover, promoting chronic sterile inflammation.

mTORC1 hyperactivation and AMPK decline

Nutrient-sensing pathways modulate autophagy through reciprocal regulation of mTORC1 and AMPK. Ageing, often accompanied by insulin resistance and metabolic inflexibility, favours chronic mTORC1 activation and reduced AMPK signalling. This shift suppresses autophagy initiation via ULK1 inhibition and diminishes the cell's ability to adapt to energetic stress.[1,2] Pharmacologic or dietary interventions that restore AMPK activity (e.g., metformin, caloric restriction mimetics) partially rescue autophagic responsiveness in aged ovaries.

Hormonal regulation of autophagy during ageing

Sex steroids directly modulate autophagy gene expression and flux. Oestrogen up-regulates Beclin-1 and LC3 transcription through oestrogen receptor alpha (ERα)-dependent signalling, whereas progesterone exerts context-dependent inhibitory effects.[3] The perimenopausal decline in oestrogen therefore removes a key stimulatory input to autophagy, compounding oxidative stress and metabolic imbalance. In the post-reproductive uterus, hypoestrogenism correlates with reduced autophagy and heightened inflammatory infiltration, consistent with accelerated tissue senescence.

FSH and LH also influence autophagic turnover in granulosa cells via cyclic adenosine monophosphate/protein kinase A (cAMP/PKA)-mediated regulation of mTORC1.[2] Dysregulated gonadotropin signalling with age may thus further disrupt autophagy-dependent folliculogenesis.

Immune remodelling and "inflammageing" in the reproductive tract

Chronic low-grade inflammation

Systemic ageing is accompanied by "inflammageing", defined as persistent, low-level activation of innate immunity characterised by elevated IL-6, TNF-α, and IL-1β. In reproductive tissues, decreased autophagic clearance of damaged mitochondria and cytosolic DNA activates pattern-recognition receptors, including NLRP3, cyclic guanosine monophosphate (GMP)–adenosine monophosphate (AMP) synthase (cGAS)–stimulator of interferon genes (STING) pathway, thereby sustaining cytokine release.[1] This inflammatory milieu disrupts endometrial receptivity and may impair blastocyst implantation, even in assisted reproduction settings.

Altered immune cell composition

Declining autophagy modifies the phenotype and function of local immune populations. In aged decidua, macrophages show reduced LC3 lipidation and

defective efferocytosis, leading to accumulation of apoptotic debris and secondary inflammation.[2] uNK cells exhibit impaired mitochondrial metabolism and decreased survival when autophagy is inhibited, limiting their capacity for vascular remodelling during early pregnancy. Reduced autophagy in stromal cells further disrupts MITF-TNFRSF14/HVEM signalling required for NK cell retention, mirroring defects seen in pregnancy loss models.[1]

Adaptive immunity and tolerance erosion

Tregs rely on autophagy to maintain metabolic quiescence and suppressive function. Age-related autophagy impairment in Tregs diminishes their stability and tolerance-inducing capacity, predisposing to autoimmune-like endometrial inflammation and implantation failure.[2] Collectively, these immune alterations reflect a collapse of the autophagy-mediated immune balance that supports successful gestation.

Impact on oocyte quality, fertilisation, and implantation

Oocyte competence

Autophagy participates in oocyte maturation by eliminating damaged mitochondria and ribosomes during germinal vesicle breakdown. With age, autophagic responsiveness to hormonal cues declines, resulting in cytoplasmic inclusions, spindle abnormalities, and reduced fertilisation potential.[2] Experimental induction of autophagy via AMPK or SIRT1 activators improves oocyte mitochondrial function and developmental competence in aged animal models, underscoring its functional significance.

Embryo–endometrium crosstalk

Successful implantation depends on synchronised autophagy between the embryo and endometrium. In aged uteri, reduced endometrial autophagy alters cytokine gradients, including IL-15 and leukaemia inhibitory factor (LIF), as well as extracellular matrix remodelling, creating a hostile environment for blastocyst adhesion.[1] Mouse studies show that pharmacologic activation of autophagy during the peri-implantation window restores receptivity and implantation rates.

Placental development

Although few human data exist, animal evidence indicates that maternal age compromises placental autophagy, resulting in increased oxidative stress and inflammatory signalling. The combination of impaired trophoblast autophagy and maternal immune dysregulation contributes to higher incidence of pre-eclampsia and foetal growth restriction in advanced-age pregnancies.[3]

Interventions to preserve autophagic capacity in ageing reproduction

1. **Caloric restriction and mimetics:** Nutrient limitation activates AMPK and SIRT1 while inhibiting mTORC1, thereby enhancing autophagy. Lifelong or mid-life caloric restriction delays reproductive senescence in animal models, preserving ovarian reserve and improving oocyte quality.[1]
2. **Pharmacological activators:** Agents such as metformin, resveratrol, and spermidine stimulate autophagic pathways and demonstrate reproductive benefits in preclinical studies; however, optimal dosing, timing, and long-term safety during pregnancy require careful evaluation.
3. **Hormone replacement strategies:** Physiological oestrogen replacement may partially restore autophagy and mitochondrial integrity in post-menopausal uterine tissue, though systemic risks necessitate individualised approaches.[3]
4. **Antioxidant and mitochondrial protectants:** Agents such as coenzyme Q10 and melatonin reduce oxidative load and indirectly sustain autophagy; small trials suggest improved oocyte parameters in older women undergoing in vitro fertilisation (IVF).
5. **Lifestyle modulation:** Physical activity and optimised metabolic control attenuate mTORC1 hyperactivity, reinforcing autophagic adaptability and immune homeostasis.

Future directions

Key research priorities include:

- Longitudinal profiling of autophagic markers in human ovarian and uterine tissues across reproductive lifespan
- Integration of multi-omics (transcriptomic, proteomic, metabolomic) to define signatures of autophagy decline
- Investigation of how age-related epigenetic changes in autophagy genes (e.g., methylation of ATG5, Beclin 1) contribute to reproductive senescence

- Development of targeted therapeutics that enhance autophagy specifically within reproductive tissues without systemic adverse effects

Summary

Female reproductive ageing exemplifies the systemic interplay between metabolic, hormonal, and immune senescence. Autophagy, by sustaining mitochondrial quality, restraining inflammation, and supporting hormonal responsiveness, acts as a central defence against reproductive decline. Its age-related attenuation accelerates ovarian depletion, impairs uterine receptivity, and increases susceptibility to pregnancy complications. Therapeutic strategies aimed at restoring autophagic competence offer promise for extending reproductive health span, although robust translational validation in humans remains essential.

Discussion

Integrative discussion

Autophagy has emerged as a fundamental regulator of reproductive health, governing cellular adaptation, immune balance, and tissue remodelling across the reproductive lifespan. Cumulative evidence from molecular, cellular, and physiological studies underscores that this evolutionarily conserved process is neither static nor uniform; it operates in a stage-specific and tissue-specific manner, responding dynamically to developmental and environmental cues. Across gametogenesis, implantation, decidualisation, and placentation, autophagic flux facilitates the removal of damaged organelles, supports cellular differentiation, and maintains immune tolerance at the maternal–foetal interface.[1,2]

A consistent theme across reproductive biology is that autophagic balance, rather than simple activation or inhibition, is critical for physiological function. Both insufficient and excessive autophagy can be deleterious, highlighting its role as a finely tuned homeostatic mechanism. During early pregnancy, autophagy sustains trophoblast invasion and immune tolerance; late in gestation, its regulated reactivation contributes to parturition. These dynamic oscillations align with distinct immunological states, from inflammation at implantation, to immune quiescence during foetal development, and subsequent reactivation during labour — indicating that autophagy synchronises immune and metabolic programmes within reproductive tissues.[1]

When autophagy is compromised, its consequences manifest across multiple biological levels. At the cellular level, defective autophagy results in oxidative stress, mitochondrial dysfunction, and protein aggregation, thereby impairing cell viability and differentiation. At the tissue level, it disrupts immune equilibrium, leading to excessive cytotoxicity or inadequate tolerance. At the systemic level, it amplifies inflammatory signalling and perturbs endocrine feedback loops. These disruptions collectively contribute to reproductive pathologies ranging from early miscarriage to pre-eclampsia and preterm birth.[2,3]

Evidence examining immune modulation at the maternal–foetal interface further highlights autophagy as integral to immune cell homeostasis. In uNK cells, macrophages, and Tregs, autophagy supports mitochondrial integrity, regulates cytokine secretion, and ensures controlled immune activation. Experimental inhibition of autophagy increases NK cell cytotoxicity and embryo resorption, whereas pharmacological induction promotes immune tolerance and foetal survival.[1] This immune–autophagy crosstalk thus represents a central node in the maintenance of successful pregnancy.

Pathological implications

Defective autophagy contributes to a spectrum of reproductive disorders. In spontaneous abortion and recurrent pregnancy loss, impaired autophagic flux in trophoblasts and immune cells triggers oxidative stress and unrestrained inflammation, compromising implantation and placental development. In pre-eclampsia, reduced autophagy exacerbates ER stress and inflammasome activation, promoting the release of anti-angiogenic factors and endothelial dysfunction. In preterm birth, autophagy deficiency enhances inflammasome activity and susceptibility to infection, accelerating premature labour.[2,3]

Beyond gestation, chronic disorders such as PCOS, POI, and endometriosis exhibit distinct patterns of autophagy dysregulation. In PCOS, reduced autophagy impairs granulosa cell metabolism and follicular maturation, linking metabolic stress to infertility. In endometriosis, autophagy appears paradoxically upregulated in certain lesion types, facilitating ectopic cell survival under stress. These divergent patterns reinforce the notion that autophagy must be contextually regulated; both deficiency and excess can drive pathology depending on the reproductive stage and tissue environment.[3]

Ageing and the temporal dimension of autophagy

Female reproductive ageing intensifies these vulnerabilities. Progressive loss of autophagic efficiency in oocytes, endometrium, and placenta contributes to diminished fertility, increased aneuploidy, and greater risk of gestational complications in advanced maternal age.[1] Mechanistically, age-related hyperactivation of mTORC1, reduced AMPK signalling, and lysosomal inefficiency limit adaptive autophagic responses. The resultant accumulation of damaged mitochondria and heightened oxidative stress fuels "inflammageing," undermining endometrial receptivity and immune tolerance.[2]

The interplay between autophagy decline, hormonal changes, and immune remodelling encapsulates a broader biological truth: reproductive ageing is not merely a hormonal phenomenon but a cellular homeostasis failure. Targeting autophagy-related pathways offers a compelling avenue to mitigate reproductive senescence, but translation to clinical application requires precise temporal and tissue targeting to avoid systemic side effects.

Therapeutic and translational perspectives

Emerging therapeutic strategies aim to modulate autophagy pharmacologically or through lifestyle interventions. mTOR inhibitors (e.g., rapamycin analogues) and AMPK activators (e.g., metformin, resveratrol) have demonstrated the ability to restore autophagic flux and improve reproductive outcomes in experimental settings. SIRT1 modulators, antioxidants, and caloric restriction mimetics further illustrate the potential to rejuvenate reproductive function via autophagy enhancement.[1]

However, the double-edged nature of autophagy poses translational challenges. Overactivation may induce cell death or disrupt developmental signalling. Therefore, future therapies must calibrate autophagic activity to specific reproductive windows — supporting implantation, maintaining tolerance, and preventing premature labour — while safeguarding foetal development.

Advances in biomarker development (e.g., circulating LC3 or Beclin-1 fragments) and targeted delivery systems could enable non-invasive monitoring and tissue-specific modulation of autophagy. These innovations will be pivotal for integrating autophagy modulation into fertility preservation and pregnancy management.

Limitations and future directions

Despite substantial progress, several key gaps persist:

- Human data remain primarily correlative; robust longitudinal and interventional studies are needed to define causal relationships between autophagy dynamics and reproductive outcomes.
- The lack of standardised assays to measure autophagic flux in clinical samples limits comparability across studies.
- The integration of omics-based approaches (transcriptomics, proteomics, metabolomics) promises a systems-level understanding but demands harmonised frameworks.
- Finally, the field requires a deeper exploration of epigenetic regulation of autophagy genes during reproductive ageing and stress adaptation.
- Collaborations across reproductive biology, immunology, and systems medicine will be essential to translate autophagy knowledge into therapeutic benefit.

Declarations

The author declares that no conflicts of interest exist. Artificial intelligence (AI) assistance (ChatGPT by OpenAI) was used for grammar correction, language enhancement, and formatting improvements during manuscript preparation. The study design, data collection, analysis, interpretation, and conclusions are entirely original and solely authored by the listed contributors.

Conclusion

Autophagy stands at the intersection of cellular survival, immune tolerance, and reproductive success. Its precise regulation orchestrates the complex transitions from gametogenesis to implantation, gestation, and parturition. Disruption of this balance — by genetic, metabolic, inflammatory, or age-related factors — compromises fertility and maternal–foetal health. Evidence from molecular to clinical studies converges on a unified concept: autophagy is a dynamic integrator of reproductive and immune homeostasis.

Future research must progress beyond descriptive associations towards temporal and mechanistic precision, defining when, where, and how autophagy can be safely modulated in human reproduction. Targeted modulation of this pathway holds promise not only for addressing infertility and pregnancy complications but also for extending reproductive health span through cellular rejuvenation and immune recalibration.

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Why Detecting Nanoplastics in Humans Matters: Exposure Routes, Biological Evidence, and Potential Health Implications

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Abstract:

Nanoplastics, defined as plastic particles smaller than one micrometre, have emerged as a growing concern in human health research. Their small size allows them to cross biological barriers and interact directly with cells and tissues. Recent studies have confirmed the presence of plastic particles in multiple human biological matrices, including blood, lung tissue, placenta, faeces, urine, vascular tissue and brain samples. These findings indicate that human exposure to nanoplastics is not merely environmental but involves internal uptake.

This review summarises current evidence on routes of human exposure and biological matrices, where nanoplastics have been detected, and potential health implications, on the basis of experimental and emerging clinical data. Ingestion and inhalation appear to be the dominant exposure pathways, with additional concern related to maternal–foetal transfer. Experimental studies suggest that nanoplastics may induce oxidative stress, inflammation, endocrine disruption and neurobiological effects, although direct causal links in humans remain limited.

Accurate detection in clinical samples is essential for risk assessment and future epidemiological studies. While techniques such as pyrolysis gas chromatography–mass spectrometry (GC–MS), Raman spectroscopy, and single-particle inductively coupled plasma mass spectrometry (ICP–MS) have enabled recent discoveries, methodological limitations persist. Standardisation of analytical workflows is required before routine clinical interpretation can be achieved.

Key words: Nanoplastics, Microplastics, Human Exposure, Blood-Brain Barrier, Inhalation, Ingestion, Public Health, Environmental Pollutants.

Introduction

Plastics are widely used in healthcare, food packaging, textiles and day-to-day consumer products due to their durability and low cost. The physical and chemical degradation of plastic materials leads to the formation of progressively smaller fragments.[1,2] While microplastics have been extensively studied, attention has increasingly shifted toward nanoplastics because of their greater biological accessibility.[3,4]

Nanoplastics occupy a size range comparable to viruses and macromolecular complexes.[4] These properties enable interactions with cellular membranes and facilitate translocation across epithelial barriers.[3,5] As a result, nanoplastics may access tissues that are typically

protected from particulate exposure, including the placenta and central nervous system.[6,7]

Over the past several years, multiple independent studies have confirmed the presence of plastic particles in human biological samples.[8-10] Detection in blood, lung tissue, placental tissue, faeces, urine, vascular specimens, and brain tissue has shifted the discussion of plastic exposure from an environmental issue to a clinical and public health concern. [6-7,11-13] Understanding how nanoplastics enter the body, where they accumulate and what effects they may exert is now relevant to medical research.[1,14]

Routes of Human Exposure

Ingestion

Dietary intake is considered the primary route of exposure to nanoplastics.[2] Plastic particles have been identified in drinking water, bottled beverages, seafood, salt and packaged foods.[2,5] Food processing and packaging practices further contribute, particularly when plastics are heated or mechanically stressed.[3]

Once ingested, nanoplastics encounter digestive enzymes and bile salts that alter particle surface properties.[3,4] Experimental models suggest that these particles can cross the intestinal epithelium through cellular uptake or paracellular transport.[1,5] After translocation, particles may enter systemic circulation and distribute to internal organs.[14]

Inhalation

Inhalation represents a second major exposure route.[9] Airborne nanoplastics originate from sources such as synthetic textiles, traffic-related emissions, industrial activity and indoor dust.[5] Due to their small size, these particles can reach the distal airways and alveoli.[9]

Human lung tissue analyses have identified common polymers, including polyethylene and polypropylene.[9] Clearance mechanisms appear limited, and retained particles may trigger local inflammatory responses or translocate into the bloodstream.[1]

Dermal exposure (skin exposure)

The skin functions as an effective barrier, but nanoscale materials may penetrate under certain conditions, particularly with repeated exposure or barrier disruption.[4] Nanoplastics are present in some cosmetic and personal-care products.[3] While systemic uptake via the skin is likely limited, localised effects and occupational exposure remain areas of concern.[5]

Maternal–foetal transfer

Detection of plastic particles in human placental tissue indicates that nanoplastics can cross the placental barrier.[6] This finding raises concern regarding prenatal exposure during critical periods of development.[1,6] Although clinical consequences have not yet been established in humans, animal studies suggest potential developmental effects.[3,14]

Biological Evidence of Nanoplastics in Humans

Nanoplastics and related microplastics have been detected in a growing range of human biological matrices.[1,10] Blood was among the first tissues studied, providing evidence of systemic distribution.[8,10] Placental detection supports the possibility of foetal exposure,[6] while lung tissue findings confirm inhalation as a relevant route.[9]

Faecal samples indicate widespread dietary exposure, though they do not distinguish between absorbed and excreted particles.[15] More recent studies reporting plastic particles in urine, vascular tissue, thrombi, joints, semen, and brain samples suggest that some particles may persist or accumulate in the body.[7,11,16] Microplastics have also been detected in human lower limb joint tissues and saphenous vein samples, further supporting systemic distribution and tissue deposition.[17,18] Identification of plastic particles in brain tissue is of particular concern, as it may reflect passage through or alteration of blood-brain barrier integrity.[7]

Potential Health Implications

Direct clinical evidence linking nanoplastics to disease in humans is currently limited.[1] However, experimental studies provide insight into possible biological effects. Cellular uptake of nanoplastics has been associated with oxidative stress, mitochondrial dysfunction and inflammatory signalling.[3-4,14]

Immune activation following particle exposure may result in chronic low-grade inflammation, a process implicated in cardiovascular, metabolic and respiratory diseases.[1,5] In addition, plastics often contain chemical additives such as bisphenols and phthalates, which are known endocrine

disruptors.[1,3] Nanoplastics may act as carriers for these compounds, enhancing cellular exposure.[14]

Animal studies also suggest potential neurotoxic effects, including neuroinflammation and altered behaviour following exposure.[3,14] The relevance of these findings to human health requires further investigation, particularly through longitudinal clinical studies.[1]

Clinical and Public Health Relevance

From a medical perspective, detection of nanoplastics in human tissues is a prerequisite for meaningful risk assessment.[1] Without reliable quantitative data, it is not possible to evaluate exposure thresholds, identify high-risk populations, or assess associations with disease outcomes.[5]

Current analytical techniques have enabled important discoveries but are not yet suitable for routine clinical use.[8,19] Challenges include contamination control, limited sensitivity for smaller particles and lack of standardised protocols.[8,10] Harmonisation of detection methods will be essential for future clinical and epidemiological research.[1]

Conclusion

The identification of nanoplastics within human tissues represents a meaningful shift in how plastic pollution is understood in relation to human health. Rather than remaining an abstract environmental issue, plastic exposure has now been shown to extend into the human body itself, confirming that contact with these materials is both direct and ongoing. Current evidence suggests that exposure is common and occurs through everyday activities, particularly through food consumption and breathing contaminated air, with early findings also indicating that exposure may begin before birth via transfer across the placenta.

At present, clear links between nanoplastic exposure and specific diseases in humans have not been firmly established. However, findings from laboratory and animal studies raise reasonable concern. These studies suggest that nanoplastics can enter cells, interfering with normal cellular functions and promoting inflammatory and oxidative processes. Their small size allows them to reach sensitive tissues, and their chemical composition may further contribute to harm by transporting additives or environmental pollutants into the body. While these mechanisms do not yet equate to proven clinical disease, they provide a credible biological basis for potential long-term effects.

Advancing knowledge in this area will require a coordinated research effort. Reliable and standardised methods for detecting nanoplastics are essential to ensure that results are comparable across studies. Equally important are long-term human investigations that can track exposure over time and assess possible associations with health outcomes. Without such data, risk assessment remains incomplete, and uncertainty persists regarding vulnerable populations and safe exposure thresholds.

From a broader medical and public health perspective, nanoplastics should be considered within the context of prevention and environmental risk management. Recognising them as a possible contributor to chronic disease burden encourages early monitoring, informed policy decisions and public awareness. As research progresses, integrating nanoplastic exposure into environmental health assessments may become an important step toward protecting population health and reducing avoidable risks in the future.

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Surgical Management of Complex and Neglected Hip Injuries Using Arthroplasty-Based Reconstruction

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Abstract:

Complex acetabular fractures, with or without hip dislocation, in elderly or osteoporotic patients present significant surgical challenges. Traditional open reduction and internal fixation (ORIF) frequently fails in this population due to poor bone quality, fracture comminution, and delayed presentation. This case series describes the use of primary total hip arthroplasty (THA) as an alternative treatment strategy in selected cases. The objective was to evaluate the role of arthroplasty-based reconstruction in the management of complex and neglected hip injuries in the elderly population. This case series includes three patients with neglected or complex acetabular fractures, with or without hip dislocation, managed with primary THA. Surgical approaches, implant selection, and reconstruction techniques were individualised for each case. Clinical presentation, surgical strategy, postoperative rehabilitation, and short-term outcomes were analysed. All patients underwent successful arthroplasty-based reconstruction using appropriate techniques, such as acetabular cages and supplementary fixation when indicated. Early mobilisation was achieved in all cases, with ambulation initiated on postoperative day (POD) 1. All patients were discharged on POD 4. Early functional recovery was achieved in all cases with satisfactory radiological alignment and joint congruity. No perioperative complications or revision surgeries were required. Primary THA with appropriate reconstructive techniques offers a reliable and effective alternative to ORIF in complex and neglected hip injuries, particularly in elderly patients. This approach provides immediate joint stability, enables early mobilisation, and reduces morbidity related to failed fixation and prolonged immobilisation.

Key words: Acetabular Fracture, Arthroplasty, Hip Dislocation, Elderly Trauma, Acetabular Cage Reconstruction.

Introduction

The epidemiology of acetabular fractures has shifted towards an ageing population. Current data indicate that approximately 20%–30% of acetabular fractures occur in patients over 60 years of age, and these injuries are increasingly associated with lower-energy trauma such as ground-level falls.[1-3] The consequences of delayed or failed fixation in this population are severe. Prolonged immobilisation leads to well-documented complications, including deep vein thrombosis, pulmonary embolism, pressure sores, pneumonia, delirium, and loss of pre-injury independence.[4-6]

Neglected acetabular fractures and chronic dislocations result in progressive articular cartilage damage, femoral head necrosis, and significant acetabular bone loss. The longer the delay in reduction, the greater the likelihood

of irreversible chondral damage, hip instability, and secondary osteoarthritis.[4]

In selected patients — particularly the elderly, osteoporotic, or those with delayed presentations — total hip arthroplasty (THA) has emerged as a viable and increasingly favoured alternative to open reduction and internal fixation (ORIF). Arthroplasty-based reconstruction offers several distinct advantages: immediate joint stability, pain relief, and, crucially, early mobilisation and weight-bearing. In elderly patients, this approach eliminates prolonged bed rest, reducing the risk of venous thromboembolism, pneumonia, and pressure ulcers, while enabling faster functional recovery.[7-9]

Recent literature supports this paradigm shift. Multiple authors have demonstrated improved early functional outcomes and reduced reoperation rates with acute or delayed THA compared to fixation alone in elderly and low-demand populations with complex acetabular fractures.[10,11]

The objective of this case series is to demonstrate the application of arthroplasty-based reconstruction in three patients with distinct presentations of complex and neglected hip injuries, highlighting surgical decision-making, reconstruction techniques, and early clinical outcomes.

Methods

Patients were selected if they were aged ≥ 70 years and presented with complex acetabular fracture patterns with significant comminution, with or without an associated femoral head fracture and/or osteonecrosis.

Preoperative evaluation included clinical examination, radiographic assessment (plain radiographs and computed tomography [CT]), and comprehensive medical optimisation in consultation with internal medicine and anaesthesia teams. The decision to pursue primary THA rather than ORIF was based on patient age and functional demands, bone quality assessment, fracture complexity, timing of injury, and patient preference following informed discussion of risks and benefits.

All patients underwent THA via a modified lateral approach. After careful capsulotomy and hip dislocation, femoral head viability was assessed, the acetabulum was debrided of pannus and damaged cartilage, and a structural bone graft was harvested from the femoral head or iliac crest as needed. Acetabular cages were used for significant defects, with cemented or uncemented cups selected based on bone quality, and uncemented stems were used in all cases.

All patients were monitored in intensive care postoperatively for one day. Prophylactic anticoagulation was administered as per institutional protocol. Physical therapy commenced on postoperative day (POD) 1, with assisted out-of-bed mobilisation. The weight-bearing protocol consisted of toe-touch weight bearing, advancing to full weight bearing as tolerated. Discharge criteria included adequate pain control, independent transfers, and clear discharge planning.

Primary outcomes assessed included surgical success (completion of planned procedure without major intraoperative complications), early mobilisation (achievement of out-of-bed ambulation by POD 1), length of hospital stay, perioperative complications, and radiological alignment at discharge. No readmissions were recorded up to 180 days post-surgery.

Case Reports

Case report 1: Neglected acetabular fracture with central hip dislocation

A 71-year-old male presented to our institution two months after sustaining a mechanical fall at home. At presentation, he reported severe left hip pain, inability to bear weight, and visible limb deformity. Prior treatment at an outside facility had included attempted closed reduction followed by upper tibial pin traction, without improvement in hip position.

On initial evaluation at our centre, the patient reported persistent pain and was completely non-ambulatory (Figure 1A and B).

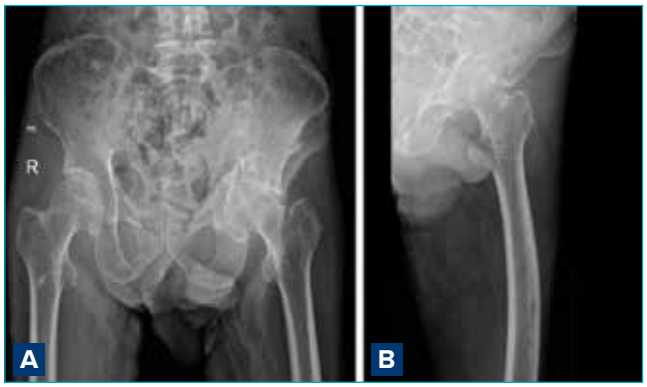


Figure 1A and B: Pelvic radiographs showing a neglected central hip dislocation of the left hip with an associated acetabular fracture pattern consistent with a central acetabular fracture with significant posterior wall involvement. The femoral head remained medially and superiorly displaced, corresponding to Paprosky Type 2C acetabular defect.[11]

Following comprehensive medical evaluation and clearance, the patient underwent left THA via a modified lateral approach. Key technical points included careful division of the gluteus medius, with anterior and posterior capsular releases to facilitate hip mobilisation (Figure 2) extraction and examination of the femoral head, which confirmed an intact articular surface); extensive removal of pannus and fibrous tissue from the acetabulum; harvest of autogenous bone graft from the resected femoral head for defect reconstruction; acetabular cup placement in near-anatomical position; insertion of a cementless femoral stem; and meticulous soft tissue repair with capsular plication.

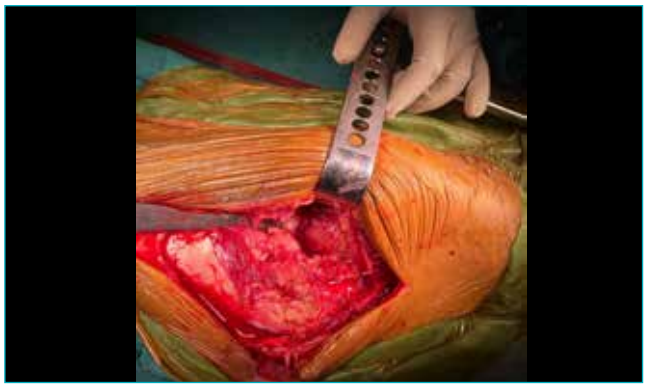


Figure 2: Modified lateral approach — care must be taken while dividing the gluteus medius and during capsulotomy.

The patient tolerated the procedure well, with no intraoperative complications. Postoperative radiographs demonstrated a well-reduced hip with maintained articular congruity and optimal component positioning (Figure 3). The patient was mobilised on POD 1 and progressed rapidly to independent ambulation with a walker. He was discharged on POD 4 with satisfactory pain control and functional mobility. At the final follow-up at four months, radiographs confirmed maintained reduction and appropriate component position.

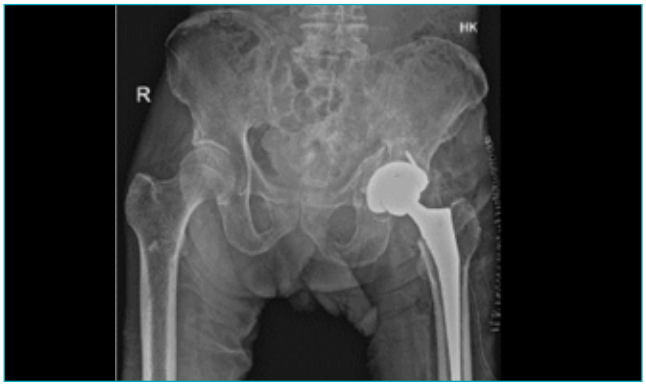


Figure 3: Postoperative X-ray showing reduced acetabular fragment with well-supported acetabular prosthesis and reduced hip joint.

Case report 2: Neglected comminuted acetabular fracture with femoral head involvement

A 73-year-old female presented one month following a fall from standing height. She reported hip pain, inability to bear weight, and progressive functional decline despite attempted conservative management with bed rest and analgesics at a peripheral facility.

Imaging at our institution revealed a chronic, highly comminuted acetabular fracture involving both the anterior and posterior walls, with significant medial wall involvement (Figure 4A and B). A separate fracture line involving the medial femoral head was identified, raising concern for femoral head fracture or impaction injury with consequent femoral head avascularity. The fracture pattern was deemed unsuitable for conventional fixation due to the degree of comminution and femoral head involvement.

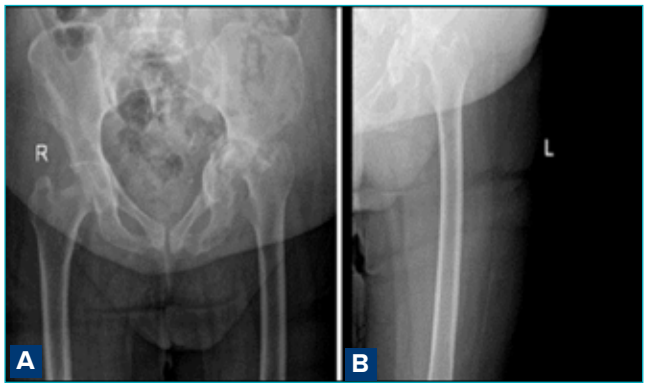


Figure 4A and B: Preoperative X-ray showing fracture of the quadrangular plate of the acetabulum with associated anterior and posterior wall fracture. The femoral head is displaced superiorly and medially due to a non-supportive acetabular rim consistent with a Paprosky Type 3B acetabular defect.

The patient, therefore, underwent left THA with acetabular cage reconstruction. The surgical technique was similar in approach, with adequate exposure of the acetabulum. Key steps included identification of the acetabular defect, placement of a structural acetabular cage to span the defect and protect graft incorporation, supplementary bone grafting to support the cage construct, cemented cup placement within the cage, tension band wiring of the greater trochanter to optimise abductor muscle function, and insertion of a cementless femoral stem (Figures 5 and 6). Careful repair of the gluteus medius was performed to maintain the abductor mechanism.

Figure 5: Bone graft harvested from the femoral head.

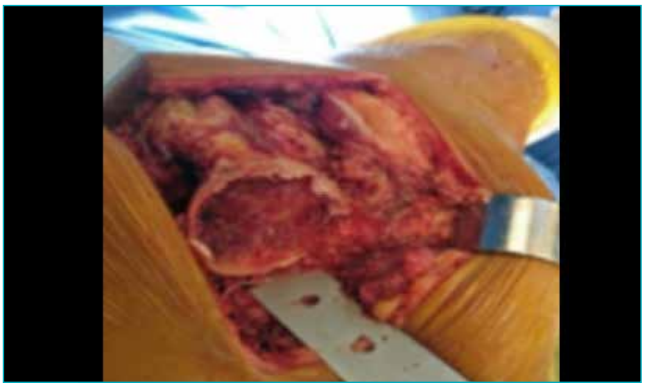


Figure 6: Fragments of the femoral head.

The procedure was completed without major intraoperative complications. Early postoperative radiographs demonstrated appropriate cage positioning, stable cup positioning within the cage, and good bony contact (Figure 7). At follow-up, radiographs showed maintenance of component position, with no evidence of subsidence or loosening.

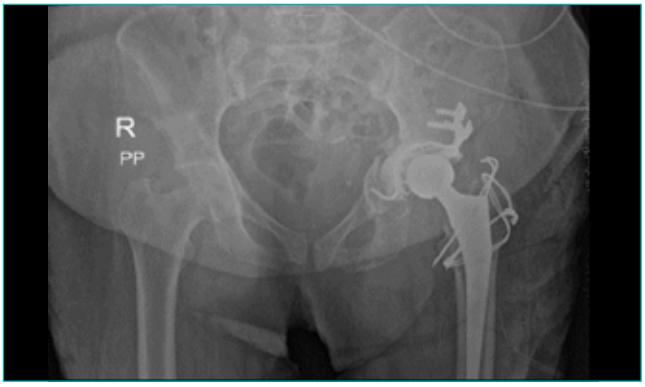


Figure 7: Postoperative X-ray showing acetabular cage in situ, stabilised with bone graft and screws in situ, along with tension-band wiring of the greater trochanter of the femur.

Case report 3: Neglected anterior column acetabular fracture with protrusio acetabuli in an elderly patient with significant comorbidities

An 83-year-old male with significant medical complexity (diabetes mellitus, hypertension, osteoporosis, early chronic kidney disease, and prior percutaneous transluminal coronary angioplasty) presented following a mechanical fall. He was previously a community ambulator living independently.

Plain radiographs and CT confirmed an anterior column fracture with significant medial wall deficiency and protrusio acetabuli (medial displacement of the

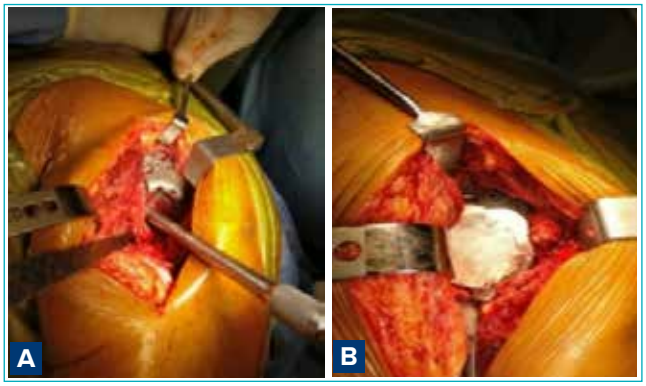
acetabulum relative to normal anatomic position) (Figure 8A and B). The acetabular defect was substantial, measuring approximately 2 × 2 cm in the medial wall region. There was no evidence of femoral head fracture.

Given his advanced age, multiple comorbidities, and poor bone quality, primary THA was elected as the most appropriate treatment.

Figure 8A and B: Preoperative imaging revealed an acetabular fracture with severe medial wall involvement and protrusio acetabuli signifying Paprosky Type 3B acetabular defect.

The patient underwent left THA with acetabular cage reconstruction and structural bone grafting. Technical nuances included careful preoperative planning to manage protrusio acetabuli and medial wall deficiency; hip dislocation and complete acetabular preparation; harvest of a structural iliac crest bone graft to reconstruct the medial wall defect; careful positioning of the structural graft to restore the hip centre of rotation; placement of a structural acetabular cage to provide load transfer and graft protection; use of morselised bone graft (harvested from the femoral head and iliac crest) to fill residual defects around the cage; cemented cup placement to optimise fixation in osteoporotic bone (Figure 9A–C); insertion of a cementless femoral stem and meticulous soft-tissue repair.

The surgery was completed without any perioperative complications. Postoperative radiographs documented appropriate structural graft incorporation, stable cage positioning, and optimal cup position (Figure 10A and B). The patient was mobilised early and discharged on POD 4. Follow-up radiographs at 12 weeks demonstrated maintained component position and early graft incorporation.



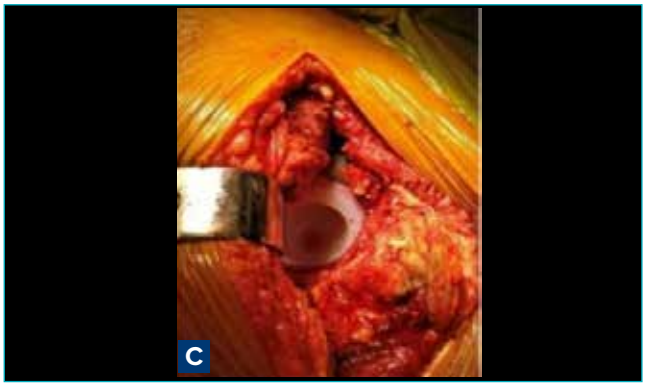


Figure 9A–C: Cage placement along with cemented cup.

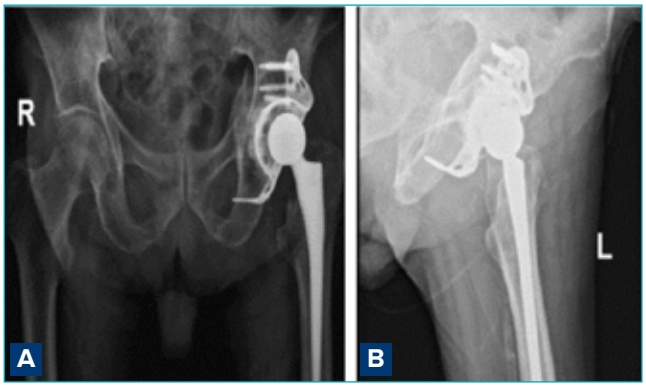


Figure 10A and B: Postoperative radiograph showing stable cage positioning and optimal cup position.

Results

All three patients presented with complex acetabular injuries that had been present for at least one month prior to definitive surgical intervention. All patients were deemed high-risk candidates for conventional ORIF based on advanced age, poor bone quality, fracture complexity, and/or medical comorbidities.

All three patients underwent successful primary THA with appropriate reconstructive techniques. Immediate

postoperative radiographs in all three cases demonstrated satisfactory hip reduction, appropriate component positioning (with acetabular and femoral components in neutral to slight anteversion and appropriate offset), maintenance of the hip centre of rotation, and adequate bony contact.

At three months follow-up, radiographs showed maintained reduction, no evidence of component subsidence, and appropriate graft incorporation patterns. Specific surgical techniques are summarised in Table 1. No intraoperative complications, including vascular injury, nerve injury, or significant blood loss requiring transfusion, were observed.

All patients achieved early mobilisation with immediate weight bearing and discharge on POD 4. No perioperative deaths or major complications were documented. At discharge, all patients demonstrated adequate pain control to participate in physical therapy, independent bed-to-chair transfers, and ambulation with a walker or crutches. No patient required readmission within 180 days of discharge.

Feature	Case 1	Case 2	Case 3
Age/Gender	71/M	73/F	83/M
Medical comorbidities	DM, HTN	DM, HTN, CKD	DM, HTN, CKD, CAD
Time to presentation	2 months	1 month	3 weeks
Injury type	Central hip dislocation + acetabular fracture	Comminuted acetabular fracture + femoral head fracture	Anterior column fracture + protrusio acetabuli
Acetabular defect: Paproski classification	Type 2C	Type 3B	Type 3B
Acetabular management	Cup placement with graft	Cage + cemented cup + graft	Cage + cemented cup + structural + morselised graft

Table 1: Summary of cases and surgical interventions.
Abbreviations: CAD: Coronary Artery Disease; CKD: Chronic Kidney Disease; DM: Diabetes Mellitus; F: Female; HTN: Hypertension; M: Male; POD: Postoperative Day.

Discussion

The management of complex and neglected hip injuries remains one of the most challenging problems, particularly in elderly populations. This case series contributes to growing evidence that primary THA, in carefully selected elderly patients with comminuted or neglected acetabular injuries, may offer better functional outcomes compared with late fixation or conversion surgery.

Historically, ORIF has been considered the gold standard treatment for acetabular fractures, and this remains true for younger patients with good bone quality and simple fracture patterns. In the elderly osteoporotic cohort with comminuted injuries, however, fixation frequently fails, and late conversion to THA carries higher morbidity. Primary arthroplasty avoids these risks.[12]

Over the past several decades, the epidemiology of acetabular fractures has shifted towards an older patient population. Ferguson *et al.* reported that up to 30% of acetabular fractures now occur in patients over 60 years of age, often following low-energy mechanisms such as ground-level falls.[2] Elderly patients frequently present with osteoporotic bone, fracture comminution, marginal impaction, and associated medical comorbidities, all of which adversely affect internal fixation stability and healing potential.

Anglen *et al.* described the “gull sign” as a radiographic marker of superior dome impaction and demonstrated its strong association with fixation failure in geriatric acetabular fractures.[1] Several authors have since confirmed that osteoporotic bone provides poor screw purchase and reduced load-bearing capacity, leading to secondary displacement, implant failure, and post-traumatic arthritis when ORIF is attempted in this population.[1,12]

Mears and Velyvis emphasised that delayed reduction significantly increases the risk of irreversible chondral injury, making anatomical reconstruction difficult or impossible.[4] In such cases, late ORIF is associated with inferior functional outcomes and a higher likelihood of subsequent conversion to THA.

Tannast *et al.* demonstrated that even in operatively treated acetabular fractures, long-term hip survivorship declines with increasing age, fracture complexity, and delayed intervention.[3] These findings underscore the limitations of joint-preserving surgery in elderly or delayed presentations.

Koval and Zuckerman highlighted the increased risk of deep vein thrombosis, pulmonary embolism, pneumonia, pressure ulcers, delirium, and loss of independence associated with prolonged immobilisation following hip injuries in older adults.[5] These complications contribute to increased morbidity, mortality, and healthcare utilisation.

Rickman *et al.*, in a systematic review, reported that fixation combined with or replaced by primary arthroplasty resulted in improved early mobilisation, reduced reoperation rates, and acceptable complication profiles in elderly patients.[6] Similarly, Carroll *et al.* found that patients treated with arthroplasty achieved faster functional recovery and shorter hospital stays compared to those managed with fixation alone.[7]

Herscovici *et al*. described the "combined hip procedure," which integrates limited fixation with immediate THA, allowing restoration of stability while enabling early weight bearing.[8] This approach has gained acceptance for complex fracture patterns involving both columns, femoral head injury, or marginal impaction.

The use of cages and bone grafting has been shown to be particularly effective in elderly patients with medial wall defects or severe comminution, where conventional press-fit fixation is unreliable. Laflamme *et al.* highlighted the technical challenges of fixing osteoporotic acetabular fractures involving the quadrilateral plate and emphasised the limitations of fixation alone in such scenarios.[9]

Arthroplasty in the setting of acetabular fractures often necessitates advanced reconstructive techniques due to bone loss, medial wall deficiency, or protrusio acetabuli. Paprosky *et al.* provided a widely accepted classification of acetabular defects and outlined reconstructive strategies including the use of acetabular cages, reinforcement rings, and structural bone grafting.[11] These constructs allow load transfer to intact pelvic bone, protect graft incorporation, and provide immediate implant stability.

An important advantage of primary THA is the avoidance of secondary conversion surgery following failed fixation. Morison *et al.* demonstrated that THA performed after failed acetabular fracture fixation is associated with higher complication rates, lower implant survivorship, greater blood loss, and greater technical difficulty than primary arthroplasty.[13] These findings support the hypothesis that, in selected patients, early arthroplasty may be a more definitive and safer option.

This case series presents short-term outcomes only. Long-term implant survival, the trajectory of any underlying osteoarthritis, and the durability of reconstruction require extended follow-up, which was not available for comprehensive assessment in all patients. Additionally, the series is small (n = 3) and is subject to selection bias toward more complex cases. Prospective comparative studies would further strengthen the evidence base in this domain.

Declarations

Acknowledgement

We would like to express our sincere gratitude to the Department of Orthopaedics, along with the associated anaesthesiology, physiotherapy and nursing teams for their invaluable support in the perioperative management and the rehabilitation of the patients included in this case. We also acknowledge the contribution of the Department of Radiology for their assistance with imaging and documentation.

We extend our appreciation to the patients and their families for their cooperation and consent, which made this study possible. We are also grateful to the institutional support staff for facilitating clinical data collection and postoperative follow-up.

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Conclusion

This case series demonstrates that primary THA with appropriate reconstructive techniques is a reliable, effective, and increasingly preferred treatment strategy for complex and neglected hip injuries, particularly in elderly, osteoporotic, or low-demand patients. Arthroplasty provides immediate joint stability, facilitates early mobilisation, reduces perioperative morbidity, and prevents the adverse outcomes associated with fixation failure. Based on these findings, a paradigm shift toward greater use of primary THA in carefully selected elderly patients with complex, neglected, or osteoporotic acetabular injuries is supported. Primary THA in this population reduces complications, improves early functional outcomes, and avoids the morbidity associated with fixation failure.

Sana Parveen, Chandeep Singh, Shitij Kacker, Sanjiv Kumar Singh Marya. Surgical Management of Complex and Neglected Hip Injuries Using Arthroplasty-Based Reconstruction. MMJ. 2026, March. Vol 3 (1).
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Bridging the Gap in the Diagnosis of Refractory Anaemia by Next-Generation Sequencing

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Abstract:

When anaemia does not respond to vitamin and iron supplements and no genitourinary or gastrointestinal cause of blood loss is found, the patient requires a bone marrow examination to exclude rare causes like myelodysplastic syndrome (MDS). However, even the bone marrow examination and usual cytogenetic testing, including karyotyping and fluorescence in situ hybridisation (FISH), may be inconclusive. In such cases, where there is a diagnostic dilemma, next-generation sequencing (NGS) may be a ray of hope. Here, we report a few cases where bone marrow aspiration, biopsy, and cytogenetics were inconclusive, and NGS helped in re-classifying these patients as MDS. NGS served as a critical bridge between clinical suspicion and definitive diagnosis when other modalities failed.

Key words: Refractory Anaemia, Myelodysplastic Syndrome, Cytogenetics, Karyotyping, Next-Generation Sequencing, Diagnostic Dilemma.

Introduction

Unexplained anaemia is found in > 15% of individuals aged over 65 years and increases by > 50% in people over 80 years. Consequently, it is a major diagnostic challenge for all general practitioners.[1] Bone marrow examination is the most common test performed for the diagnosis of anaemias or cytopenias when other causes like nutritional deficiencies, drug-induced causes, heavy metal toxicity, etc. are excluded. In some of these patients, even a bone marrow examination and cytogenetics by karyotyping or fluorescence in situ hybridisation (FISH) are normal and may not be diagnostic. Patients with cytopenias but without sufficient dysplastic changes or myelodysplastic syndrome (MDS)-defining cytogenetic alterations are considered to have idiopathic cytopenia of unknown significance (ICUS), and patients with cytopenias and with MDS-defining genetic alterations are considered to have clonal cytopenias with unknown significance (CCUS).[2] Next-generation sequencing (NGS) can help in such cases and has revolutionised the diagnosis of MDS.

Case Reports

Case report 1

An 80-year-old hypertensive male presented with progressive anaemia over the last 3 months. His haemoglobin had decreased from 12 g/dL to 10 g/dL. White blood cell counts and platelets were normal. His mean corpuscular volume (MCV) was 84 fL, and the peripheral blood film did not show any immature or dysplastic cells. The reticulocyte count was 0.4%, while iron and vitamin B12 profiles were normal. He had a history of myocardial infarction 3 years prior, treated with coronary

stenting, and was on aspirin. He was a vegetarian, non-alcoholic, and denied a history of melena or bleeding. He had received intravenous iron and oral vitamin B12 supplements without improvement. Initially reluctant to undergo invasive testing, he eventually consented to bone marrow aspiration, biopsy, and genetic testing (karyotyping, FISH, and NGS). Bone marrow revealed pure red cell aplasia (PRCA) without dysplastic changes in the myeloid or megakaryocytic series. Evaluation for Parvovirus B19 (antibodies and deoxyribonucleic acid [DNA] polymerase chain reaction [PCR]) and a positron emission tomography-computed tomography (PET-CT) scan were normal. Cytogenetics (karyotyping and MDS FISH) were reported to be normal; however, NGS revealed a DNA methyltransferase 3 alpha (DNMT3A) gene mutation. While the DNMT3A mutation is rare in patients presenting solely with PRCA, its presence is a significant indicator of an increased risk of MDS and progression to acute myeloid leukaemia (AML).

Case report 2

A 65-year-old male was planned for total knee replacement for osteoarthritis in bilateral knees. On pre-anaesthetic evaluation, he was found to have pancytopenia with haemoglobin 9 g/dL, white cell count 3400/µL, and platelet count 50,000/µL. MCV was 102 fL, and the reticulocyte count was 1.4%. His surgery was deferred, and he was referred to the haematology clinic for further evaluation. He reported using alternative medicine for knee pain for 6 months. He was a non-smoker and non-alcoholic with no history of fever, weight loss, or jaundice. Peripheral blood film revealed macrocytic anaemia without dysplastic cells or blasts. The iron and vitamin B12 profiles were normal, and ultrasound of the abdomen did not reveal any abnormality. Bone marrow showed variable cellularity, ranging from 5% in some areas to 90% in other areas, without significant dyspoietic changes. The heavy metal profile was normal. Karyotyping and the MDS FISH panel were normal, but NGS revealed tumour protein p53 (TP53) gene variant. He was diagnosed as MDS with a TP53 mutation, and because his cytopenias progressed, he was started on azacitidine-based therapy.

Case report 3

A 62-year-old male with hypertension on amlodipine and telmisartan had noticed a decrease in his haemoglobin over a period of 6 months. He had noticed a fall in haemoglobin from 13 g/dL to 12 g/dL and then 11 g/dL over a period of 6 months; otherwise, his haemoglobin had always been more than 14 g/dL prior to this. He did not have any other active complaints. He was non-vegetarian and an occasional alcoholic. His peripheral blood film showed normocytic normochromic anaemia with normal differential white cell counts and platelets. Iron, vitamin B12, and folate profiles were normal, and there was no history of alternative drugs, melena, or jaundice. After initially refusing, he consented to a bone marrow test when haemoglobin dropped to 9.5 g/dL. Bone marrow biopsy showed dyserythropoiesis with 25% ring sideroblasts. The cytogenetic and MDS FISH panel were normal, but NGS for the myelodysplastic syndrome panel showed a splicing factor 3b subunit 1 (SF3B1) mutation. He was given options of erythropoietin and luspatercept, and was started on erythropoietin injections, to which he responded with rise in haemoglobin to 12 g/dL after 8 weeks.

Case report 4

A 65-year-old female was planned for cholecystectomy for cholelithiasis. There was no other significant past medical history. Her pre-surgery evaluation revealed haemoglobin of 9.5 g/dL with normal white cell and platelet counts. Her peripheral blood smear and nutritional workup (iron, ferritin, vitamin B12, folate) were normal. Bone marrow revealed trilineage haematopoiesis with mild megaloblastic changes. Karyotyping and FISH for MDS were normal, and NGS (MDS panel) showed tet methylcytosine dioxygenase 2 (TET2) and additional sex combs-like 1 (ASXL1) mutations. She is currently on regular follow-up, maintaining haemoglobin between 9.5 to 10.5 g/dL without symptoms for the last 9 months.

The key clinical and laboratory features of the cases are summarised in Table 1.

Case report	Age/Sex	Presenting cytopenia	BM morphology	NGS findings	Clinical course
1	80 M	Anaemia (Refractory)	Pure red cell aplasia	DNMT3A	Started on ESA
2	65 M	Pancytopenia	Normocellular, no dysplasia	TP53	Started azacitidine
3	62 M	Anaemia (Progressive)	25% ring sideroblasts	SF3B1	Responded to ESA
4	65 F	Anaemia (Incidental)	Mild megaloblastic	TET2, ASXL1	Stable observation

Table 1: Summary of cases.

Abbreviations: ASXL1: Additional Sex Combs-Like 1; DNMT3A: Deoxyribonucleic Acid Methyltransferase 3 Alpha; ESA: Erythropoiesis-Stimulating Agents; M: Male, F: Female, BM: Bone Marrow, NGS: Next-Generation Sequencing; SF3B1: Splicing Factor 3b Subunit 1; TET2: Tet Methylcytosine Dioxygenase 2; TP53: Tumour Protein p53.

Discussion

Anaemia is the most common disease in the world. It is prevalent among all age groups. The aetiopathogenesis of anaemia varies with the age of the patient. In children, worm infestation leading to iron loss from the gut is the most common cause. In females, menorrhagia and associated low iron intake are the most common causes. In adults and the elderly, there could be multiple causes of anaemia, including bleeding from haemorrhoids, alcohol intake, ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin leading to gastrointestinal ulcers, and colonic neoplasms. Most of these cases have a known pathology, and treatment is directed towards that cause. However, there is a group of refractory anaemia where the patient needs more than a routine evaluation to find out the cause of anaemia, and such patients need referral to a clinical haematologist. These patients have refractory anaemia, or cytopenias of undetermined significance, and such patients are usually elderly. MDS patients can present with anaemia or cytopenias and require bone marrow examination and genetic testing for the diagnosis.

The patients presented here were interesting cases of anaemia who were refractory to treatment with haematinics, and even the bone marrow biopsy and cytogenetics by karyotyping and FISH did not reveal any abnormality. These individuals had normal peripheral blood values or only mild cytopenias that do not fulfil the diagnostic criteria for MDS. However, NGS clinched the diagnosis and guided further management. As with many other malignancies, MDS predominantly affects the elderly population with a median age at diagnosis of 60–70 years. Cytopenias and dysplasia in ≥ 10% of cells from one lineage are the sine qua non for the diagnosis of MDS.[2] Diagnosis of MDS in patients with non-specific morphological changes can be difficult. NGS can identify at least one somatic mutation in > 90% of patients with MDS.[2,3] The introduction of NGS has facilitated the diagnosis of early stages of MDS and has increased our understanding of the genetic changes associated with the development and progression of MDS.[4,5] Supportive mutation information may be particularly helpful in cases with borderline morphologic dysplasia that complicate the use of cytopenias to establish an MDS diagnosis. The common NGS mutations found in MDS include SF3B1, TET2, ASXL1, serine and arginine rich splicing factor 2 (SRSF2), runt-related transcription factor 1 (RUNX1), DNMT3A, enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) and TP53.[6]

DNMT3A mutations occur early in the course of MDS and suggest an early genetic event in leukaemogenesis. Patients with DNMT3A mutations have a worse overall survival and more rapid progression to AML.[6] TP53 mutations in MDS are associated with very aggressive disease.

Determination of variant allele frequency (VAF), usually > 25%, has been set for the diagnostic assessment to distinguish MDS from clonal haematopoiesis of indeterminate potential (CHIP) or CCUS.[7] CHIP is said to be present when a healthy individual lacks haematological malignancy or clonal disorder, but carries a genetic mutation. Patients who have cytopenias without typical findings of MDS but have clonal mutations (by cytogenetics or NGS) are referred to as CCUS. These cases often represent a diagnostic "grey zone" where

traditional morphology and gold-standard tests reach their limits. The mutation spectrum of CCUS patients is similar to mutations seen in MDS.[6,7] There is no defined treatment of CCUS and patients with symptomatic cytopenias should be treated in clinical trials and those with MDS will require definitive treatment.

Conclusion

When the diagnosis of anaemia or cytopenia is challenging, and the bone marrow and routine cytogenetics are not diagnostic of MDS, then NGS can help in resolving the diagnostic dilemma. NGS should be routinely incorporated into the diagnostic workup for refractory cytopenias to ensure accurate diagnosis, early intervention, risk stratification, and the implementation of personalised management strategies, and such patients should be referred to a clinical haematologist.

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Challenges of Blood Centres in Providing Compatible Packed Red Blood Cells in Thalassaemia Patients

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Abstract:

Thalassaemia is a hereditary haemoglobinopathy characterised by ineffective erythropoiesis and chronic anaemia, necessitating lifelong regular packed red blood cell (PRBC) transfusions. While transfusion therapy remains the cornerstone of management and significantly improves survival and quality of life, it presents complex challenges for both patients and blood centres. Repeated transfusions expose patients to risks such as alloimmunisation, autoantibody formation, transfusional iron overload, and transfusion-transmitted infections (TTIs), all of which complicate long-term care and transfusion support. Alloimmunisation, in particular, poses a major obstacle by limiting the availability of compatible PRBC units and increasing the risk of haemolytic transfusion reactions. From the blood centre perspective, ensuring the timely provision of antigen-matched, compatible blood for multi-transfused thalassaemia patients is demanding due to limited donor phenotyping, scarcity of rare blood groups, and the need for advanced immunohaematology testing. The implementation of extended antigen matching, molecular genotyping, maintenance of rare donor registries, and regular antibody screening are critical strategies to mitigate transfusion-related complications. However, these measures require significant infrastructure, expertise, and financial investment, which may be challenging in resource-constrained settings. This article highlights the multifaceted challenges faced by blood centres in providing compatible PRBCs to thalassaemia patients and emphasises the importance of a proactive, multidisciplinary transfusion strategy. Strengthening donor programmes, adopting advanced testing technologies, and fostering collaboration among transfusion services are essential to improving transfusion safety and outcomes in transfusion-dependent thalassaemia.

Key words: Thalassaemia, Alloimmunisation, Iron Overload, Chronic Anaemia, Transfusion-Transmitted Infections, Red Blood Cell Transfusions.

Introduction

Thalassaemia is a genetic blood disorder characterised by defective haemoglobin production, leading to chronic anaemia and necessitating lifelong red blood cell (RBC) transfusions. While transfusions significantly enhance the quality of life for patients, they also present numerous challenges, both for the patients and for blood bankers who are responsible for ensuring safe and effective transfusion therapy. These challenges range from alloimmunisation and iron overload to the availability of compatible donor units and the risks of transfusion-transmitted infections.[1] Addressing these challenges requires a comprehensive, multidisciplinary approach to optimise transfusion outcomes and improve patient care.

Challenges for Thalassaemia Patients

1. Frequent transfusions and alloimmunisation

Patients with thalassaemia require regular blood transfusions, typically every two to four weeks, to maintain adequate haemoglobin levels. However, repeated exposure to donor RBCs increases the risk of alloimmunisation. Alloimmunisation occurs when the immune system recognises donor RBC antigens as foreign, leading to the production of antibodies against them. This can result in haemolytic transfusion reactions, complicating future transfusions by making it difficult to find compatible donor units.[2] Studies suggest that extended phenotype-matched transfusions can help mitigate this risk by matching more RBC antigens between donors and recipients.[3] However, implementing extended antigen matching requires extensive donor phenotyping and increased resources, which may not always be feasible, especially in resource-limited settings. The development of multiple alloantibodies further complicates transfusion therapy and can necessitate specialised immunohaematology techniques to identify compatible blood.[4]

2. Iron overload and its consequences

Chronic RBC transfusions lead to excessive iron accumulation in the body, a condition known as transfusional iron overload. Since the human body lacks a natural mechanism to excrete excess iron, it gradually accumulates in vital organs such as the heart, liver, and endocrine glands, leading to severe complications, including:[5]

- **Cardiomyopathy and heart failure:** Iron deposition in the myocardium can cause arrhythmias and cardiomyopathy, which are major causes of mortality in thalassaemia patients.
- **Liver cirrhosis and fibrosis:** Chronic iron overload can lead to hepatic dysfunction, cirrhosis, and an increased risk of hepatocellular carcinoma.
- **Endocrine dysfunction:** Iron accumulation in endocrine glands can lead to diabetes, hypogonadism, growth retardation, and thyroid dysfunction.

Iron chelation therapy is essential to remove excess iron from the body, but patient compliance remains a significant challenge due to the side effects, high cost, and the need for lifelong adherence to treatment. Some chelating agents require continuous infusion, further increasing the treatment burden.[5]

3. Risk of transfusion-transmitted infections (TTIs)

Despite stringent donor screening and improved testing technologies, the risk of transfusion-transmitted infections remains a concern for thalassaemia patients who require frequent transfusions. Infectious agents such as hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) can still pose a threat, especially in regions with high disease prevalence or limited screening infrastructure.[4]

Emerging infectious diseases present additional challenges, as new pathogens may not be detected by conventional screening methods. Viruses such as Zika virus and dengue virus have raised concerns regarding transfusion safety in endemic regions. Continuous advancements in blood screening technologies and improved donor selection criteria are necessary to mitigate these risks.[6]

4. Development of autoantibodies

Some thalassaemia patients develop autoantibodies against their own RBCs, a condition known as autoimmune haemolytic anaemia (AIHA). This makes transfusion management even more challenging, as cross-matching becomes increasingly difficult. Patients with both alloantibodies and autoantibodies may experience severe haemolytic reactions, necessitating corticosteroid treatment or immunosuppressive therapy in severe cases. Finding compatible donor units for such patients requires advanced immunohaematology techniques, specialised expertise, and often, access to international rare donor registries.[2]

Role of Blood Bankers in Transfusion Management

Blood bankers play a critical role in optimising transfusion therapy for thalassaemia patients. Their responsibilities extend beyond simple blood typing and include:[3]

- Conducting regular antibody screening to detect alloimmunisation at an early stage
- Utilising advanced serological and molecular typing techniques to improve donor-recipient matching
- Maintaining registries of rare phenotype donors to facilitate the provision of compatible blood
- Implementing quality assurance measures to minimise transfusion-related risks

Challenges for Blood Bankers

1. Finding antigen-matched blood

Providing antigen-matched blood is essential to minimise alloimmunisation and transfusion complications. However, the availability of such units remains limited, particularly in regions where comprehensive donor phenotyping is not routinely performed.[1] This challenge is particularly pronounced for multi-transfused patients who have developed multiple antibodies, necessitating extensive donor screening and molecular genotyping to identify compatible units.[4]

2. Managing limited rare blood stocks

Maintaining an adequate inventory of rare blood types is a constant challenge for blood banks. Patients who require Rhesus- (Rh-) and Kell-matched blood place additional pressure on blood banks to recruit and retain donors with specific phenotypes. Strategies to address this challenge include implementing donor phenotyping programmes, establishing rare donor registries, and encouraging repeat donations from antigen-matched donors.[6]

3. Advanced testing and phenotyping

Serological and molecular techniques, such as polymerase chain reaction (PCR)-based genotyping, enable precise antigen matching and reduce the likelihood of alloimmunisation. However, these methods are costly and not widely available in all blood centres. Investment in advanced blood typing technologies and automation is essential to enhance transfusion safety and efficiency.[3]

4. Emergency situations

In emergency scenarios requiring immediate transfusion, identifying compatible blood can be time-consuming. In the absence of pre-transfusion extended antigen typing, there is an increased risk of transfusing incompatible units, leading to adverse reactions. Blood banks must implement rapid crossmatching techniques and emergency transfusion protocols to ensure timely and safe transfusions for thalassaemia patients.[4]

The Way Forward

To overcome these challenges, several strategies can be implemented:

- **Establishing rare blood donor registries:** Blood banks should collaborate with national and international donor registries to maintain a readily available stock of antigen-negative blood.[1]
- **Routine extended antigen typing:** Implementing molecular and serological typing for both patients and donors can help in finding compatible matches and reducing the risk of alloimmunisation.[5]
- **Encouraging regular blood donations:** Awareness campaigns, donor incentives, and public education can help increase the pool of voluntary blood donors, ensuring a steady supply of compatible units.[4]
- **Investment in advanced immunohaematology techniques:** Blood banks should adopt automation, molecular genotyping, and solid phase red cell adherence (SPRCA) methods for accurate and rapid antibody detection.[4]
- **Early alloimmunisation prevention strategies:** Providing extended antigen-matched blood from the first transfusion can help prevent alloantibody formation, significantly improving long-term transfusion outcomes in thalassaemia patients.[4]

Conclusion

Thalassaemia remains a major transfusion-dependent disorder requiring meticulous blood management strategies. The challenges faced by patients, including alloimmunisation, iron overload, TTIs and autoantibody formation, demand a proactive approach to transfusion care. Blood bankers, in turn, must manage antigen-matching challenges, limited donor availability and the financial burden of advanced serological and molecular testing.[4]

A comprehensive transfusion management plan should include routine phenotyping of patients and donors, maintenance rare donor inventories, and promotion of voluntary blood donation programmes. Additionally, integrating molecular diagnostic tools in blood banks can improve transfusion compatibility and reduce complications in chronically transfused patients.[6]

Collaboration among transfusion centres, blood banks, and healthcare professionals is essential to enhance transfusion safety and ensure that thalassaemia patients receive the best possible care. Future advancements in immunohaematology, including gene therapy and novel transfusion protocols, may further revolutionise the management of thalassaemia, ultimately reducing dependence on blood transfusions.[6]

The key to improving transfusion outcomes lies in early intervention, technological advancements, and increasing public awareness about the importance of rare blood donations. By addressing these challenges, transfusion management for thalassaemia patients can be significantly improved, ensuring safer and more efficient care.[6]

Sangeeta Pathak. Challenges of Blood Centres in Providing Compatible Packed Red Blood Cells in thalassaemia Patients. MMJ. 2026, March. Vol 3 (1).
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A Prospective Study of Singing on the Development of Cacti and Succulent Plants – A Medical Satire

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Abstract:

A prospective study was conducted to determine if singing could nullify the effects of neglect, overwatering, and other parameters on cacti and succulents. Singing was found to have a positive impact on plants. Application of these findings to healthcare professionals at Max Healthcare may improve clinical care and lead to happier patients.

Key words: Cacti, Succulents, Singing, Happiness.

Introduction

Before introducing any new method of treatment, experimental studies are needed to validate its viability and use on human beings. Plants serve as ideal subjects to determine whether a procedure is feasible. Plants, too, have feelings, and it has been carefully observed that when they are treated with love, fertiliser, and water, they tend to thrive. Rapid growth was noted amongst the Cycas plants in Max Hospital, Saket, when provided with fertiliser and water at regular intervals; daily observation from the windows of the operating room, between surgeries, has borne this out. Chowdhary and Gupta[1] noted that music assisted the growth of marigolds (*Tagetes* species) and chickpeas (*Cicer arietinum*), while noise hindered it. Jung and colleagues[2] suggested that sound could benefit growth in plants. These studies demonstrated beneficial growth despite the absence of an auditory mechanism in plants. It remains unclear whether sound vibration can cause harm or whether prolonged exposure may inhibit, rather than enhance, growth.

It was speculated whether singing, in addition, would be an asset in plant growth. Dr. Sunil Katoch is well established as a soloist, while Dr. Sameer Anand is a vocalist in his own right. It was decided that Dr. H. N. Bajaj could also be included, but the demise of two plants in two consecutive days after his attempts as a crooner quickly led to his re-designation as 'Marg Darshak', in a planning and supportive role. It was felt that his voice would not pass the principle of 'Primum non nocere'.

Materials and Methods

Five cacti and five succulent plants of the same age and weight were placed on windowsills. A similar regimen of minimal water and fertiliser was administered regularly. It was decided that Dr. Sameer would employ his vocal cords to the best of his ability, using a mixture of songs from various movies. To obviate any bias, Dr. Katoch sang the same songs towards the evening. Out-patient department (OPD) timings and operating theatre timings were carefully managed with the cooperation of helpful nursing staff, theatre managers, and indulgent patients. The senior member of the team, Dr. H. N. Bajaj, undertook the job of assessing the findings.

The following parameters were recorded: neglect, overwatering, unsolicited touching, spike density, leaf turgidity, gardener guilt, and the effect of singing.

Observations and Results

While the detailed parameter analysis is documented and available upon request, an abbreviated format has been used in the interest of brevity. The editorial board was unanimous that this article deserved publication since keeping plants on windowsills is a usual practice, neglect is commonplace, and singing to them is in vogue since time immemorial. Many notable playback songsters have entered the portals of Bollywood by honing their skills using this method. It is hoped that one day members of the Max medical profession, too, would make a similar grand entry.

Cacti

It was noted that the cacti on the windowsill continued to thrive despite neglect.

Overwatering was rarely a problem as surplus water simply drained out of the containers. Unsolicited touching occasionally led to impalement of the skin and visits to the infirmary for emergency extraction of embedded spikes. The density of the latter maintained its character and continued to vigorously defend the plant from any predatory advance. Since cacti are bereft of leaves, there was no question of assessing leaf turgidity. Gardener guilt remained an issue, with most shying away. Singing was undoubtedly effective ($p < 0.001$) in adding to the growth of the plant. The choice of song, timing, and duration seemed to be well tolerated by these botanical specimens.

Succulents

On the contrary, succulents were far more sensitive. They responded poorly to neglect and demonstrated yellowing of leaves, such that it seemed they were afflicted with an agricultural version of jaundice. They disliked being watered and reminded of one's childhood when a daily bath was de rigueur, and excuses were trotted out with isochronous regularity. Our succulents shunned touch, as if they were more sacrosanct than Roman Vestal Virgins. Gardener guilt was also an issue as the majority were invariably found in the staff canteen, engaged in light refreshment. Singing was completely therapeutic, even when Dr. Anand rendered a few Tamil and Bhojpuri numbers, followed by Dr. Katoch with nostalgic melodies in the style of Kundan Lal Sehgal, which largely appeal to seniors.

The neighbours were occasionally seen wiping their eyes at the conclusion of the recital. It is extremely difficult to say if their emotional response was due to his songs or due to their perceived gratitude at the conclusion of his recital. Nevertheless, the botanical specimens appeared to flourish thereafter. It was noted that they exhibited rapid sequestration of any surplus water and responded with an outburst of fresh growth.

Discussion

This study clearly shows that plants are responsive biological organisms that respond well to carefully regulated doses of fertiliser and water. Overwatering is likely to harm the plant unless the container permits the excess water to drain adequately. Clearly, it may be inferred that they do not like "wet feet."

It can be deduced from this study that singing to plants is an effective way to bond with them. Plants respond with vigorous growth. Care has to be taken that the singers are musically inclined and not excessively loud or discordant, as this may influence the overall effect. At the same time, it becomes clear that singers need not be professionals.

Though the numbers in this study are small, these findings establish that there can be no strategic detachment between cacti and succulents (or any plant), as the requirements are determined to be more or less the same. The succulents did seem startled and perhaps sceptical about the procedure, but they rapidly settled down and enjoyed the singing of both Dr. Anand and Dr. Katoch. Certainly, it would be torture and unimaginable cruelty if Dr. H. N. Bajaj were to warble as well.

The next part of the study was deemed unnecessary. It was to focus on the effect of singing on our patients. However, the easy availability of music and songs on mobile phones renders this objective unnecessary, since patients can switch on or off these devices whenever so inclined. Extrapolating these data affirms that singing and music may serve as useful additions to patient well-being. This significant finding may be of value to consultants at Max Hospital. Perhaps one may find them singing in the hospital corridors, as they go about their ward rounds. Certainly, patients would be happier.

Declarations

Conflict of interest

This facetious study is entirely self-funded, and there are no potential biases.

Disclaimer

No malice is intended towards the participating plants or colleagues. Those who feel strongly about cruelty towards plants will be glad to learn that no plant died. Rather, they are robust and flourishing.

Editor's Comment

This article is written as a tongue-in-cheek observational study by our spine orthopaedics team. There are numerous studies suggesting that plants respond to environmental stimuli. Additionally, music therapy has a recognised role in healing and post-traumatic stress disorder.[3,4]

Conclusion

This light-hearted yet thoughtfully conducted study reinforces an enduring truth: attentive care, balanced nourishment, and a touch of melody can work wonders — even for the stoic cactus and the sensitive succulent. While firmly rooted in satire, our observations echo a broader principle applicable to both botany and medicine: environments enriched with warmth, rhythm, and mindful engagement foster growth and well-being.

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REVIEW ARTICLES

Egg Freezing: From Experimental Concept to Mainstream Reproductive Strategy — Process, Nuances, and Clinical Reality

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Abstract:

Oocyte cryopreservation (OC), known as egg freezing, has transitioned from an experimental technique to an established component of modern reproductive medicine. Once limited by low survival rates, advances in laboratory cryobiology, particularly the vitrification process, have transformed this procedure as a viable option for fertility preservation across a wide range of clinical and social indications. This review traces the historical evolution of egg freezing, explains the biological and technical principles underlying the procedure and highlights its indications, risks, benefits, and limitations along with ethical viewpoints.

This review delineates various indications for fertility preservation, encompassing elective or social egg freezing for age-related fertility decline, non-malignant diseases such as endometriosis, autoimmune disorders, genetic predispositions to premature ovarian insufficiency, and oncofertility. Recent advancements, such as newer stimulation protocols including dual or double stimulation along with enhancements in vitrification techniques, are progressively refining clinical practice and outcomes. This article highlights the current evidence, clinical outcomes, and nuanced realities of egg freezing, emphasising the importance of informed decision-making and realistic expectations in reproductive planning.

Key words: Egg Freezing, Social Egg Freezing, Fertility Preservation, Oocyte Cryopreservation, Vitrification.

Introduction

Over the last two decades, reproductive timelines have shifted dramatically across societies. Women are pursuing higher education, professional careers, financial stability, and personal milestones before considering parenthood. Simultaneously, survival rates in cancer and other chronic illnesses have improved, bringing fertility preservation into sharp clinical focus. Against this backdrop, egg freezing has emerged as a powerful, yet often misunderstood tool.

Egg freezing resides at the intersection of medicine, ethics, economics, and societal transformation. The realities and nuances of egg freezing encompass the inherent biological limitations of reproductive ageing, inter-individual variability in ovarian response, laboratory-dependent factors, and disparities in costs and access, with unpredictability in forecasting individual live birth outcomes.[1] However, widespread awareness has also brought misconceptions such as “fertility insurance,” a phrase that oversimplifies biological reality and understates its inherent uncertainties.

For clinicians outside reproductive medicine, the challenge lies in understanding where egg freezing is genuinely beneficial, what its risks are, and how to counsel patients accurately. This review aims to bridge that gap by providing a practical, evidence-based framework

to understand egg freezing in contemporary clinical practice.[2,3]

Methodology

This review was conducted as a narrative analysis based on a comprehensive literature search to consolidate existing knowledge on oocyte cryopreservation (OC), with a focus on its clinical implications and subtleties. A thorough search of PubMed/MEDLINE was performed to identify relevant peer-reviewed publications in English.

Eligible publications encompassed original research, systematic reviews, meta-analyses, narrative reviews and professional society guidelines addressing technical aspects, clinical outcomes, medical and non-medical indications, effectiveness, safety, and ethical considerations of OC. Animal studies and single case reports were omitted. Data were qualitatively analysed and thematically categorised in accordance with the objectives of the review.

Historical Evolution of Egg Freezing

For several decades, egg freezing remained an experimental procedure dating back to the early 1980s. Early lab techniques like slow-freezing frequently resulted in ice crystal formation, meiotic spindle damage and chromosomal misalignment, leading to inconsistent survival and pregnancy rates.[1]

By the late 2000s, a major turning point occurred with the introduction of vitrification, a rapid freezing technique where the oocytes are cooled rapidly to -196 °C, and they become vitrified or "glass-like". This significantly reduces the chances of ice crystal formation with improved oocyte survival, fertilisation, and embryo development rates. In 2012–2013, the American Society for Reproductive Medicine (ASRM) formally removed the "Experimental" label from egg freezing, recognising it as an established clinical procedure. This reclassification paved the way for broader applications, including elective (social) egg freezing and fertility preservation for medical indications.[2,3]

Biology of the Oocyte: Why Freezing Is Uniquely Challenging[1,2]

An understanding of oocyte biology is fundamental to appreciating the challenges of egg freezing. Human oocytes are the largest cells in the body, rich in cytoplasm and water content. They are arrested in metaphase II of meiosis, containing a delicate spindle apparatus essential for accurate chromosomal segregation.

Female reproductive ageing is characterised by both a quantitative and qualitative decline in oocytes. With advancing age, rates of aneuploidy increase, mitochondrial function deteriorates, and deoxyribonucleic acid (DNA) repair capacity diminishes.

Egg freezing does not reverse ageing; it merely pauses the biological clock at the age at which the eggs are frozen. This distinction is critical in patient counselling.

Indications of Egg Freezing[4,5]

I. Elective (Social) fertility preservation

Social egg freezing refers to fertility preservation undertaken without an immediate medical indication, allowing women to plan parenthood according to personal, professional and social considerations. Age at freezing remains the most important determinant of success. Optimal outcomes are observed when freezing is performed before 35 years of age, with diminishing benefits beyond 38 years and significantly reduced success after 40 years.[6]

II. Reproductive health concerns

1. **Endometriosis**

   Endometriosis poses a unique challenge. Both the disease and its surgical treatment can compromise ovarian reserve. Egg freezing may be considered prior to ovarian endometrioma surgery or in women demonstrating declining ovarian reserve with endometriosis.

2. **Genetic diseases**

   Primary ovarian insufficiency (POI), Turner syndrome, Fragile X premutation, X chromosome deletion, etc.

3. **Autoimmune diseases**

   Conditions like systemic lupus erythematosus (SLE) may necessitate gonadotoxic therapies, warranting fertility preservation.

III. Oncofertility

Fertility preservation is now an integral component of cancer care. Egg freezing is recommended for

women undergoing various oncological treatments such as chemotherapy, radiation, bone marrow transplantation amongst others.

IV. Male factor

Surgical sperm retrieval surgery: Where sperm retrieval is unsuccessful, no sperm are retrieved on the day of oocyte retrieval, or the husband's unavailability on the day of oocyte retrieval.

V. Donor oocyte banking/Assisted reproductive technology (ART) banks

Enhances flexibility and availability in egg donation cycles, allowing better synchronisation and wider access.

VI. Fertility preservation in transgender men

Prior to gender-affirming treatment.

Step-by-Step Egg Freezing Procedure[2,4,5]

I. Patient selection, counselling and screening

The process begins with a comprehensive evaluation involving consultations with a fertility specialist and tests to assess ovarian reserve and overall health. Counselling must emphasise that outcomes are probabilistic rather than guaranteed.

Key considerations include:

- Chronological age
- Ovarian reserve markers (reproductive hormone blood tests like follicle-stimulating hormone [FSH], luteinising hormone [LH], oestradiol, and anti-Müllerian hormone [AMH]; ultrasound parameter: antral follicle count)
- Medical history (endometriosis, tuberculosis, autoimmune disorders, prior ovarian surgery, cancer and onco-therapies)
- Reproductive goals and timelines

II. Controlled ovarian stimulation and egg retrieval procedure

Controlled ovarian stimulation involves daily hormonal injections to induce multifollicular development, monitored through ultrasounds and hormonal assays to tailor the individual response. Once the follicles attain the desired size, transvaginal ultrasound-guided oocyte retrieval is performed under short general anaesthesia as a day care procedure. The procedure is generally safe, with low complication rates. Typically, this process starts during the first 2–3 days of menstruation. It requires approximately 2–3 weeks for completion. However, in oncology patients, it is initiated anytime during the menstrual cycle as a random-start stimulation protocol.

III. Laboratory aspects of oocyte freezing: Vitrification

Retrieved oocytes are assessed by an embryologist and the mature metaphase II oocytes are cryopreserved using the vitrification process (Figure 1). Vitrification is now the global gold standard, achieving post-thaw survival rates exceeding 90%, with fertilisation and implantation rates comparable to fresh oocytes.[7]

Figure 1: Stages of oocyte maturation: **A.** Prophase I – Geminal vesicle; **B.** Metaphase I oocyte; **C.** Metaphase II oocyte with polar body; **D.** Degenerated oocyte.[8]
Abbreviations: DEG: Degenerated Oocyte; MI: Metaphase I; MII: Metaphase II; PI: Prophase I.

Risks and complications[9]

A. **Short-term risks:** Ovarian hyperstimulation syndrome (OHSS), procedural complications related to oocyte retrieval and anaesthetic risks

B. **Emotional and financial burden:** Distress if expectations are unrealistic, or if multiple cycles are required

C. **False reassurance:** No oocytes retrieved, empty follicle syndrome, or no mature metaphase II (MII) oocytes suitable for freezing

D. **Long-term risks:** Maternal and paternal age at pregnancy: Obstetric risks like miscarriages, congenital anomalies, gestational diabetes mellitus, pre-eclampsia, preterm labour, foetal growth restriction

Optimal age and success rate

Egg quality declines non-linearly, accelerating after 35 years of age. The probability of a live birth derived from preserved oocytes is around 60% in women younger than 35 years and 29% in women older than 35 years. Considering cumulative attrition across all stages, cryopreservation of approximately 8–15 mature oocytes in women younger than 35 years and 15–20 oocytes in women older than 35 years is recommended to achieve a projected 60%–70% chance of live birth.[6] Notably, a 42-year-old woman has a 6.6% chance of giving birth with her own fresh oocytes, whereas if she freezes her eggs at the age of 30, she has more than 40% chance of a successful live birth.[10] These findings highlight that freezing fewer, better quality eggs under 35 years yields optimal outcomes (Table 1).

Stage	Key determinants	Expected attrition
Egg (Oocyte)	The woman's age and the number of metaphase II (MII) mature oocytes frozen	Oocyte quality
Survival	Vitrification technique, lab expertise	Post-thaw oocyte recovery
Sperm age and quality	Semen quality	Male factor
Embryo	Gamete quality, lab skills	Embryo quality
Live birth	Maternal and paternal age, uterine parameters and overall maternal health	Implantation issues, obstetric risks

Table 1: Determinants of success.

Myths, nuances, and reality

- **Myth:** Egg freezing guarantees future pregnancy; **Reality:** Egg freezing preserves potential but does not guarantee a live birth.
- **Myth:** Age alone matters; **Reality:** The number of oocytes frozen matters as much due to attrition effects and is age-stratified.
- **Myth:** Hormone stimulation leads to long-term endocrine or oncological risks; **Reality:** Current evidence shows that ovarian stimulation produces short-term hormone exposure and is not associated with a demonstrable increase in cancer risks.
- **Myth:** Egg freezing is better than embryo freezing; **Reality:** Embryo freezing has a higher per-unit successful live birth rate.
- **Myth:** Vitrification is a perfect 'time capsule'; **Reality:** It is not a rejuvenation machine that stops ageing or repairs DNA damage.

Changing Trends and Usage Rates of Frozen Oocytes

A retrospective 12-year study conducted by Rohatgi *et al.* and presented at the Royal College of Obstetricians and Gynaecologists (RCOG) World Congress, London, 2025, highlighted a favourable transition in reproductive dynamics in urban India, with egg freezing gaining recognition as a reproductive choice that enhances individual reproductive autonomy. Interestingly, following the coronavirus disease 2019 (COVID-19) pandemic, there was a sharp rise (67.25%) in the number of women who underwent social egg freezing, in contrast to only 24.6% pre-COVID-19. The most common age group was 31–35 years (37.70%), followed by 36–40 years (32.8%) and the oldest was 47 years

of age. Total 9.83% had repeat egg freezing cycles, and again maximum repeat cycles were done post pandemic in the year 2023 in the age group of 35–36 years. Another interesting finding of this study was a low utilisation rate of only 9.8%, underscoring societal challenges and financial limitations. These findings emphasise the need for strengthened education and support to empower women in planning their reproductive journeys.

Egg Freezing in India: Legal and Ethical Considerations

In India, egg freezing is regulated under the Assisted Reproductive Technology (Regulation) Act, 2021 and corresponding rules. It occupies a distinctive legal and ethical position within assisted reproduction involving invasive medical intervention for future therapeutic intent, thus creating long-lived reproductive material for deferred use and sits at the intersection of autonomy, future-oriented consent, equity and responsibility with emerging challenges posed by extended storage, posthumous use and evolving technologies.[11]

Technological Advances in Egg Freezing[12]

- Vitrification 2.0 and automated freezing systems reduce manual error and improve post-thaw survival rates.
- Artificial intelligence (AI) in OC involves non-invasive analysis tools such as VIOLET, which uses a light microscope to capture images of mature oocytes before freezing and instantly grades the quality of each egg, giving more individualised data for blastocyst formation and its potential live birth outcomes.
- AI-driven timing optimisation using the IndividuaLised oocyte retrieval Estimator based on gradient-boosted Trees Integrating Attentions (IL-ETIA) forecasts the optimal interval between ovulation trigger and oocyte retrieval.
- AI-guided mechanical oocyte profiling utilises a novel instrument with micromachined probes to measure an egg's mechanical properties non-destructively, giving a quantitative quality score prior to freezing.
- Artificial ovary constructs are scaffolds seeded with follicles designed to mimic natural ovarian function.
- In vitro maturation (IVM) refers to the maturation of immature oocytes in vitro in the laboratory.

Conclusion

Egg freezing, as a reproductive choice, sits at the intersection of biology, probability, technology and social narrative. It is a powerful tool when paired with timely planning, judicious counselling, and realistic expectations. Today, egg freezing in India is emerging as a strategic technological advancement, translating OC from promise to practice.

Tanya Buckshee Rohatgi, Nipasa Sarma. Egg Freezing: From Experimental Concept to Mainstream Reproductive Strategy — Process, Nuances, and Clinical Reality. MMJ. 2026, March. Vol 3 (1).
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CASE STUDIES

Preterm Premature Rupture of Membranes at 27 Weeks Gestation with Vaginal Colonisation by *Haemophilus influenzae*: A Case Report

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Abstract:

Preterm premature rupture of membranes (PPROM) is a significant contributor to preterm births and is associated with increased maternal and neonatal morbidity and mortality. Early identification and appropriate management are crucial to prolong gestation and minimise complications. We report a case of PPROM at 27 weeks of gestation complicated by vaginal colonisation with *Haemophilus influenzae,* highlighting the importance of microbiological evaluation in such scenarios.

Key words: Preterm Premature Rupture of Membranes, *Haemophilus influenzae*, Preterm Birth, Antenatal Infection, Neonatal Sepsis.

Introduction

A high vaginal swab (HVS) culture during preterm labour is important as it identifies infections that can induce preterm labour or lead to complications in the newborn or the mother, enabling targeted antibiotic therapy to improve outcomes. It helps in the diagnosis of bacterial vaginosis and chorioamnionitis, both of which are strongly associated with preterm labour and severe neonatal complications such as sepsis.[1]

Several pathogens have been implicated in preterm labour, among which *Haemophilus influenzae (H. influenzae)* is a lesser-known but important organism. Although typically a respiratory commensal, *H. influenzae* can colonise the female genital tract[2] and cause infections such as pelvic inflammatory disease and vulvovaginitis. During pregnancy, it has been associated with miscarriage, intra-amniotic infection, preterm childbirth, and, in severe cases, systemic infections such as sepsis or bacteraemia. Notably, strains isolated from the genital tract are usually non-typeable *H. influenzae* (NTHi), which have a recognised ability to cause invasive maternal and neonatal disease.[1] We have highlighted here a clinical case of preterm labour where *H. influenzae* was isolated from the HVS.

Case Report

A 28-year-old woman, gravida 2, para 1, live 1 (G2P1L1), presented at 27 weeks of gestation with complaints of leaking per vaginum since the morning. She denied any associated pain, fever, vaginal bleeding, or uterine tenderness. On examination, the patient was found to be stable, afebrile, and normotensive. On per-abdominal examination, the uterus was found to be relaxed, with no signs of tenderness or contractions. Per speculum examination showed clear fluid leaking per vaginum; digital per vaginal examination was deferred to avoid ascending infection. On ultrasound examination, a single

live intrauterine pregnancy at 27 weeks, with a reduced amniotic fluid index, was noted. An HVS was sent for culture, which showed growth of *H. influenzae*. The isolate was sensitive to azithromycin, ciprofloxacin, and levofloxacin, but resistant to amoxycillin-clavulanic acid, ampicillin-sulbactam, ampicillin, cefuroxime, cefixime, ceftriaxone, and co-trimoxazole. All other tests were within normal limits; there was no leukocytosis or elevated C-reactive protein.

The patient was admitted for inpatient monitoring and started on azithromycin tailored to culture sensitivity. Antenatal corticosteroids (betamethasone 12 mg intramuscularly, two doses 24 hours apart) for foetal lung maturity were given, along with magnesium sulphate for neuroprotection, considering the risk of imminent preterm birth. Serial monitoring of maternal vitals, signs of infection, and foetal wellbeing was done. The pregnancy was conservatively managed with close surveillance. No signs of chorioamnionitis or foetal compromise were observed during the initial 72 hours. The patient remained stable and was managed expectantly to prolong gestation. Neonatal and infectious disease teams were involved in planning neonatal care and potential sepsis screening post-delivery.

Discussion

Preterm premature rupture of membranes (PPROM) refers to the rupture of foetal membranes before 37 weeks of gestation and prior to the onset of labour. It complicates approximately 2%–3% of all pregnancies and accounts for nearly one-third of preterm deliveries.[3,4] The presence of genitourinary tract infections, including colonisation with atypical organisms such as *H. influenzae*, can increase the risk of ascending infection and adverse neonatal outcomes.[5]

H. influenzae is an uncommon cause of vaginal colonisation during pregnancy but can be associated with chorioamnionitis, neonatal sepsis, and poor pregnancy outcomes if not promptly identified and treated. PPROM presents a complex clinical scenario, balancing the risks of prematurity against those of infection.[4] Identification of pathogenic organisms via vaginal cultures is vital in guiding appropriate antibiotic therapy and improving perinatal outcomes. In another study, the overall rate of invasive *H. influenzae* infections linked to pregnancy was similar to the incidence of early-onset neonatal sepsis caused by group B *Streptococcus*, and notably higher than the rate of pregnancy-related listeriosis.[5] Pregnant individuals face a 17-fold higher risk of developing invasive *H. influenzae* infections, most commonly due to non-typeable strains. When such infections occur within the first 24 weeks of gestation, they are linked to a foetal loss rate exceeding 90%.[5] Case studies have documented intra-amniotic infections with histological signs of acute necrotising chorioamnionitis, indicating that maternal *H. influenzae* infections can extend into the amniotic cavity and potentially affect the foetus.[6] During pregnancy, changes in hormonal, metabolic, and immune functions that support foetal development may also facilitate the movement of *H. influenzae* from the vaginal area into the uterine cavity, potentially raising the risk of placental infection.[7] Strains of *H. influenzae* linked to maternal infections are frequently associated with ascending infections and tend to show a particular affinity for the genital tract.[4]

Treatment of *H. influenzae* vaginal colonisation in pregnancy primarily involves the use of broad-spectrum antibiotics, with third-generation cephalosporins such as ceftriaxone or cefotaxime commonly recommended due to their proven efficacy against *H. influenzae* and favourable safety profile during pregnancy. In cases of polymicrobial infections, which are frequent in obstetric settings, combination antibiotic therapy may be required. A typical regimen includes ampicillin with gentamicin; however, gentamicin's limited activity against *H. influenzae* and its potential for nephrotoxicity and ototoxicity must be considered. For patients with penicillin allergies, alternative antibiotics such as clindamycin or azithromycin can be used, depending on the susceptibility profile of the isolated strain.[8]

Our isolate was sensitive to macrolides and fluoroquinolones, but resistant to β-lactams and their combinations with β-lactamase inhibitors. β-lactam resistance, including resistance to amoxicillin-clavulanate and ceftriaxone, cannot be explained solely by β-lactamase production, because clavulanic acid (a β-lactamase inhibitor) should restore activity in β-lactamase-producing strains. This isolate is most likely a β-lactamase-negative, ampicillin-resistant (BLNAR) strain. Such strains are known to have mutations in the ftsI gene, which encodes penicillin-binding protein 3 (PBP3). This leads to reduced binding affinity for β-lactams, resistance to ampicillin, amoxicillin-clavulanate, and

some cephalosporins (e.g., ceftriaxone), in the absence of β-lactamase production. These strains are not neutralised by β-lactamase inhibitors like clavulanic acid because the resistance is due to altered PBPs, not enzymatic degradation.[8] Sensitivity to macrolides and fluoroquinolones indicates the absence of efflux pump overexpression or target-site mutations (e.g., in 23S ribosomal ribonucleic acid [rRNA] or deoxyribonucleic acid [DNA] gyrase/topoisomerase genes). Hence, azithromycin and ciprofloxacin remain effective.

This case highlights the importance of thorough microbiological evaluation in cases of PPROM and emphasises individualised management. The use of chocolate agar during microbiological processing can aid the isolation of *H. influenzae*. Additionally, satellitism using a staphylococcal streak on sheep blood agar can facilitate prompt identification. Timely identification and treatment of atypical pathogens such as *H. influenzae* can help reduce maternal and neonatal complications while safely prolonging pregnancy when possible.

Declarations

This study was not funded by any person or organisation. All authors agree to the content of the manuscript. Patient details have been de-identified and are not mentioned to maintain confidentiality and privacy.

IEC REF NUMBER: BHR/MSSH/MHPL/DWARKA/MHEC/MICRO/25-01.

Conclusion

This case highlights the importance of considering atypical pathogens such as *H. influenzae* in PPROM. Early microbiological identification and susceptibility-guided therapy enabled appropriate management and safe prolongation of pregnancy without maternal or foetal complications. Routine vaginal cultures in PPROM can aid in timely, targeted treatment and may help improve perinatal outcomes.

Jharna Mandal, Sunanda Joshi, Ritu Garg. Preterm Premature Rupture of Membranes at 27 Weeks Gestation with Vaginal Colonisation by *Haemophilus influenzae*: A Case Report. MMJ. 2026, March. Vol 3 (1).
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Hepatic Hereditary Haemorrhagic Telangiectasia: A Case Report

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Abstract:

Hereditary haemorrhagic telangiectasia (HHT), also referred to as Osler-Weber-Rendu syndrome, is a rare autosomal dominant disorder characterised by abnormal vasculogenesis affecting the skin, mucosal surfaces, and visceral organs. Radiological imaging — particularly ultrasound, triple-phase contrast-enhanced computed tomography (CECT), and magnetic resonance imaging (MRI) — serves as a crucial tool for the evaluation of hepatic involvement in these patients. This case report discusses a 74-year-old male who presented to the outpatient department with abdominal pain. The report provides an overview of the characteristic imaging findings of hepatic HHT and discusses the relevant clinical symptomatology and therapeutic strategies.

Key words: Hereditary Haemorrhagic Telangiectasia, Osler-Weber-Rendu Syndrome, Triple-Phase Contrast-Enhanced Computed Tomography, Magnetic Resonance Imaging.

Introduction

Hereditary haemorrhagic telangiectasia (HHT) is a rare autosomal dominant genetic disorder. It is also known as Osler-Weber-Rendu syndrome. It causes abnormal development of blood vessels in areas like the skin, mucous membranes, and internal organs, including the lungs, liver, and brain. This condition is caused by mutations in the activin A receptor type II-like 1 (ACVRL1), endoglin (ENG), or SMAD family member 4 (SMAD4) genes, all of which play a role in blood vessel formation.

Diagnosis is based on internationally recognised Curaçao (or consensus) criteria,[1] which focus on four key features:

(i) Recurrent spontaneous nosebleeds (epistaxis)

(ii) A family history of HHT

(iii) Mucocutaneous telangiectasias

(iv) Involvement of internal organs

Based on the number of criteria present, the diagnosis is classified as definite (three or more criteria), possible/suspected (two criteria), or unlikely (one or none).[2]

Among the organs affected by HHT, the liver is most frequently involved.[3] Approximately one-third of patients develop hepatic arteriovenous malformations, which are a growing clinical concern.[1] Liver involvement can vary widely — from small telangiectasias to larger, confluent vascular lesions. In most cases, these malformations do not cause symptoms, with fewer than 10% of patients experiencing related clinical signs.[4]

When present, symptoms typically depend on the dominant type of hepatic vascular shunting: arteriovenous, arterioportal, or portovenous.[5] Imaging studies, such as ultrasound, computed tomography (CT) scans, and magnetic resonance imaging (MRI), are vital for assessing liver complications.[2] However, multiphasic CT is considered the most effective non-invasive method for diagnosing hepatic involvement in HHT and identifying the specific types of shunts.[5]

Clinical manifestations vary according to the type and extent of vascular shunting: arteriosystemic (arteriovenous) shunts can result in high-output cardiac failure (HOCF); arterioportal shunting may lead to portal hypertension,[2] whereas portovenous shunts can cause hepatic encephalopathy. In addition, diversion of blood from the mesenteric circulation through the hepatic artery may lead to mesenteric ischaemia.[5]

Case Report

A 74-year-old male patient presented to the outpatient department with complaints of abdominal pain. An ultrasound examination done earlier revealed mild intrahepatic bile duct dilatation, with no other significant abnormalities. Subsequently, the patient was advised to undergo triple-phase CT of the abdomen, which revealed findings consistent with HHT.

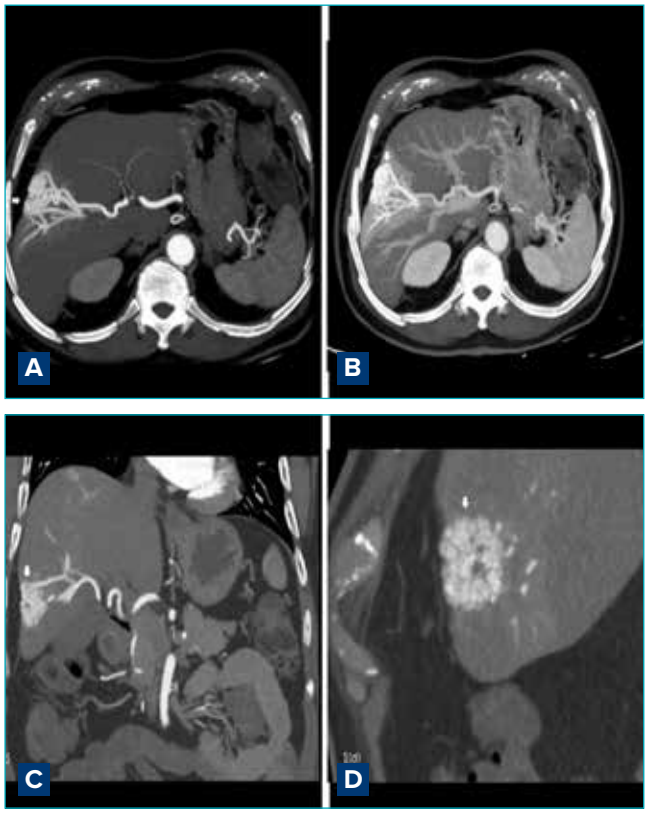

Figure 1: **A, B.** Axial; **C.** Coronal; and **D.** Sagittal triple-phase computed tomography (CT) images in the arterial phase showing a dilated hepatic artery and multiple telangiectatic vessels (arrow), along with hepatic arterioportal shunting, marked by early opacification of the portal vein.

Radiological findings

Triple phase CT abdomen revealed a dilated hepatic artery and multiple telangiectatic vessels along with hepatic arterioportal shunting marked by early opacification of portal vein during arterial phase (Figure 1A–D). Two foci of hyper vascular lesions with hepatic arterioportal shunting were seen during portal phase (Figure 2A–C). Multiple telangiectatic vessels were seen during delayed phase (Figure 3A and B). Three-dimensional (3D)-reconstructed coronal images revealed a dilated hepatic artery and vascular telangiectasia (Figure 4A and B).

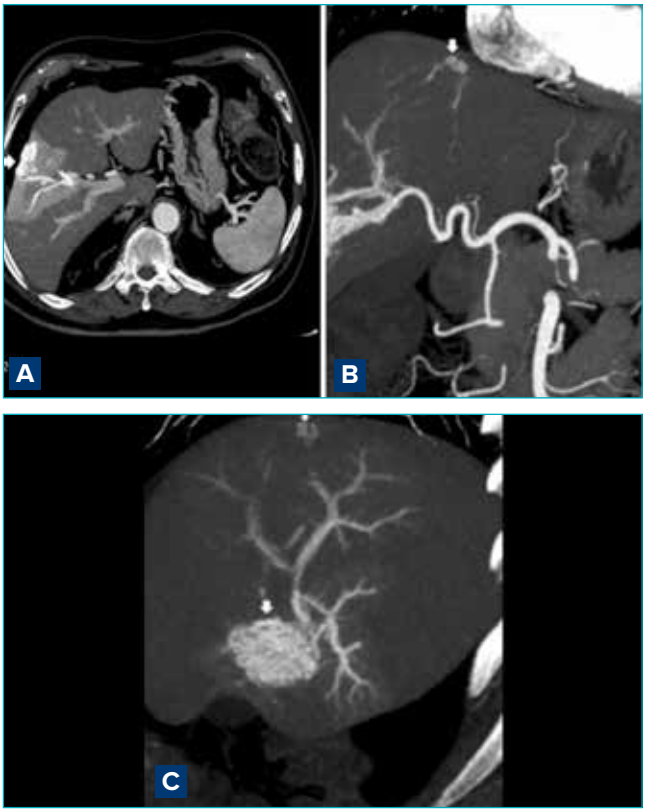

Figure 2: **A,** Axial; **B.** Coronal; **C.** Sagittal triple-phase computed tomography (CT) images during portal phase showing two foci of hyper vascular lesions (arrow) with hepatic arterioportal shunting.

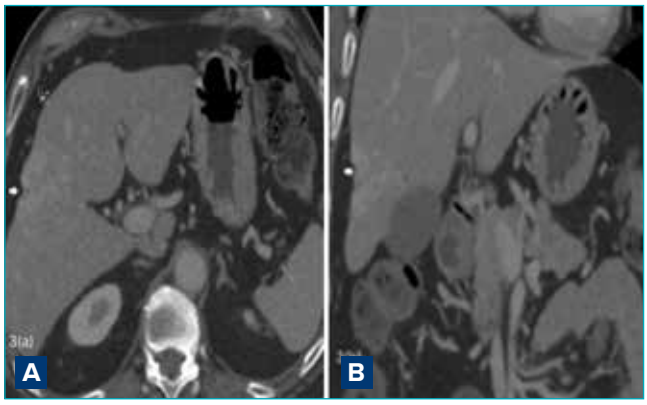

Figure 3: A. Axial; **B.** Coronal triple-phase computed tomography (CT) images during the delayed phase showing multiple telangiectatic vessels (arrow).

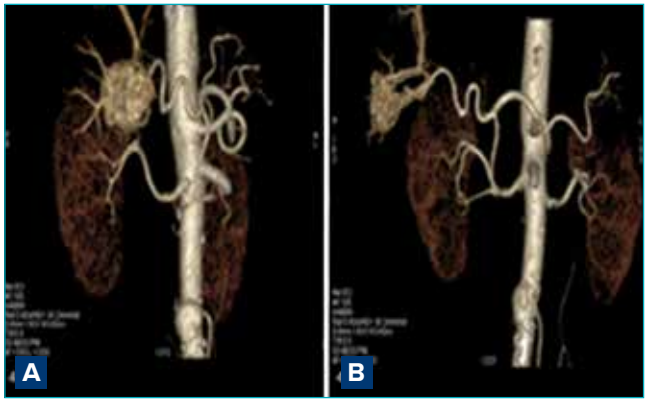

Figure 4A and B: Three-dimensional (3D) reconstructed coronal images showing a dilated hepatic artery and vascular telangiectasias.

Discussion

In HHT, liver involvement typically features widespread intrahepatic vascular malformations that result in blood flow shunting — including arteriovenous, arterioportal, and/or portovenous pathways. In more than two-thirds of cases, the type of shunt can be identified on imaging by observing early or selective contrast enhancement of the hepatic veins (suggesting arteriovenous shunting) or the portal veins (indicating arterioportal shunting) during different imaging phases. These hepatic changes may appear either as diffuse telangiectasias scattered throughout the liver or as distinct arteriovenous malformations.

Although the relationship between specific gene mutations and clinical presentation is still being studied, hepatic involvement is most commonly associated with activin receptor-like kinase 1 (ALK1) gene mutations and is rare in patients with ENG mutations.[6] Typical imaging findings in HHT-related liver disease include dilated, tortuous branches of the hepatic artery, along with premature filling of the portal vein (Figure 1A–D), heterogenous hepatic parenchymal enhancement during the arterial phase, and multiple hepatic nodules. In the present case, a triple-phase contrast-enhanced CT (CECT) scan was performed, which showed normal contrast uptake in the main portal vein and all three hepatic veins. However, arterial phase opacification of the peripheral portal vein branches was observed, consistent with arterioportal shunting (Figure 1A–D).[4]

Treatment of hepatic vascular malformations is symptom-driven. In patients with arteriovenous shunts causing HOCF, management includes diuretics, salt restriction, and anti-angiogenic medications. In cases of arterioportal shunting leading to portal hypertension, treatment options include fluid restriction and beta-blockers.[2] Despite these management strategies, liver transplantation remains the only curative treatment for hepatic involvement in HHT.[6] However, asymptomatic individuals with hepatic vascular malformations typically do not require treatment, as most remain free of complications.[2]

Conclusion

This case report describes the characteristic imaging findings of hepatic involvement in HHT, emphasising the importance of recognising different vascular shunts and arteriovenous malformations, which directly influence clinical manifestations and guide patient management. Further imaging evaluation is required to assess pulmonary and cerebral involvement.

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Isolated Unilateral Absence of Pulmonary Artery in an Adult

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Abstract:

Unilateral absence of pulmonary artery (UAPA) is an uncommon condition, with a prevalence of 1 in 200,000 young adults, which is characterised by congenital absence of either the left or right pulmonary artery and may be associated with or without other cardiac diseases. While the UAPA declares itself in infancy when associated with other congenital anomalies, patients with isolated UAPA usually remain asymptomatic and present in adulthood with symptoms such as dyspnoea, haemoptysis, recurrent infections, etc. We encountered an adult male patient who presented with haemoptysis and was diagnosed on further examination to have an absent right pulmonary artery. Considering the rarity and non-specific presentation of isolated UAPA, this case is being reported.

Key words: Unilateral Absence of Pulmonary Artery, Haemoptysis, Congenital Cardiac Anomaly.

Introduction

Unilateral pulmonary artery agenesis is a rare congenital abnormality characterised by the congenital absence of either the left or right pulmonary artery due to failure of the sixth ipsilateral aortic arch during embryogenesis.[1] Most commonly, unilateral absence of pulmonary artery (UAPA) occurs in conjunction with cardiovascular abnormalities such as right aortic arch, patent ductus arteriosus, tetralogy of Fallot, or cardiac septal defects, but rarely, it can present in an isolated manner.[2,3] Isolated UAPA (IUAPA) involves the right lung in about two-thirds of cases.[4] Due to embryologic relationships, UAPA commonly occurs on the side of the chest opposite the aortic arch.[5] In adults, it is often detected incidentally on chest computed tomography (CT) imaging performed for other indications. There is limited knowledge on the incidence, presentation, and management of IUAPA. We report such a case in an adult with non-specific symptoms.[2-4]

Case Report

A 36-year-old male presented with a history of recurrent haemoptysis since three days. There was no fever, cough, expectoration, chest pain, breathlessness, palpitation or syncope. Family history was negative for any congenital heart disease. There was a past medical history of preterm birth, and the patient underwent left cheiloplasty in childhood (no documents available at present). The patient denied any history of smoking, alcohol or drug abuse.

Physical examination revealed a fairly built male adult. Vitals were within normal limits. There was no clubbing, cyanosis, hepatomegaly, or pedal oedema. Jugular venous pressure was not raised. Respiratory and cardiovascular examinations were normal, except for a medial shift of the apex beat to the fifth intercostal space, just lateral to the left sternal border.

Electrocardiogram, two-dimensional echocardiography, and resting arterial blood gas analysis were within normal limits. Spirometry was not performed in view of active haemoptysis. Chest X-ray posteroanterior view (Figure 1) showed reduced right lung volume with ipsilateral shift of mediastinum.

Figure 1: Chest X-ray posteroanterior view showing a small right hemithorax with shift of the mediastinum towards the right side.

CT pulmonary angiography (Figures 2–4) showed proximal interruption of the right pulmonary artery with narrowed right pulmonary veins and multiple systemic collaterals supplying the right hilum. There were ipsilateral right-sided pulmonary hypoplasia, reticulations, small cysts in the right basal segments, and serrated pleural thickening, with hyperinflated left lung and hypertrophied left pulmonary artery and veins.

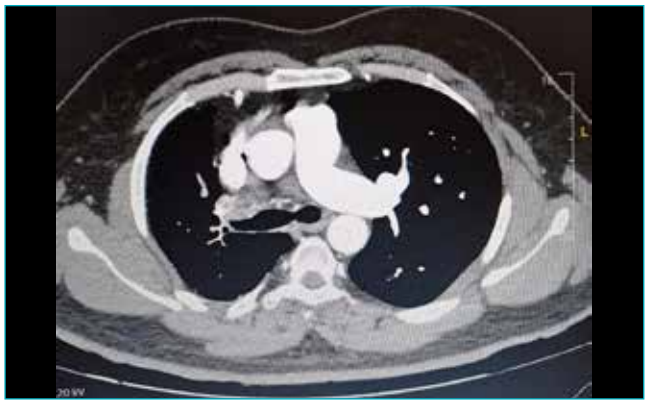

Figure 2: Computed tomography pulmonary angiography showing proximal interruption of the right pulmonary artery and hypertrophied left pulmonary artery and veins.

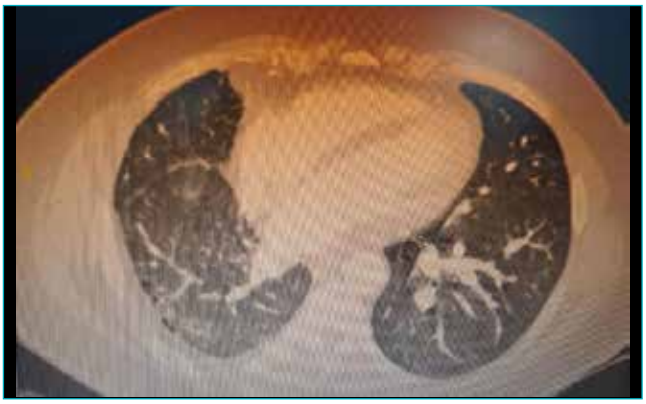

Figure 3: Ipsilateral right-sided pulmonary hypoplasia, reticulations, small cysts in the right basal segments, and serrated pleural thickening with hyperinflated left lung.

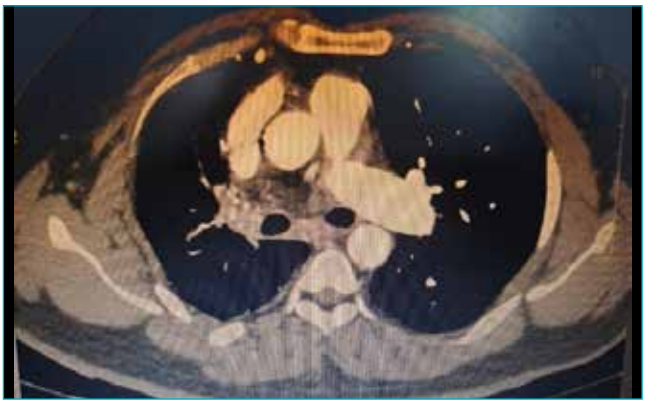

Figure 4: Narrowed right pulmonary veins and multiple systemic collaterals supplying the right hilum.

A diagnosis of absent right pulmonary artery was made, and symptomatic treatment was given to the patient. Haemoptysis subsided within the next 24 hours.

Discussion

Embryologically, pulmonary vasculature develops from three principal sources. The main pulmonary artery is derived from the arterial portion of the truncus arteriosus. The extrapulmonary portion of pulmonary arteries develops from the respective sixth branchial arch, while the intrapulmonary vasculature develops from their respective mesenchymal tissue surrounding the lung buds. Agenesis of pulmonary artery is due to the involution of sixth branchial arch. Since the intrapulmonary vasculature, which develops from the respiratory mesenchyme, is normal in these patients, the lung receives blood retrogradely from collateral arteries and from a persistent ductus arteriosus.[6] “Interruption” is a term that has also been used by several authors for

this condition.[7] Earlier, the term "absence of pulmonary artery" was widely used for this condition. However, recent consensus in the scientific literature states that as the intrapulmonary vascular network is still intact, the term "interruption of the pulmonary artery" is preferred over "absence of pulmonary artery".[8] Common collaterals supplying the lung include bronchial arteries, transpleural branches of intercostals, internal mammary, subclavian, and innominate arteries.[9] Rarely, collaterals from the coronary arteries also supply the lung with an absent pulmonary artery.[4] Most commonly, UAPA occurs in conjunction with cardiovascular abnormalities such as tetralogy of Fallot or cardiac septal defects, but it can also occur in an isolated manner.[2,3] Isolated UAPA involves the right lung in about two thirds of cases.[4] Due to embryologic relationships, UAPA commonly occurs on the side of the chest opposite the aortic arch.[5] During the first half of the 20th century, all recorded cases of absent pulmonary artery were from the autopsy series.[4]

Subsequently, with the availability of cardiac surgery in the early seventies for cyanotic heart diseases, many more cases were identified at the time of surgery.[3,10] After the development of angiographic techniques, diagnosis of this entity was possible without surgery or autopsy.[11] The advent of CT in the last quarter of the 20th century made the diagnosis of this entity even easier. Patients were diagnosed with this abnormality when CT was performed for the evaluation of other unrelated chest problems or during the work-up of symptoms related to this abnormality, e.g. haemoptysis and dyspnoea.[7,8]

Occasionally, these cases can also be diagnosed when a chest X-ray is performed as part of a routine check-up or during a pre-employment examination. A small hemithorax with diffuse reticulations due to collateral blood supply from the systemic circulation to the lung points towards the possibility of an absent pulmonary artery and the need for further work-up.[4,8] However, a smaller hemithorax may also be seen in scimitar syndrome and hypoplastic lung. Congenital hypoplastic lung and absent or hypoplastic pulmonary artery disease can be excluded from scimitar syndrome by the presence of normal venous drainage to the left atrium.[3,8]

On CT scan, the affected part of the pulmonary artery terminates within 1 cm of its origin. Direct anastomosis of transpleural collateral vessels with peripheral branches of the pulmonary artery appears as serrated thickening of the pleura and subpleural parenchymal bands on CT film. Such a CT appearance may mimic interlobular septal thickening as seen in idiopathic pulmonary fibrosis (IPF).[10] Contrast-enhanced CT of the chest not only diagnoses an absent pulmonary artery but also provides information about mediastinal structures and lung parenchyma. As per Shostak E *et al*, invasive angiography is better in certain aspects as it provides better delineation and haemodynamic data; however, pulmonary angiography should be reserved only for those having structural cardiac anomalies on echocardiography.[12]

A subject with an IUAPA may experience recurrent respiratory infections, dyspnoea on exertion, high-altitude pulmonary oedema, pulmonary hypertension in the contralateral lung or haemoptysis.[13] Haemoptysis occurs in about 20% of cases and is usually self-limiting. Occasional case reports of massive haemoptysis and death are available in the literature.[4] Rupture of an aneurysm between systemic to pulmonary collateral is said to be responsible for haemoptysis.

There is no consensus regarding treatment of this condition. However, those who are asymptomatic or have minor symptoms should be observed closely for the development of pulmonary arterial hypertension. Medical treatment of pulmonary hypertension in patients with UAPA without associated congenital heart disease is not yet available.[12] Surgical options to correct pulmonary hypertension, when present, include anastomosis of the hilar arteries of the affected lung to the main pulmonary artery.[12] Pneumonectomy is to be considered in cases with massive haemoptysis.[14] In patients with poor pulmonary reserve and/or comorbid conditions, selective embolisation of the systemic artery is indicated for the management of haemoptysis.[13]

Conclusion

IUAPA is a rare congenital anomaly that may remain clinically silent until adulthood and is often detected incidentally on imaging performed for unrelated indications. Awareness of its characteristic radiological features is essential to avoid misdiagnosis and to distinguish it from other causes of a small hemithorax such as scimitar syndrome or pulmonary hypoplasia. CT pulmonary angiography plays a pivotal role in diagnosis by accurately delineating vascular anatomy, systemic collaterals, and associated parenchymal changes. Management remains individualised, with close follow-up required to monitor for complications such as pulmonary hypertension and haemoptysis.

Nikhil Tomar, Taha Nabeel, Pritha Nayyar, Ashish Jain. Isolated Unilateral Absence of Pulmonary Artery in an Adult. MMJ. 2026, March. Vol 3 (1).
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Within Hours: A Catastrophic Reaction to Fludarabine in Fanconi Anaemia

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Abstract:

Fanconi anaemia (FA) is a rare genetic disorder characterised by bone marrow failure and a high predisposition to malignancy. Haematopoietic stem cell transplantation (HSCT) is the definitive treatment for the haematological manifestations. However, patients with FA exhibit extreme sensitivity to standard conditioning regimens. We present a case of a patient with a confirmed FA complementation group A (FANCA) mutation who developed fatal, rapid-onset acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) approximately three hours after the administration of the first dose of fludarabine as part of a reduced-intensity conditioning (RIC) regimen for an allogeneic HSCT. The patient experienced rapid clinical deterioration, including fever, hypotension, profound hypoxia, and ultimately cardiac arrest, leading to death within 24 hours of drug administration. This case highlights the critical vulnerability of FA patients to severe, precipitous drug toxicity in this high-risk population, although a drug reaction or idiosyncratic reaction seems most likely.

Key words: Fanconi Anaemia, Fludarabine, Acute Lung Injury, Acute Respiratory Distress Syndrome, Haematopoietic Stem Cell Transplantation, Drug Toxicity.

Introduction

Fanconi anaemia (FA) is an autosomal recessive or X-linked disorder caused by mutations in genes responsible for deoxyribonucleic acid (DNA) repair. This condition leads to progressive bone marrow failure, congenital anomalies, and an increased risk of cancer. Allogeneic haematopoietic stem cell transplantation (HSCT) remains the primary curative treatment for the haematological complications of FA. However, the use of conventional myeloablative conditioning regimens has historically resulted in high rates of toxicity and mortality due to the underlying cellular hypersensitivity of FA patients to DNA-damaging agents.[1,2] Reduced-intensity conditioning (RIC) regimens utilising agents like fludarabine have improved outcomes, but toxicity concerns persist. Fludarabine-induced pulmonary toxicity is a recognised adverse event, typically manifesting as a later-onset interstitial pneumonitis or acute respiratory distress syndrome (ARDS) with a median onset of 21 days.[3] We report an exceptionally rare case of immediate, fatal ARDS onset within hours of initial fludarabine exposure in a patient with FA, underscoring a unique and heightened susceptibility to this agent.

Case Report

A patient diagnosed with FA, confirmed by the identification of a pathogenic FA complementation group A (FANCA) mutation and presenting with severe pancytopenia, was admitted to the Department of Haematology-Oncology and Bone Marrow Transplantation for a planned allogeneic HSCT. The donor was a fully human leukocyte antigen (HLA)-matched sibling. A standard RIC regimen, which included fludarabine, was initiated. Figure 1 shows the initial chest X-ray (CXR) taken after insertion of the peripherally inserted central catheter (PICC) line.

Approximately three hours following the administration of the initial dose of fludarabine, the patient experienced abrupt and rapid clinical deterioration. This acute event was characterised by the onset of recurrent high-grade fever, systemic hypotension, and profound hypoxia that necessitated immediate high-flow oxygen support and escalation of care. A CXR was performed, which revealed widespread bilateral diffuse haziness consistent with ARDS (Figure 2), whereas the CXR prior to fludarabine administration was normal (Figure 1). Despite aggressive resuscitation efforts and intensive supportive care, the patient's condition rapidly progressed to irreversible respiratory failure. The patient expired within 24 hours of receiving the initial fludarabine dose.

Figure 1: Showing a normal chest X-ray.

Figure 2: Showing bilateral infiltrates which developed after four hours of 1st chest X-ray.

Discussion

This case highlights the extreme and immediate vulnerability of patients with FA to the severe toxicities of conditioning agents, even those typically considered less myeloablative or associated with later-onset toxicities. Fludarabine pulmonary toxicity is a known, albeit generally uncommon, adverse event following HSCT, usually developing one to two weeks after the final course of chemotherapy or a median of 21 days post-transplant.[3,4]

The temporal association of drug administration and the development of acute respiratory failure in a patient with normal lungs points towards a drug-induced idiosyncratic reaction. The underlying genetic defect in DNA repair mechanisms specific to FA as a likely predisposing factor cannot be excluded.

This critical outcome underscores a vital clinical necessity: the implementation of hyper-vigilant monitoring protocols for FA patients during the administration of all conditioning agents. At the earliest sign of pulmonary compromise, fever, or any worsening clinical status due to infection, immediate cessation of potentially causative agents must be considered. This case serves as a stark reminder of the unique high-risk profile of the FA patient group, where standard drug kinetics and toxicity profiles may not apply.

Conclusion

Fludarabine can induce a rare, rapid-onset fatal acute lung injury (ALI) in patients with FA receiving HSCT conditioning. Clinicians must maintain a high index of suspicion for atypical and severe toxicities in this population and employ highly cautious and individualised treatment protocols.

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Malignant Prostatic Gastrointestinal Stromal Tumour Presenting with Acute Intestinal Obstruction and Urinary Retention: A Rare Case Report

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Abstract:

Gastrointestinal stromal tumours (GISTs) are mesenchymal neoplasms that most commonly arise from the gastrointestinal tract. Prostatic GIST is an extremely rare form of extra-GIST that often presents with obstructive urological and gastrointestinal symptoms. A 39-year-old male presented with acute intestinal obstruction and urinary retention, with a one-month history of intermittent obstructive symptoms. He had been diagnosed with prostatic GIST five years previously and treated with imatinib, which resulted in initial tumour regression. The patient, who had known diabetes mellitus and untreated tuberculosis, developed worsening symptoms and was scheduled for definitive surgical management at Max Super Speciality Hospital, Lucknow. Intraoperatively, a large abdominopelvic mass adherent to the bladder and rectum was excised via a complex multivisceral surgical approach. Histopathology and immunohistochemistry confirmed a malignant GIST. Prostatic GIST is a rare and aggressive tumour that may present with life-threatening obstructive complications. Despite long-term tyrosine kinase inhibitor (TKI) therapy, surgical resection remains essential in cases of progression or acute obstruction.

Key words: Prostatic Gastrointestinal Stromal Tumour (GIST), Extra-GIST, Acute Intestinal Obstruction, Acute Urinary Retention, Malignant GIST, Imatinib Therapy.

Introduction

Gastrointestinal stromal tumours (GIST) represent the most common mesenchymal tumours of the gastrointestinal tract and originate from the interstitial cells of Cajal (ICC). The stomach and small intestine are the most frequently involved sites. Extra-gastrointestinal stromal tumours (EGISTs) are rare, accounting for less than 5% of all GISTs, and arise outside the gastrointestinal tract, including the retroperitoneum, mesentery, and pelvis.[1] Prostatic GIST is an exceedingly rare entity that poses significant diagnostic and therapeutic challenges. Due to its location, it often presents with urinary retention, bowel obstruction, or pelvic mass effects, and may be mistaken for more common prostatic malignancies.[2] The advent of tyrosine kinase inhibitors (TKIs) such as imatinib has revolutionised the management of GIST, however, surgery remains the cornerstone in symptomatic, progressive, or malignant disease.[3]

Case Report

A 39-year-old male presented with acute intestinal obstruction and acute urinary retention. He reported a one-month history of intermittent abdominal distension, constipation, and difficulty in micturition. The patient had previously undergone a prostatic biopsy at a government tertiary care centre five years earlier, where prostatic GIST was diagnosed. He was started on imatinib therapy, following which the tumour initially regressed. He had known diabetes mellitus and a history of tuberculosis, for which he was not receiving active treatment.

On presentation, the patient was catheterised for urinary retention and stabilised. Clinical and radiological evaluation revealed a large pelvic mass causing compression of both urinary and gastrointestinal structures. In view of acute obstruction and disease progression, surgical intervention was planned at Max Super Speciality Hospital, Lucknow, UP.

Intraoperative findings and procedure

A midline abdominal incision revealed a large abdominopelvic mass measuring 15.0 × 13.0 × 9.5 cm, adherent to the urinary bladder and rectum. The urinary bladder was grossly thickened and distended. The mass was abutting the bilateral ureters. There was no ascites or major vascular encasement.

Surgical steps included:

- Initial dissection between the bladder and the mass; the bladder was abutting but not involved, and planes were maintained
- Bilateral ureters were carefully dissected away from the mass up to the bladder base
- Anterior dissection was carried out up to the pubic bone
- Posteriorly, the mass was dissected from the rectum up to its mid-part; however, due to rectal wall adherence, the rectum was divided between the upper and mid-segments
- Further posterior dissection was performed up to the pelvic floor muscles
- The bladder neck was divided to expose the prostate, and the mass was excised
- The urethra was transacted at the bony level and sent for frozen section examination, which showed negative margins
- Bladder neck was anastomosed to the urethra using 4-0 polydioxanone (PDS) double-needle sutures over a Foley catheter
- Suprapubic cystostomy and colostomy were performed
- Drain placement was performed, and the abdomen was closed in layers

The surgery lasted for 8 hours, with an estimated blood loss of approximately 1 L. The postoperative course was uneventful, and the patient was discharged on postoperative Day 7 with regular follow-up.

Histopathological findings

Gross examination revealed a well-encapsulated tumour with areas of necrosis (Figure 1).

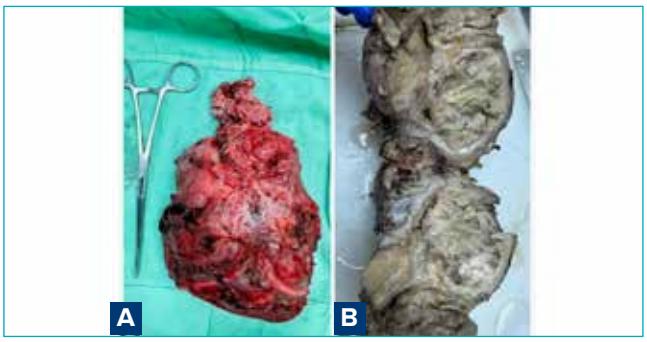

Figure 1: Gross morphology of prostatic gastrointestinal stromal tumour: **A.** Resected abdominopelvic mass showing a large, lobulated, irregular tumour with congested and haemorrhagic external surface; **B.** Cut surface of the tumour revealing a solid, grey-white to grey-tan appearance with areas of necrosis.

Microscopic examination showed a highly cellular tumour composed of spindle and epithelioid cells arranged in storiform, fibrosarcomatous, and epithelioid patterns. Extensive areas of hypercellularity, marked cytological atypia, and frequent mitoses, including atypical forms (30–35 per 50 high-power fields), were noted (Figures 2 and 3).

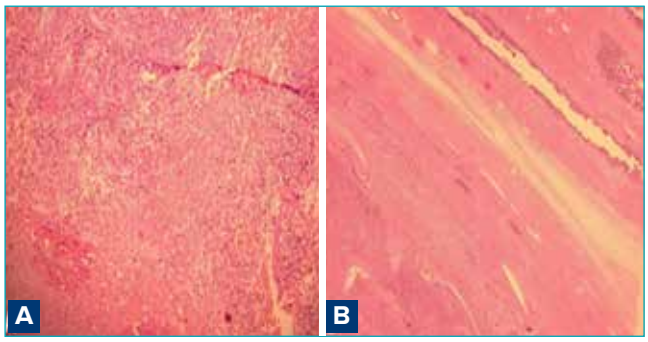

Figure 2: Side-by-side photomicrographs of malignant prostatic gastrointestinal stromal tumour (haematoxylin and eosin [H&E]): **A.** Tumour showing extensive serpentine areas of necrosis; **B.** Tumour with adjacent seminal vesicle.

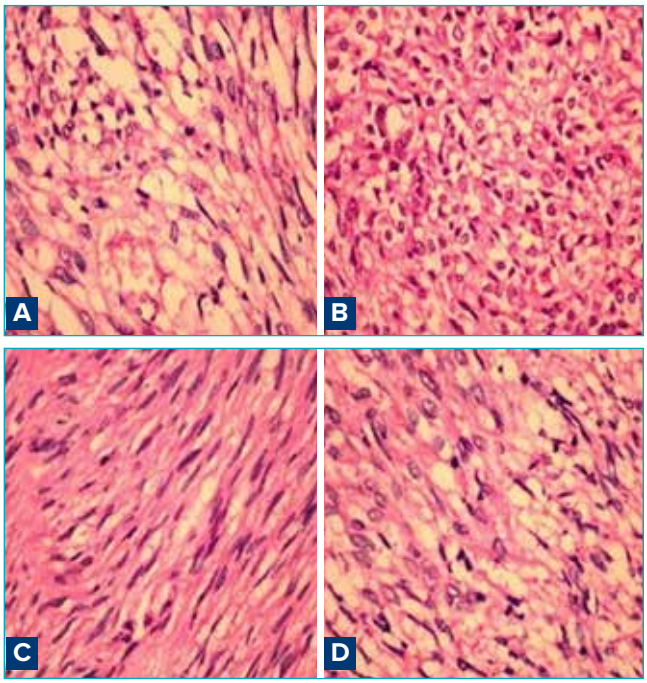

Figure 3: Histopathological features of malignant prostatic gastrointestinal stromal tumour (haematoxylin and eosin [H&E], ×600): **A.** Tumour showing atypical mitotic figures; **B.** Epithelioid tumour cell morphology; **C.** Spindle cell pattern arranged in fascicles; **D.** High-grade tumour area with marked cellularity and nuclear atypia.

An initial diagnosis of malignant spindle cell tumour was considered. Immunohistochemical evaluation showe:

- Desmin: Negative (Figure 4A)
- CD117 (c-KIT): Positive (Figure 4B)
- DOG-1: Positive (Figure 4C)
- S-100: Negative (Figure 4D)
- CD34: Positive
- SMA: Negative

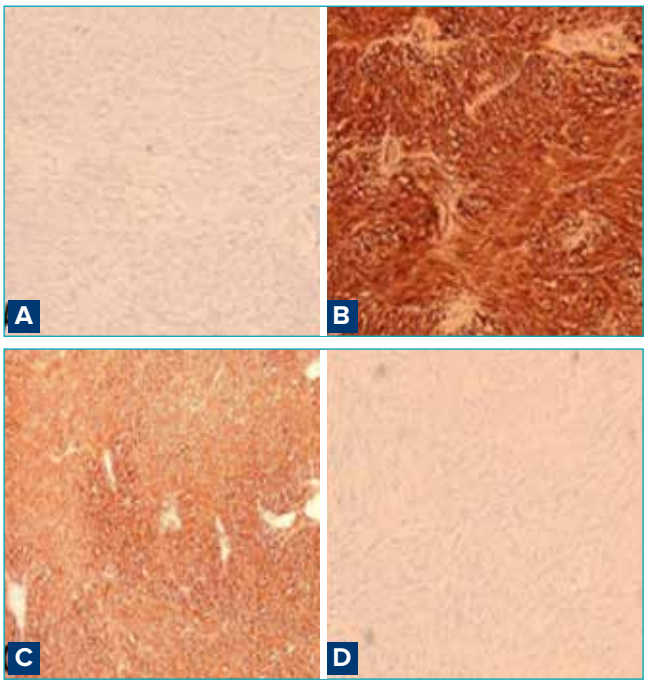

Figure 4: Immunohistochemical profile of prostatic gastrointestinal stromal tumour: **A.** Desmin: Negative; **B.** CD-117 (c-KIT): Diffuse strong cytoplasmic and membranous positivity in tumour cells; **C.** DOG-1: Diffuse strong cytoplasmic positivity confirming gastrointestinal stromal tumour lineage; **D.** S-100: Negative.

Based on these findings, a final diagnosis of malignant GIST was established.[4,5]

Discussion

The cell of origin of GIST is ICC, the pacemaker cell of the gastrointestinal muscles. It is known that ICC expresses the gene product of KIT (CD117), a proto-oncogene that encodes the receptor tyrosine kinase, Kit. Because these ICC cells may exist in diverse anatomic sites, it is possible to explain EGIST of unusual sites such as those of the uterus, vagina, prostate, and bladder.[6]

Prostatic GIST is an exceptionally rare variant of EGIST, with very few cases reported in the literature. Its presentation is often delayed and dominated by obstructive urinary and bowel symptoms due to its pelvic location.[2]

The main clinical manifestations of patients with primary EGIST of the prostate include urinary frequency, urgency, dysuria, acute urinary retention, vague perineal pain, and constipation or a combination of one or more of these symptoms. Compared with other GISTs, EGIST masses can grow to a larger volume in the peritoneal cavity and retroperitoneal space, so cases of EGIST are difficult to detect early and need prompt imaging techniques.[7]

The presented case involved a large mass in the prostate gland, requiring differential diagnosis from other prostatic malignancies such as prostate cancer. However, unlike prostate cancer, which occurs in the elderly, EGISTs can also affect younger patients.

Imatinib is the first-line therapy for unresectable, recurrent, or metastatic GIST and can be used as neoadjuvant or adjuvant therapy.[3] While long-term imatinib therapy may lead to tumour regression, resistance or progression can occur, as seen in the presented case. Therefore, radical prostatectomy is the most common form of surgical management. As lymph node metastasis is not common, extensive lymph node dissection is not required.

Malignant features such as high mitotic index, necrosis, cellular atypia, and large tumour size are associated with poor prognosis.[8] In such cases, aggressive surgical resection with negative margins remains essential for symptom control and disease management.

The presented case highlights the importance of timely surgical intervention in patients with progressive symptoms despite prolonged targeted therapy, and the need for a multidisciplinary approach in managing rare pelvic GISTs.

Conclusion

Prostatic GIST is a rare and aggressive tumour that may present with acute intestinal obstruction and urinary retention. Although TKIs play a crucial role in management, surgery remains indispensable in cases of malignant transformation or life-threatening obstructive complications. Early recognition and comprehensive treatment are key to improving outcomes.

Chakradhar Singh, Shashank Chaudhary, Anju Shukla. Malignant Prostatic Gastrointestinal Stromal Tumour Presenting with Acute Intestinal Obstruction and Urinary Retention: A Rare Case Report. MMJ. 2026, March. Vol 3 (1).

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Severe Catatonia Presenting with Seizure, Autonomic Storm and Reversible Cardiomyopathy: A Diagnostic Challenge in the Intensive Care Unit

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Abstract:

Catatonia is a complex neuropsychiatric syndrome that may present with a variety of motor, behavioural, and autonomic abnormalities. Severe catatonia as presented in this case, may mimic organic, infectious, or toxicological emergencies leading to delays in diagnosis. We describe a 37-year-old woman with major depressive disorder receiving multiple antidepressants who presented with profuse sweating, involuntary movements, and generalised stiffening. She developed a seizure with subsequent respiratory compromise requiring intubation. Initial evaluation revealed autonomic instability, severe left ventricular dysfunction, high anion gap metabolic acidosis, and bilateral pneumonitis on imaging. A comprehensive workup for infectious encephalitis, autoimmune disease, serotonin syndrome, toxic ingestion, and structural brain pathology was negative. Despite empirical antibiotics and steroids, her neurological status as assessed by the Glasgow Coma Scale (GCS) remained poor with no eye opening, or motor response, and an unassessable verbal response due to intubation (E1VtM1). After organic causes were excluded, a trial of lorazepam and olanzapine was initiated with gradual and sustained neurological improvement, confirming the diagnosis of catatonia. She was successfully extubated on Intensive Care Unit (ICU) Day 11 and discharged from the ICU in stable condition. Catatonia may present with autonomic dysregulation and critical illness, mimicking life-threatening medical conditions. Early recognition and a lorazepam challenge are essential to prevent unnecessary delays in treatment.

Key words: Catatonia, Autonomic Dysfunction, Lorazepam Challenge, Depression, Intensive Care Unit (ICU), Encephalopathy.

Introduction

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines catatonia as the presence of three or more of the following — catalepsy, waxy flexibility, stupor, agitation, mutism, negativism, posturing, mannerisms, stereotypies, grimacing, echolalia, and echopraxia.[1] Catatonia in the Intensive Care Unit (ICU) is often misdiagnosed mainly because of the non-specific symptoms and resemblance with sepsis and other sepsis mimics, such as thyroid storm, as well as a lack of familiarity with the syndrome. The approach in such cases is often based on a search for an organic cause. There is a lack of literature on catatonia and its management in the ICU, with very few case series describing its occurrence in the ICU and the need for awareness among intensivists.[2,3]

Case Report

A 37-year-old woman with major depressive disorder receiving bupropion, escitalopram and cariprazine presented to the emergency department with profuse sweating, involuntary body movement and generalised stiffening for 30 minutes. She had been in a low mood for two days prior to presentation.

On examination, she had sinus tachycardia with a pulse rate of 150 beats per minute (bpm), hypertension (blood pressure [BP] 190/100 mmHg), tachypnoea, and diaphoresis. Systemic examination revealed bilateral crepitations in the chest, laboured breathing, and oxygen saturation of 90% on room air. The patient developed a seizure with a threatened airway. Antiepileptics were administered, and she was intubated in the emergency department in view of a poor Glasgow Coma Scale (GCS) score and impending airway compromise. Initial arterial blood gases showed high anion gap metabolic acidosis with a lactate level of 15 mmol/L, likely secondary to ongoing seizure activity.

Her past history was significant for infertility treatment for six to seven years, and a history of laparoscopic cholecystectomy one month prior. She had also been experiencing a low mood for the preceding two days. There was a history of antidepressant dose modification 15 days prior to presentation. She had been prescribed bupropion, escitalopram and cariprazine as prescribed by her psychiatrist.

Initial differentials included unknown drug ingestion, serotonin syndrome, encephalitis or meningitis, and stroke. The patient was shifted to the ICU for further management. On arrival at the ICU, she developed hypotension. Point-of-care ultrasound (POCUS) revealed severe left ventricular (LV) dysfunction and a plethoric inferior vena cava (IVC). Vasopressors were initiated, and invasive positive pressure ventilation (IPPV) was continued with fentanyl sedation. She was started on empirical antibiotics. A comprehensive panel of tests and imaging studies was planned to rule out the differential diagnoses. A psychiatry consultation was obtained, and all the antidepressants were withheld.

Initial investigations showed a total leukocyte count of 27,000/µL with neutrophilic predominance, and normal liver and kidney function tests. Magnetic resonance imaging (MRI) of the brain with contrast was normal, with no focal parenchymal or intracranial abnormalities. Lumbar puncture was performed, which was normal, and the cerebrospinal fluid (CSF) encephalitis panel was negative. A tropical fever workup was negative. A urine drug assay to rule out poisoning or overdose was normal. Creatine kinase was 787 IU/L, making serotonin syndrome less likely.

High-resolution computed tomography (HRCT) of the thorax showed patchy and confluent areas of ground-glass opacities and consolidative changes in both upper and lower lobes. Based on these findings, antibiotic coverage was broadened to include atypical organisms. Mild elevation of cardiac biomarkers was noted, and two-dimensional (2D) echocardiography revealed poor LV function with global hypokinesia and Grade II diastolic dysfunction. Digoxin was added in view of tachycardia and poor LV function, and a diuretic infusion was started.

Ultrasound of the abdomen was performed to identify an alternative source of sepsis and showed Grade II fatty liver. Blood, tracheal, and urine cultures were negative. Serum ammonia levels and thyroid profile were within normal limits. The Venereal Disease Research Laboratory (VDRL) test was negative.

On ICU Day 2, the patient's haemodynamics improved. Autonomic dysfunction was noted in the form of pinpoint pupils, sweating, and labile blood pressure. However, in view of a persistently poor GCS, electroencephalography (EEG) was performed and was normal. Bronchoscopy was done, and bronchoalveolar lavage (BAL) samples were obtained, which were sterile.

The patient was empirically started on pulse steroid therapy, as there had been no improvement in GCS over the preceding 72 hours. However, she remained unconscious and unresponsive for the next three days despite steroids. The anti-N-methyl-D-aspartate (NMDA) receptor antibody panel was negative.

Since all organic and metabolic causes had been ruled out, the patient was started on intravenous lorazepam, amantadine, and olanzapine, considering the possibility of catatonia.

During the following days, the patient remained unresponsive with a GCS of E1VtM1 — no eye opening, an unassessable verbal response due to intubation, and no motor response — while receiving mechanical ventilation

and supportive ICU care. Repeat echocardiography showed improvement in LV function.

On ICU Day 7, the patient developed left lung collapse associated with hypoxaemia. Bronchoscopy and lavage were performed and showed growth of *Acinetobacter baumannii*, for which minocycline was added. A plan for tracheostomy was discussed with family members in view of persistently poor GCS and ventilator-associated pneumonia.

However, over the next 48 hours, her GCS improved. On ICU Day 10, the patient underwent a spontaneous breathing trial, which she tolerated well. Extubation was deferred for a further 24 hours due to upper airway oedema. A short course of dexamethasone was administered, and the patient was successfully extubated on ICU Day 11. She required non-invasive ventilation (NIV) support for the next 48 hours due to basal atelectasis and obesity. Lorazepam and olanzapine were gradually tapered. As she showed neurological recovery with lorazepam and olanzapine therapy, the diagnosis of catatonia was confirmed.

After a successful swallowing assessment, she was started on oral feeding. The patient was shifted to the ward in stable condition after four days.

Discussion

In mechanically ventilated patients, the application of diagnostic tools such as the Bush–Francis Catatonia Rating Scale is often not feasible, which may hinder timely recognition of catatonia. In this case, the patient presented primarily with non-specific features of autonomic dysfunction, leading to a diagnostic delay and a subsequent delay in initiating targeted therapy.[4] After ruling out the common causes of altered mental state, including serotonin syndrome, the diagnosis of catatonia was considered and was treated accordingly. This highlights the importance of considering catatonia as a potential differential diagnosis in critically ill patients who present with clinical features resembling sepsis, especially when the clinical course is atypical or unresponsive to standard management.

Conclusion

This case illustrates the diagnostic challenge of severe catatonia presenting with autonomic instability, seizures, and reversible cardiomyopathy in the intensive care setting. The overlap with infectious and metabolic emergencies can delay diagnosis and treatment. A high index of suspicion, early psychiatric involvement, and a timely lorazepam challenge are crucial for accurate diagnosis and effective management, potentially reducing morbidity and ICU stay.

Richa Lohani, Nitin Garg, Shobhit Garg. Severe Catatonia Presenting with Seizure, Autonomic Storm and Reversible Cardiomyopathy: A Diagnostic Challenge in the Intensive Care Unit. MMJ. 2026, March. Vol 3 (1).
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Adrenal Cortical Adenoma with Histoplasmosis in an Immunocompetent Host – An Incidental Discovery

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Abstract:

Adrenal involvement in histoplasmosis is typically associated with disseminated infection in immunocompromised individuals. Isolated adrenal histoplasmosis in immunocompetent hosts is rare and frequently mimics neoplastic pathology. A 47-year-old immunocompetent male presented with an incidentally discovered 7 cm left adrenal mass. Hormonal evaluation was unremarkable. He underwent robotic adrenalectomy with cholecystectomy for concurrent gallstones. Gross pathology revealed a well-encapsulated adrenal mass with necrosis. Microscopy demonstrated an adrenocortical adenoma with extensive granulomatous inflammation containing numerous intracellular budding yeasts morphologically consistent with *Histoplasma capsulatum*. The patient had no systemic symptoms of fungal infection. This case highlights the diagnostic challenge posed by unilateral adrenal histoplasmosis in immunocompetent individuals. Histopathology remains essential for diagnosis, particularly when radiologic and biochemical features suggest an adrenal neoplasm. Awareness of this entity is crucial to avoid misdiagnosis and to guide appropriate postoperative management.

Key words: Histoplasmosis, Immunocompetent, Fungal Infection, Adrenal Gland.

Introduction

Histoplasmosis is a systemic fungal infection caused by *Histoplasma capsulatum*, a dimorphic fungus endemic in several regions worldwide, particularly areas rich in bird and bat guano.[1,2] Infection typically occurs via inhalation of microconidia, and while pulmonary involvement is most common, dissemination may occur in susceptible hosts. Isolated adrenal histoplasmosis (IAH) in immunocompetent individuals is distinctly uncommon. Most reported cases describe bilateral adrenal enlargement, whereas unilateral disease may mimic an adrenal neoplasm clinically and radiologically.[3–5]

We report an unusual case of unilateral adrenal histoplasmosis incidentally identified in an immunocompetent adult undergoing adrenalectomy for a presumed cortical neoplasm.

Case Report

A 47-year-old male with no significant past medical, personal, or family history presented with an incidentally detected left adrenal mass measuring 7.0 × 5.0 cm. The lesion was discovered during evaluation for unrelated symptoms. He also had multiple gallstones identified on imaging. He denied fever, weight loss, respiratory symptoms, or features of endocrine dysfunction.

Clinical evaluation

Physical examination was unremarkable. Patient had a history of old malunited pelvic injury with non-union of

sacrum and sacral nerves 2–4 (S2–S4) nerve injury; for which he underwent open reduction and internal fixation with bone grafting and sacroiliac fixation in the year 2018.

Computed tomography (CT) findings showed central hypodensity and peripheral enhancement. Functional adrenal evaluation including serum cortisol, 24-hour urinary free cortisol, urinary vanillylmandelic acid (VMA), aldosterone–direct renin ratio (ARR), 24-hour urinary metanephrine, and dehydroepiandrosterone sulphate (DHEA-S) was within normal limits. These findings effectively excluded pheochromocytoma and other hormonally active adrenal tumours.

A large unilateral adrenal mass suspicious for a neoplasm was identified, leading the surgical team to recommend excision, with a provisional diagnosis of a non-functional adrenocortical adenoma.

Hospital course

The patient underwent left robotic adrenalectomy and cholecystectomy. Intraoperatively, a 7–8 cm left adrenal tumour and gallstones were identified. The postoperative period was uneventful, and the patient was discharged in stable condition on postoperative Day 3 with advice for follow-up after receipt of the histopathology report.

Histopathology

Gross examination of the left adrenal specimen showed dimensions of 11.0 × 9.0 × 5.0 cm and a weight of 180 g. The cut surface revealed a well-encapsulated yellow mass measuring 7.0 × 4.5 × 5.5 cm, with focal areas of necrosis and haemorrhage.

On microscopy, sheets of enlarged cells with distinct cell borders and abundant foamy cytoplasm, resembling zona fasciculata, were observed, along with extensive serpentine areas of necrosis surrounded by granulomatous inflammation (Figure 1A). The inflammatory infiltrate comprised foam cells, multinucleated giant cells, neutrophils, lymphocytes, and plasma cells (Figure 1B). Numerous small (2–5 µm), uniform, oval, budding yeast forms with eccentric nuclei were clustered within histiocytes, morphologically consistent with *Histoplasma capsulatum*. Periodic acid–Schiff (PAS) and Grocott-Gomori methenamine silver (GMS) stains confirmed the diagnosis of adrenal histoplasmosis (Figures 2 and 3).

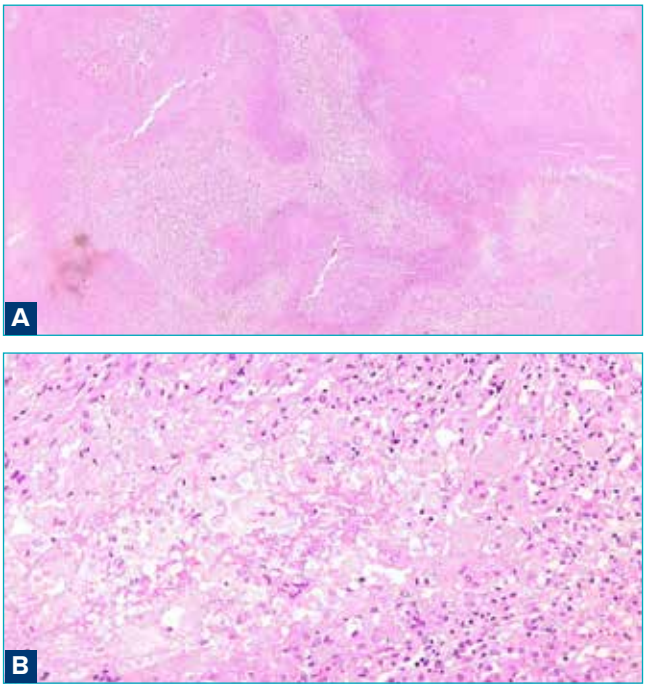

Figure 1: Haematoxylin and Eosin (H&E) stain: **A.** Tissue section showing extensive areas of serpiginous necrosis with surrounding granulomatous inflammation within the adrenal lesion (H&E, ×10); **B.** Demonstrating sheets of histiocytes, multinucleated giant cells, and foamy macrophages. Numerous small oval yeast forms are visible within the cytoplasm of histiocytes. (H&E, ×10).

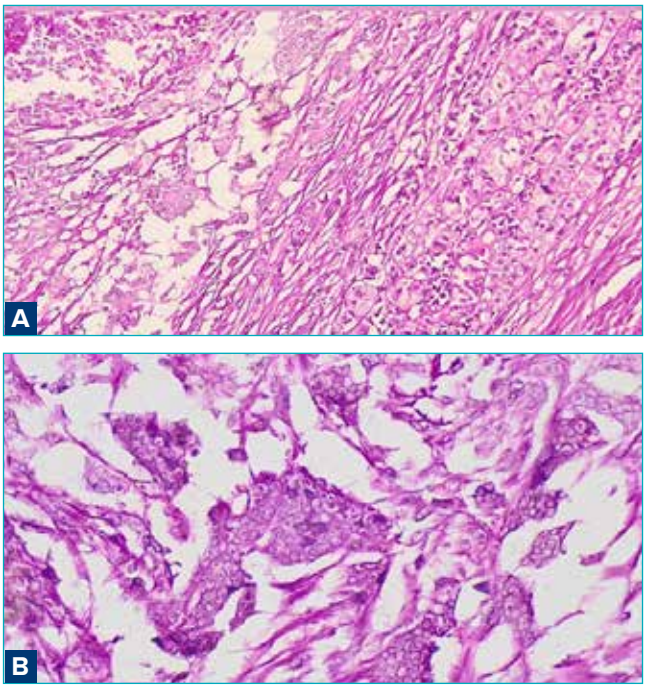

Figure 2: Periodic Acid–Schiff (PAS) stain: **A.** PAS stain demonstrating intracellular yeast forms of *Histoplasma*, which appear magenta and are concentrated within histiocytes and areas of necrotic debris (PAS, ×20); **B.** Higher power showing clusters of small budding fungal yeasts with characteristic eccentric nuclei, consistent with *Histoplasma capsulatum* (PAS, ×40).

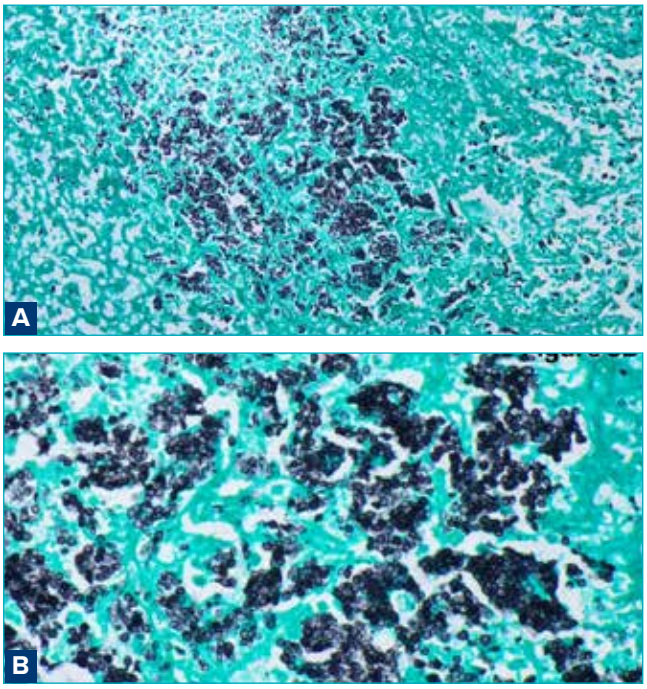

Figure 3: Grocott-Gomori methenamine silver (GMS) stains: **A.** GMS stain highlighting numerous 2–5 µm Histoplasma yeast forms, which appear as black, round to oval organisms clustered within histiocytes and necrotic tissue (GMS, ×20); **B.** Lower power GMS view showing dense aggregates of fungal organisms distributed within areas of granulomatous inflammation and necrosis (GMS, ×40).

Discussion

Adrenal involvement in histoplasmosis is typically associated with progressive disseminated histoplasmosis in immunocompromised hosts, including patients with human immunodeficiency virus (HIV), transplant recipients, or those on long-term corticosteroids.[1,2,6] In contrast, isolated adrenal histoplasmosis in an immunocompetent individual, as in this case, is distinctly unusual but increasingly recognised.[5,7]

The adrenal glands' rich sinusoidal vasculature and lipid-rich cortex create an environment conducive to fungal proliferation.[8,9] While bilateral adrenal involvement often leads to adrenal insufficiency, unilateral disease may remain subtle or entirely asymptomatic.[10] In this patient, the infection was discovered incidentally, highlighting the diagnostic challenges posed by atypical presentations.

Radiologically, adrenal histoplasmosis can mimic primary adrenal malignancies, metastases, or granulomatous diseases due to heterogeneous enhancement, necrosis, or occasional calcification.[6,10] Hormonal assays are essential to exclude functional adrenal tumours; all results were normal in this case.

Histopathology remains the gold standard, with the presence of intracellular budding yeasts serving as the defining diagnostic feature.[10]

Management of adrenal histoplasmosis is individualised. Disseminated disease warrants prolonged antifungal therapy, typically itraconazole or amphotericin B, depending on severity.[1,6] In contrast, incidentally detected, localised infections following complete surgical excision may not require additional systemic treatment. Infectious disease consultation is recommended to guide individualised management decisions.

Conclusion

Isolated adrenal histoplasmosis in immunocompetent individuals is a rare entity that can closely mimic adrenal neoplasms on clinical, biochemical, and radiological evaluation. This case underscores the importance of considering infectious aetiologies, particularly histoplasmosis, in the differential diagnosis of unilateral adrenal masses, even in the absence of systemic symptoms or immunosuppression. Definitive diagnosis relies on histopathological examination with appropriate fungal stains, as imaging and hormonal studies alone may be misleading. Awareness of this uncommon presentation is essential for accurate diagnosis, avoidance of overtreatment, and appropriate postoperative management, including judicious use of antifungal therapy in selected cases.

Aditi Senapati, Anju Shukla, Rahul Yadav. Adrenal Cortical Adenoma with Histoplasmosis in an Immunocompetent Host – An Incidental Discovery. MMJ. 2026, March. Vol 3 (1).

DOI: https://doi.org/10.62830/mmj3-01-18

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Delayed Serum Sickness after Immunosuppressive Therapy with Horse Antithymocyte Globulin in Severe Aplastic Anaemia: A Case Report

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Abstract:

Serum sickness (SS) is an immune-complex–mediated illness that frequently occurs in patients after polyclonal antibody therapy, such as thymoglobulin. Although SS has been described secondary to thymoglobulin therapy in adults, the administration of horse antithymocyte globulin (ATG) has been associated with SS in 1% to 10% of cases. Early recognition and accurate diagnosis are key for managing thymoglobulin-induced SS, as treatment is highly effective in achieving good outcomes.

Key words: Antithymocyte Globulin (ATG), Neutropenia, Serum Sickness (SS).

Introduction

Severe acquired aplastic anaemia (AA) is a life-threatening disorder characterised by pancytopenia and bone marrow hypocellularity.[1] T-cell-mediated destruction of haematopoietic progenitor and stem cells is implicated in the pathogenesis of most cases. Overall, 60%–70% of patients with AA achieve a haematological response after a single course of immunosuppressive therapy (IST).

The most effective IST regimen consists of horse antithymocyte globulin (hATG) in combination with ciclosporin A, which has been shown to be superior to either agent alone or to combinations other than hATG with ciclosporin.[2,3] ATG is a heterologous antiserum derived from animals immunised with human lymphocytes. Most large clinical trials in AA have utilised hATG, which is therefore considered the standard for AA treatment. As foreign proteins, antithymocyte globulin (ATG) preparations can elicit strong immune responses in humans.[4] The formation of circulating immune complexes between foreign antigens and host antibodies may result in tissue deposition, leading to serum sickness (SS), which typically occurs around 7–10 days after initiation of ATG therapy.[4]

Case Report

A 50-year-old female presented with complaints of generalised weakness and decreased appetite. There was no history of fever or bleeding from any site.

A complete blood count (CBC) showed haemoglobin (Hb) of 3.8 g/dL, total leukocyte count (TLC) of 5,570/uL, platelet count of 50,000/uL, and neutrophils of 36%. Bone marrow examination was suggestive of pancytopenia with severe neutropenia, and bone marrow biopsy revealed < 10% cellularity. Paroxysmal nocturnal haemoglobinuria (PNH) testing was negative. She received a total of seven units of blood transfusion over two months at her local centre.

She was started on ciclosporin, a thrombopoietin receptor agonist, and danazol; however, danazol was discontinued after 15 days. After two months of therapy, she came to our centre, where investigations showed Hb of 7 g/dL, TLC of 6,810/uL, platelet count of 33,000/uL, and neutrophils of 43%. Liver and kidney function tests were normal, and viral markers were negative. Since she did not show any significant improvement, she was started on hATG (Thymogam) at a dose of 40 mg/kg/day for four days, along with ciclosporin 4.5 mg/kg/day and eltrombopag 150 mg daily.

Prior to ATG infusion, premedication with antihistamines, hydrocortisone, and antipyretics was administered. During the first day of ATG infusion, she developed fever with rigors without hypotension, for which antipyretics and hydrocortisone were repeated. She tolerated the remaining three days of ATG infusion without complications and was discharged on Day 5. At discharge, she was continued on prednisolone 1 mg/kg/day along with other supportive medications. Twelve days after intravenous (IV) thymoglobulin therapy, she presented with chills, lip swelling, myalgias, right eye conjunctival haemorrhage, rash over both legs, and bilateral sole pain with itching (Figure 1A and B).

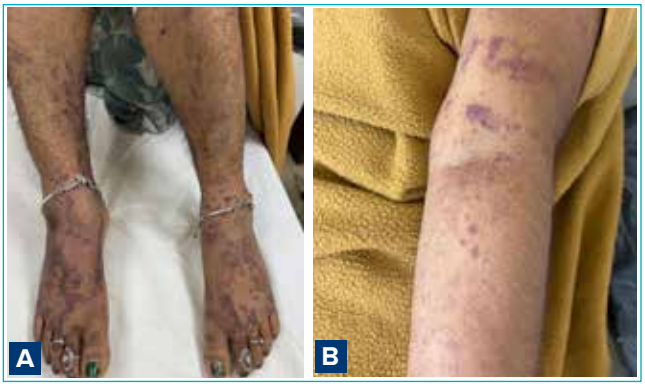

Figure 1A and B: Initial presentation of serum sickness.

She was diagnosed with SS secondary to IV ATG and was started on IV methylprednisolone 120 mg stat, followed by prednisolone 2 mg/kg/day for three days, with subsequent tapering. By Day 3 and Day 6 of steroid therapy, she showed marked symptomatic improvement (Figures 2 and 3) and is continuing on regular outpatient follow-up.

Figure 2: On Day 3 of steroid therapy.

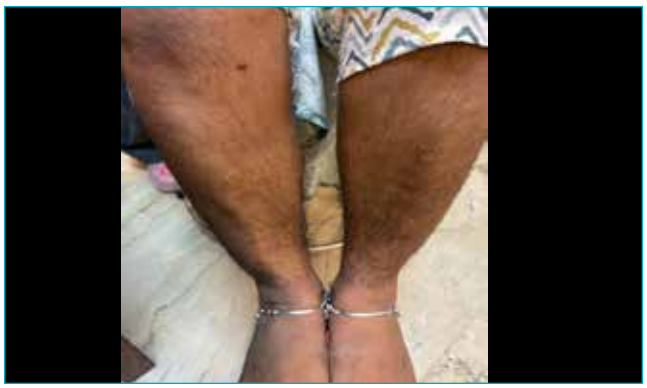

Figure 3: On Day 6 of steroid therapy.

Discussion

ATGs are antibodies used for immunosuppression against human T cells and are typically derived by injecting human thymocytes into animals such as horses or rabbits.[5] ATG is believed to protect allografts by reducing inflammatory damage, modulating allorecognition processes, and attenuating the immune response, while increasing sensitivity to oral maintenance IST.[6]

The administration of rabbit or horse ATG has been associated with SS in approximately 1%–10% of cases.[4,7,8] Risk factors include older age, higher levels of heterologous protein, type of ATG preparation, prior exposure to the antigen or source animal, and a history of hypergammaglobulinaemia or cryoglobulinaemia.[4] SS is characterised by fever, lymphadenopathy, pruritic rash, polyarthralgia, and polyarthritis, typically developing 7–10 days after exposure to the exogenous antigen.[6] A maculopapular or urticarial rash is usually the earliest manifestation. In severe cases, immune-complex–mediated small-vessel vasculitis may lead to glomerulonephritis and tissue injury.[6] Angioedema may also be present. Polyarthritis commonly involves

large joints but may occasionally affect the spine or temporomandibular joint. The clinical presentation can be nonspecific and may mimic acute infections or rheumatologic conditions, leading to delays in diagnosis. SS is primarily a clinical diagnosis, and treatment should not be delayed while awaiting laboratory confirmation.[6]

SS is generally self-limiting and resolves once the inciting antigen is cleared. Due to its rarity, current treatment recommendations are based on clinical experience and case reports. Discontinuation and avoidance of re-exposure to the offending agent are essential. Mild cases may be managed symptomatically with non-steroidal anti-inflammatory drugs (NSAIDs) for fever and arthralgia, antihistamines, and topical corticosteroids for pruritic rash.[6] Severe cases — especially those with disabling symptoms, haemodynamic instability, glomerulonephritis, or vasculitis — require high-dose oral or IV corticosteroids. These are typically administered for three days, followed by a rapid taper, with symptom resolution expected within 10 ± 2 days.[6]

Conclusion

Severe acquired AA remains a life-threatening condition in which IST with hATG and ciclosporin represents the standard of care for patients who are not candidates for stem cell transplantation.[1,2] While ATG-based regimens are highly effective, they are associated with immune-mediated adverse effects such as SS.[4] Prompt clinical recognition and early initiation of high-dose corticosteroids resulted in rapid symptom resolution and a favourable outcome.[6]

Krishna Kant Singh. Delayed Serum Sickness after Immunosuppressive Therapy with Horse Antithymocyte Globulin in Severe Aplastic Anaemia: A Case Report. MMJ. 2026, March. Vol 3 (1).
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A Race Against Time: Collaborative Emergency and Cardiothoracic and Vascular Surgery: Led Endovascular Repair in Traumatic Aortic Transection with Polytrauma

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Abstract:

Blunt traumatic aortic transection is one of the most lethal injuries following high-energy deceleration trauma. Early diagnosis, prompt haemodynamic stabilisation, and seamless coordination between emergency medicine and cardiothoracic and vascular surgery (CTVS) teams are critical to survival. A 38-year-old male presented to the emergency department after a high-velocity road traffic accident with multiple injuries, including a right femoral deformity and upper abdominal pain radiating to the back. The emergency physician initiated advanced trauma life support (ATLS)–based resuscitation and ordered urgent computed tomography (CT) polytrauma imaging, which revealed a contained rupture of the descending thoracic aorta, 4.5 cm distal to the left subclavian artery, associated with mediastinal haematoma compressing the oesophagus, mild haemopericardium, bilateral pulmonary contusions, and a comminuted right femoral fracture. Recognising the critical nature of the injury, the emergency team activated the multidisciplinary trauma protocol, involving the CTVS and orthopaedic teams. Following rapid stabilisation, thoracic endovascular aortic repair (TEVAR) using a Medtronic Endurant stent graft (24/24/100 mm) was performed through right femoral artery exposure, achieving immediate haemodynamic control. Subsequently, the patient underwent open reduction and internal fixation (ORIF) for the femur fracture. Postoperatively, mild hypoxaemia due to fat embolism was managed conservatively. The patient made a full recovery, maintaining stable haemodynamics and oxygenation at discharge. This case highlights how rapid emergency leadership and precise CTVS intervention can transform an otherwise fatal aortic transection into a survivable event. Early clinical suspicion, timely imaging, and multidisciplinary teamwork remain the cornerstones of modern trauma success.

Key words: Traumatic Aortic Rupture, Thoracic Endovascular Aortic Repair (TEVAR), Emergency Medicine, Cardiothoracic and Vascular Surgery (CTVS), Fat Embolism.

Introduction

Blunt traumatic aortic injury is a time-critical vascular emergency accounting for approximately 20% of deaths following high-speed motor vehicle collisions.[1] It typically occurs at the aortic isthmus, just distal to the left subclavian artery, where the fixed and mobile segments of the aorta meet.[2] While the majority of patients succumb

at the scene, those who reach the hospital alive have a limited window for diagnosis and intervention. The emergency physician's role is pivotal — ensuring early recognition, stabilisation, and activation of a coordinated trauma response involving the cardiothoracic and vascular surgery (CTVS) team for definitive repair.[3] With the advent of thoracic endovascular aortic repair (TEVAR), outcomes in blunt trauma aortic injury have improved substantially compared to open surgical approaches, reducing mortality, morbidity, and recovery time.[4-6] This case exemplifies outstanding teamwork between emergency medicine and CTVS teams, showcasing how time-sensitive decision-making and multidisciplinary precision led to survival from a near-fatal injury.

Case Report

Initial presentation and assessment

A 38-year-old male was brought to the emergency department following a high-energy two-wheeler accident. On arrival, he was conscious and oriented (Glasgow Coma Scale [GCS] 15/15) and haemodynamically stable.

Primary survey: No airway compromise, equal bilateral breath sounds, no external bleeding.

Secondary survey: Scalp abrasions, no abdominal tenderness, and right thigh deformity with shortening, suggesting femoral fracture. The emergency medicine physician initiated advanced trauma life support (ATLS)–based stabilisation, including oxygen supplementation, fluid resuscitation and blood transfusion.

Imaging and diagnostic findings

Contrast-enhanced computed tomography (CECT) polytrauma revealed:

- **Aorta:** Acute transection with limited dissection 4–6 cm distal to the left subclavian artery, forming a contained pseudoaneurysm with mediastinal haematoma compressing the oesophagus
- **Thoracic findings:** Mild haemopericardium, bilateral pulmonary contusions, and thrombus extending to the pulmonary artery bifurcation
- **Brain:** Small bilateral frontal contusions without mass effect
- **Musculoskeletal:** Comminuted right femoral shaft fracture with posterior displacement

Emergency and surgical management

Recognising the imminent risk of rupture, the emergency medicine team activated the multidisciplinary trauma protocol, alerting the CTVS, orthopaedics, and neurosurgery teams. After stabilisation, the patient was shifted to the hybrid operating suite for emergency TEVAR on 27th September 2025.

Procedure details

- **Access:** Right femoral artery open exposure and left femoral artery catheterisation
- **Device:** Medtronic Endurant stent graft (24/24/100 mm)
- **Result:** Successful sealing of the pseudoaneurysm; no endoleak; haemodynamics normalised intraoperatively

The patient was extubated the next morning and remained stable under intensive monitoring. Neurosurgical management of frontal contusions was conservative. After stabilisation, open reduction and internal fixation (ORIF) with intramedullary nailing of the right femur was performed by the orthopaedics team. Within 30 hours post-ORIF, the patient developed irritability and desaturation. Computed tomography pulmonary angiography (CTPA) ruled out pulmonary embolism; fat embolism syndrome was diagnosed clinically. Conservative management with oxygen, fluids, and corticosteroids led to steady improvement. The patient was discharged in a fully alert and haemodynamically stable condition, requiring assistance with ambulation.

Discussion

Traumatic aortic transection represents a critical challenge in emergency trauma care. Mortality remains high without rapid diagnosis and intervention.[5] In this case, early recognition by the emergency physician, guided by mechanism-based suspicion, was pivotal. Activation of the hybrid trauma response ensured simultaneous stabilisation and endovascular repair within hours, demonstrating exemplary emergency–CTVS synergy. Endovascular repair (TEVAR) has now replaced open repair as the standard of care for descending thoracic aortic injuries due to its reduced risk of bleeding, paraplegia, and mortality.[7,8] The multidisciplinary collaboration extended beyond surgery — orthopaedic, neurosurgical, and internal medicine teams coordinated seamlessly, allowing

safe sequential management of injuries. Continuous postoperative vigilance for complications like fat embolism was crucial to overall recovery.[9] This case exemplifies modern trauma management principles — speed, system activation, and multidisciplinary precision — that transform outcomes in previously unsurvivable injuries.

Informed Consent

Written informed consent for publication of this case and accompanying clinical details was obtained from the patient and family.

Conclusion

This case demonstrates that timely suspicion, rapid imaging, and coordinated multidisciplinary intervention — led by emergency medicine and executed by the CTVS team — can convert a catastrophic aortic transection into a survival success. The keys to the outcome were time, teamwork, and technical excellence.

Abhijeet Devidas Kayarkar, Chiranjeevi, Dheeraj Nair, Neerav Bansal, Pramod Sharma, Tarun Sikarwar. A Race Against Time: Collaborative Emergency and Cardiothoracic and Vascular Surgery: Led Endovascular Repair in Traumatic Aortic Transection with Polytrauma. MMJ. 2026, March. Vol 3 (1).
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Histoplasmosis – An Infrequent Cause of Fever

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Abstract:

Histoplasmosis is a systemic fungal infection caused by *Histoplasma capsulatum*, commonly seen in immunocompromised or elderly individuals with environmental exposure. A 65-year-old male taxi driver from Gurugram, with a history of diabetes mellitus and hypertension, presented with a 10-day history of high-grade fever, nausea, anorexia, weakness, and unintentional weight loss. Laboratory investigation showed anaemia (haemoglobin [Hb] 9.2 g/dL), hyponatraemia (sodium [Na] 123.7 mEq/L), elevated liver enzymes (alkaline phosphatase [ALP] 576 U/L, gamma-glutamyl transferase [GGT] 207 U/L), hypoalbuminaemia, and markedly raised C-reactive protein (CRP) 157.7 mg/L. Imaging revealed right middle zone consolidation, mild pleural and pericardial effusions, and hepatosplenomegaly. Serological and microbiological tests for dengue, malaria, typhoid, and viral hepatitis were negative. The patient showed partial improvement with antibiotics; however, fever recurred, and bone marrow aspiration (BMA) demonstrated intracellular yeast-like organisms morphologically consistent with *H. capsulatum*.

Key words: Histoplasmosis, *Histoplasma capsulatum*, Seizures, Liposomal Amphotericin B, Itraconazole.

Introduction

Histoplasmosis is a global disease, endemic to regions across all six inhabited continents. Most epidemiological research on histoplasmosis has been conducted in the United States, where the infection has a broad geographic distribution. Recent syntheses of multiple studies have demonstrated a scattered global distribution of histoplasmosis, with case series reported from Brazil, South Africa, and India, and isolated cases documented in Central and South America, northern sub-Saharan Africa, Oceania, and Europe.[1] Although Randhawa's 1970 review identified 30 autochthonous cases of histoplasmosis in Southeast Asia, the epidemiology of this fungal infection in the region has remained relatively unexplored.[2]

Histoplasmosis is a systemic fungal infection caused by *Histoplasma capsulatum*, a dimorphic fungus commonly found in soil[3] contaminated with bird or bat droppings. The disease is endemic in certain regions, particularly river valleys and areas with high humidity. Infection occurs primarily through inhalation of fungal spores, which convert to the yeast form within the lungs and may subsequently disseminate throughout the body, especially in immunocompromised individuals.[4,5]

In India, histoplasmosis cases are likely underdiagnosed and under-reported, although areas of high prevalence include the eastern states of West Bengal and Assam, through which the Ganges[3] and Brahmaputra rivers flow. Areas outside these traditional riverine foci, including

several eastern and northern states such as Bihar, Delhi, Haryana, Rajasthan, Punjab, and Uttar Pradesh, have also documented cases.[6] India may therefore represent a region of substantial underdiagnosis.[7] In this study, five individuals, residing in the eastern part of India, were identified with histoplasmosis between December 2022 and April 2024. Notably, all patients were human immunodeficiency virus (HIV)-negative but had underlying comorbidities such as diabetes or renal impairment. While many infections remain asymptomatic or self-limiting, histoplasmosis can present with a wide spectrum of clinical manifestations ranging from mild respiratory illness[8] to severe disseminated disease. Due to its nonspecific symptoms and resemblance to other pulmonary or systemic diseases such as tuberculosis, diagnosis is often challenging and delayed. Early recognition and appropriate antifungal therapy are crucial to prevent complications and improve patient outcomes.

This case study reports the clinical presentation, diagnostic challenges, and management of a patient diagnosed with histoplasmosis, highlighting the importance of considering fungal infections in the differential diagnosis of chronic or unexplained febrile illnesses.

Case Report

A 65-year-old male taxi driver from Gurugram, with a 20-year occupational history involving environmental exposure and known comorbidities of diabetes mellitus and hypertension under moderate control, presented with a 10-day history of intermittent moderate- to high-grade fever, increased urinary frequency, loss of appetite, generalised weakness, and unintentional weight loss. His oral intake had declined, and he felt too weak to even go to the washroom unaided. He had previously been admitted to a nursing home for 7 days, where he received intravenous (IV) antibiotics and supportive care, but showed no clinical improvement.

On examination, the patient appeared dehydrated, anaemic, and icteric, with abdominal distension and right lower lobe crepitations. Laboratory investigations revealed anaemia (haemoglobin [Hb] 9.2 g/dL), hyponatraemia (sodium [Na] 123.7 mEq/L), elevated liver enzymes (alkaline phosphatase [ALP] 576 U/L, gamma-glutamyl transferase [GGT] 207 U/L), hypoalbuminaemia (2.8 g/dL), and elevated C-reactive protein (CRP) (157.7 mg/L). Serological tests for dengue, malaria, typhoid, and viral hepatitis were negative.

X-ray investigation

Chest X-ray and computed tomography (CT) thorax showed bilateral mild pleural effusion with right middle zone consolidation and minimal pericardial effusion. Ultrasonography revealed hepatosplenomegaly. The patient showed partial improvement after 7 days of antibiotic therapy. Based on his clinical condition, he was discharged on cefotaxime (Monocef) and azithromycin (Azee), with advice to follow up. At review, he reported ongoing anorexia and weakness, despite discontinuing his oral hypoglycaemic agents (OHAs). The essential blood profile showed mild improvements.

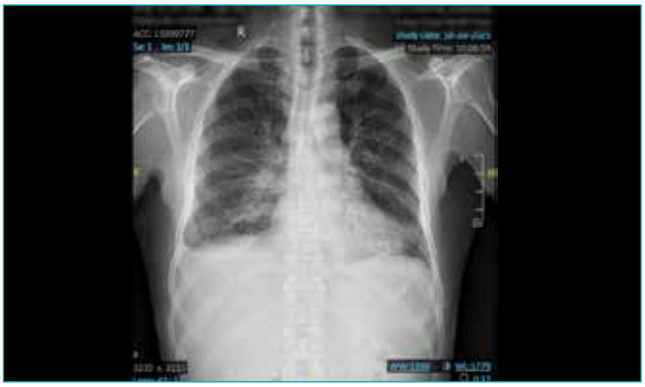

Figure 1: Chest X-ray (Posteroanterior [PA] view) showing prominent bronchovascular markings with inhomogeneous haziness and fibrotic opacities in the bilateral lower lung zones. Blunting of the right costophrenic angle suggests a right-sided pleural effusion.

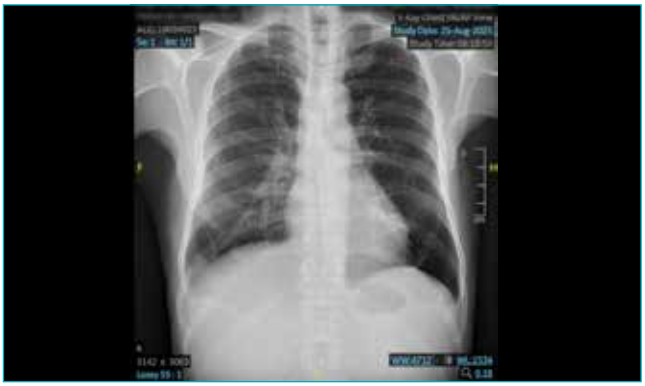

Figure 2: Follow-up chest X-ray (Posteroanterior [PA] view) demonstrating interval resolution of pleural effusion with mild residual prominence of bronchovascular markings. Cardiac silhouette and mediastinal contours are normal.

Nearly one month later, the patient presented with acute neurological symptoms (generalised tonic clonic seizures [GTCS] and unconsciousness) alongside a protracted fever of unknown origin (FUO). Extensive investigations revealed significant systemic pathology, including sepsis, pneumonia, biventricular effusions (pleural and pericardial), pancytopenia (anaemia, leukopenia, thrombocytopenia), electrolyte imbalance, and immune suppression (CD4 count 138.56/μL) Bone marrow findings reassuringly excluded acute leukaemia, suggesting the cytopenias were likely secondary to overwhelming systemic illness (sepsis, chronic disease, nutritional deficits).

Bone marrow investigation

Bone marrow aspiration subsequently demonstrated intracellular yeast-like organisms morphologically consistent with *H. capsulatum* (Figure 3A and B). The patient was commenced on liposomal amphotericin B (3–5 mg/kg IV daily for 1–2 weeks), followed by step-down therapy with itraconazole (200 mg three times daily for 3 days, then 200 mg twice daily for 12 weeks). Follow-up phase showed slow but consistent improvement across all parameters.

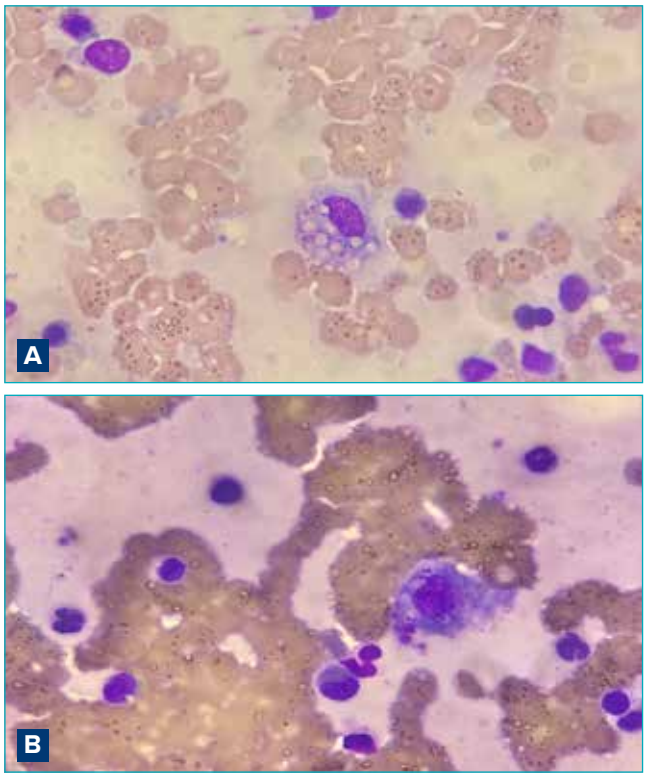

Figure 3A and B: Bone marrow aspiration stains showing ring-like structures within white blood cell cytoplasm, suggestive of histoplasmosis.

Medications for histoplasmosis

Severe cases: Treatment with IV amphotericin B.

Mild to moderate cases: Treatment often begins with itraconazole.

Follow-up therapy: After initial treatment for severe cases, itraconazole was continued as maintenance therapy to prevent relapse. Fluconazole, voriconazole, posaconazole, and isavuconazole may be used as alternatives, particularly for patients with contraindications or side effects to amphotericin B or itraconazole.

Duration: Treatment duration depends on disease severity and the patient's immune status and may extend to one year or longer.

Antiretroviral therapy (ART): For patients with HIV, ART should be started immediately to improve outcomes and support immune recovery.

Relapse risk: Non-adherence to treatment.

Prophylaxis: Itraconazole prophylaxis may be used to prevent histoplasmosis in patients with severely compromised immune systems (CD4 counts < 100/μL) during outbreaks.

Discussion

H. capsulatum was first discovered in 1905 by Samuel T. Darling, but only in the 1930s was it recognised as a widespread infection. *H. capsulatum* is a dimorphic fungus that exists as a mould in the environment and as yeast-like structures with septate hyphae at 37°C in tissues.[9] Human infection occurs following inhalation of the fungus (in the form of microconidia or hyphal fragments), which reaches the alveoli and transforms into the yeast phase. Most infected individuals remain asymptomatic, but symptomatic patients face a substantial risk of mortality and severe morbidity depending on the host's immune status.

Disseminated histoplasmosis is an opportunistic fungal infection caused by *H. capsulatum*, typically seen in immunocompromised or elderly individuals. *Histoplasma* can also exist inside the host in a latent form with the potential for reactivation.[5] Histoplasmosis is often difficult to diagnose because its symptoms are similar to many other illnesses. This fungal infection can

mimic community-acquired pneumonia,[4] tuberculosis, lymphoma, sarcoidosis, and cancer.[5]

The patient presented in this case study, with a background of diabetes mellitus, prolonged fever, hepatosplenomegaly, weight loss, and pulmonary involvement, raising suspicion for disseminated fungal infection. The seizure was likely provoked by the severe systemic illness (sepsis, electrolyte imbalance, or fever). The significant immune suppression is a major concern and likely contributed to the development of multiple infections, including the fungal esophagitis. The coexistence of cardiac (left ventricular failure [LVF]) and hepatic dysfunction (chronic liver disease [CLD]) complicated the management and likely contributed to the effusions and hypoproteinaemia. Bone marrow examination confirmed histoplasmosis, explaining the systemic symptoms and multi-organ involvement. Pleural and pericardial effusions likely resulted from inflammatory and infective processes secondary to dissemination. *Histoplasma* causing hemophagocytic lymphohistiocytosis (HLH) is a severe complication and is associated with high mortality.[11] This is caused by uncontrolled activation of the T cell, resulting in a cytokine storm. The clinical features of HLH mimic that of severe sepsis, and thus, HLH may be missed in the setting of an overwhelming infection.

Histoplasmosis is common along the Mississippi and Ohio river valleys. Only 27% of infectious disease physicians (IDP) observed histoplasmosis outside these endemic areas.[4] The Infectious Diseases Society of America (IDSA) guidelines for the management of histoplasmosis were revised 15 years ago. In a survey, only 46% (253/551) of respondents were patients with histoplasmosis. In regions considered endemic, 82% (158/193) of physicians reported histoplasmosis cases, compared with 27% (95/358) in regions not classically considered endemic ($p < 0.001$).[4,13] In Max Hospital laboratory, around 6 cases have been reported so far, as shared by the pathologist.

Most IDP follow IDSA treatment guidelines, recommending itraconazole[6] for acute pulmonary[7] histoplasmosis (189/253 [75%]), mild-to-moderate disseminated disease (189/253 [75%]), and as step-down therapy for severe disseminated histoplasmosis with (232/253 [92%]) or without (145/253 [57%]) central nervous system involvement. No consensus recommendations were observed for survey questions regarding immunocompromised patients.

A timely diagnosis requires a high index of clinical suspicion by clinicians. Clinicians often rely on a history of exposure to areas considered endemic for *Histoplasma*, such as the Ohio and Mississippi river valleys. Despite substantial evidence of its global presence, *Histoplasma* is still regarded by many as predominantly endemic to specific regions of North America.[4,8] This perception can result in clinicians failing to consider histoplasmosis on a differential diagnosis, contributing to delayed diagnosis and poor outcomes.

IDSA last updated clinical guidelines for the management of histoplasmosis in 2007, using literature from 1st January 1999 through 31st June 2006.[3] Since the release of the guidelines, new treatment options have been developed. Posaconazole was approved by the United States Food and Drug Administration (US-FDA) shortly before the release of the 2007 guidelines, and isavuconazole was approved in 2015. Both maintain in vitro activity against *Histoplasma* even in the setting of fluconazole resistance,[5,10] though there are limited clinical data to support their use in treating histoplasmosis.[11-12] Since the arrival of these new medications, there have been no changes to clinical practice recommendations,[13] and very little new data have been published to guide therapy. Additionally, the population at risk of developing clinically significant histoplasmosis has increased substantially, with millions of patients receiving an ever-expanding variety of immunosuppressive medications and/or living with immunosuppressive medical conditions.

Conclusion

The present case illustrates how disseminated histoplasmosis can mimic other systemic illnesses, highlighting the need for clinical vigilance, timely diagnostic evaluation, and early recognition with prompt antifungal treatment to prevent severe complications and improve patient outcomes.

Rajiv Dang, Krishna Veni, Gaurav Kapoor, Akash Banwari, Sujata Yadav, Nitin Dayal. Histoplasmosis – An Infrequent Cause of Fever. MMJ. 2026, March. Vol 3 (1).

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Nonaka Myopathy: First Report of a Rare Mutation from India (c.1571C>T)

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Abstract:

A young male presented with long-standing foot drop with no significant personal or family history. On detailed clinical examination, the patient exhibited quadriparesis, distal more than proximal, predominantly affecting the lower limbs. Initial evaluation at another centre revealed no significant abnormalities. Examination demonstrated significant distal motor weakness, while sensory examination was unremarkable. Nerve conduction studies and creatine phosphokinase (CPK) levels were normal. The patient refused a muscle biopsy. A possibility of distal myopathy, with a differential diagnosis of Charcot–Marie–Tooth disease, was considered. Whole-exome sequencing was done, which identified c.1571C>T mutation suggestive of Nonaka myopathy. This represents the first report of this rare mutation from India. The prognosis of the disease remains poor, with a possibility of the patient becoming wheelchair bound by 10–15 years of diagnosis. However, the life expectancy remains normal as cardiovascular muscles are not affected. This case emphasises the need for a detailed genetic evaluation for patients diagnosed with rare neurological disorders.

Key words: Nonaka Myopathy, Inclusion Body, Foot Drop.

Introduction

Glucosamine N-acetylmannosamine kinase (GNE) myopathy, also known as Nonaka myopathy or hereditary inclusion body myopathy (HIBM), is a rare and progressive autosomal recessive disorder caused by mutations in the GNE gene.[1] In 1981, Ikuya Nonaka and colleagues described a rare distal myopathy with rimmed vacuoles and lamellar body depositions called distal myopathy with rimmed vacuoles (DMRV) or Nonaka myopathy.[2] In 2001, the Mitrani-Rosenbaum group identified mutations in the GNE gene, which encodes N-acetylglucosamine epimerase/GNE.[3]

Case Report

A 22-year-old male presented with progressive quadriparesis for 7 years. He was born of a non-consanguineous marriage and had an uneventful perinatal and neonatal period. He remained healthy until the age of 15, when he began to lag behind his cousins while walking. He subsequently developed difficulty in clearing the ground while walking, frequent tripping, and an inability to retain his footwear. Over the next 2 years, he developed difficulty in gripping objects with his hands. There was no history suggestive of proximal upper limb weakness, voice change, dysarthria, dysphagia, visual complaints, or facial weakness.

On examination, the patient was moderately built. Higher mental functions were intact. Neck weakness was present. Shoulder strength was normal, while weakness was observed across all the muscles at the elbow and small muscles of the upper limbs symmetrically. Wasting of the small muscles of the hand was noted. The lower limbs had significant weakness at the hip and ankle. The patient was noted to have bilateral foot drop.

A workup revealed normal haemogram, liver and kidney function tests. Creatine phosphokinase (CPK) levels were within normal limits. Electromyography (EMG) was suggestive of a myopathic pattern in both proximal and distal muscles of the upper and lower limbs. Protein electrophoresis and vasculitic profile were unremarkable. A muscle biopsy could not be performed. After obtaining a written consent, the genetic analysis was sent to MedGenome Laboratories. Whole-exome sequencing (WES) showed a heterozygous missence mutation on Exon 9 of the GNE gene on chromosome 9 (c.1571C>T), classified as pathogenic. This resulted in an amino acid substitution of valine for alanine at codon 524 (p.Ala524Val).

Discussion

The observed variation lies within the regulator of optimum kinases (ROK) family domain of the GNE protein. Early-onset cases of GNE myopathy are rare,[1] generally manifesting in the third decade of life. However, early-onset cases before the age of 10 and late-onset cases in the fifth decade of life have also been reported.[4] The primary presentation of the disease is foot drop. Progressively, the patient develops weakness in the hamstrings and hips. However, characteristic sparing of the quadriceps is noted. Investigations may reveal a normal or mildly increased creatine kinase (CK) level. The clinical and biochemical findings of the present case were comparable to those of previously reported cases. Magnetic resonance imaging (MRI) may show short tau inversion recovery (STIR) hyperintensity with fatty infiltration in the affected muscles. Muscle biopsy may show rimmed vacuoles, fibre size variation, amyloid deposition, endomysial fibrosis, and 14–18 nm filamentous inclusions, without inflammatory infiltrates. The patient declined muscle biopsy due to personal reasons.

More than 1,000 individuals with GNE myopathy and about 255 GNE variants have been reported worldwide. Most of the pathogenic variants are missense mutations. Other less common mutations include insertions, deletions, large deletions, intronic mutations, and splice-site mutations. Diagnosis of GNE myopathy is confirmed by homozygous or compound heterozygous GNE gene mutations.[1]

Thirty-one patients with undiagnosed genetic myopathies in the Indian subcontinent were found to harbour a pathogenic GNE mutation. In a review of 207 genetic myopathies from the Indian subcontinent, GNE mutations contributed to 28% of cases.[5] The c.2179G>A (p.Val727Met) variant is a common mutation in India, identified in approximately 75% of GNE-myopathy patients in a reported Indian cohort. It also accounts for 32.7% of all GNE mutations reported in Indian studies, supporting p.Val727Met as a likely founder mutation in the Indian subcontinent.

Khadilkar *et al.* have recently documented an interesting occurrence of homozygous mutation c.1853T>C (p.I618T) (24.5%) in the Rajasthani Jain and Maheshwari communities, a founder mutation encountered exclusively in European Roma Gypsies.[6,7] The present mutation was previously reported in a single patient from mainland China.[8]

Declarations

Informed consent: Written informed consent was taken from the patient.

Conflict of interest: Nil.

Conclusion

GNE mutation is a rare genetic myopathy caused by a missense mutation in the GNE gene. This case represents the first report of the c.1571C>T mutation from India.

Abhishek Wankar. Nonaka Myopathy: First Report of a Rare Mutation from India (c.1571C>T). MMJ. 2026, March. Vol 3 (1).

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Reconstruction of a Shattered Larynx Following Gunshot Injury: A Case Report and Comprehensive Review

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Abstract:

Penetrating trauma to the larynx, particularly from ballistic injuries, poses significant clinical and surgical challenges. These injuries often result in loss of airway patency, voice, and swallowing function due to cartilaginous fragmentation and soft tissue disruption. We report a case of a 21-year-old male with a completely shattered larynx secondary to a gunshot injury. Surgical reconstruction via a laryngofissure approach with rib cartilage grafting, custom laryngeal stenting, and post-operative rehabilitation achieved airway and phonatory restoration. This case highlights the vital role of multidisciplinary management in severe laryngeal trauma and provides a comprehensive review of the current literature on reconstructive techniques and outcomes.

Key words: Laryngeal Trauma, Gunshot Injury, Laryngeal Reconstruction, Costal Cartilage Graft, Airway Stenting.

Introduction

Traumatic laryngeal injuries are uncommon, with an estimated incidence of less than 1% of all neck traumas, yet they can be immediately life-threatening or may result in long-term morbidity if not appropriately managed. Gunshot wounds, in particular, generate high-velocity, high-energy tissue destruction leading to comminuted fractures, mucosal tears, airway compromise, and increased aspiration risks.[1]

The larynx is a complex anatomical structure responsible for airway protection, respiration, and phonation. Damage to the cartilaginous framework, especially when involving the thyroid and cricoid cartilages, disrupts these vital functions. Traditional reconstructive surgery following such trauma faces significant barriers due to tissue loss, infection risk, and the challenges of maintaining lumen patency and vocal function.

The most commonly used classification of laryngeal trauma in the literature is Schaefer–Fuhrman classification; this is mainly based on clinical findings and comprises of five groups:[2]

1. **Group I**: Minor laryngeal oedema or lacerations
2. **Group II:** Demonstrable oedema or haematomas without exposed cartilage
3. **Group III:** Massive oedema or mucosal lacerations with exposed cartilage, displaced cartilaginous fractures, or vocal fold immobility
4. **Group IV:** Destabilisation of laryngeal structure, including the disruption of the anterior commissure, more than two unstable displaced fracture or severe mucosal injury
5. **Group V:** Complete laryngotracheal separation

Management of laryngeal trauma based on Schaefer–Fuhrman classification can be categorised according to the following:[3]

1. **Nonsurgical/conservative management:** Observation, delivery of humidified air, and voice rest for Group I
2. **Surgical options:** Group II–V, which include:
    - **Endoscopy alone:** In cases where there is uncertainty regarding the degree of injury following physical examination, fiberoptic examination, and computed tomography (CT)
    - **Endoscopy with exploration:** Large mucosal laceration, exposed cartilage, multiple displaced cartilaginous fractures, vocal cord immobility, fractured cricoid cartilage, laceration of anterior commissure or free margin of the vocal cord and disruption of the cricoarytenoid joint
    - **Endoscopy with exploration and stenting:** Comminuted laryngeal fractures, massive mucosal injuries, and disruption of the anterior commissure

Case Report

A 21-year-old male presented to our tertiary care ear nose and throat (ENT) unit with a tracheostomy in situ and profound aphonia. He had sustained a gunshot wound to the anterior neck 1 year back followed by an emergency tracheostomy and debridement done at a peripheral centre. He arrived haemodynamically stable but with tracheostomy in situ and mild dysphagia.

Clinical examination revealed anterior neck scarring and a healed entry wound. Fiberoptic laryngoscopy showed supraglottic and glottic narrowing with fixed left hemilarynx. Bilateral vocal cords could not be appreciated (Figure 1). CT scan of the neck showed fragmentation and destruction of both thyroid laminae, a disrupted cricoid ring, and gross anatomical distortion of the glottis and subglottis. There was no obvious airway lumen, and residual mucosal tissue appeared severely inflamed (Figure 2).

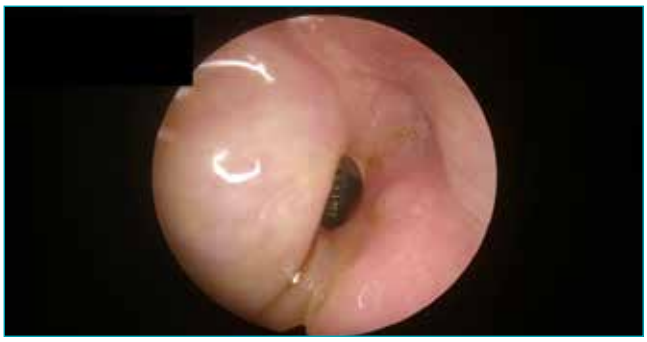

Figure 1: Fiberoptic laryngoscopic view showing severe supraglottic and glottic narrowing with non-visualisation of true vocal cords due to post-traumatic distortion of the laryngeal framework.

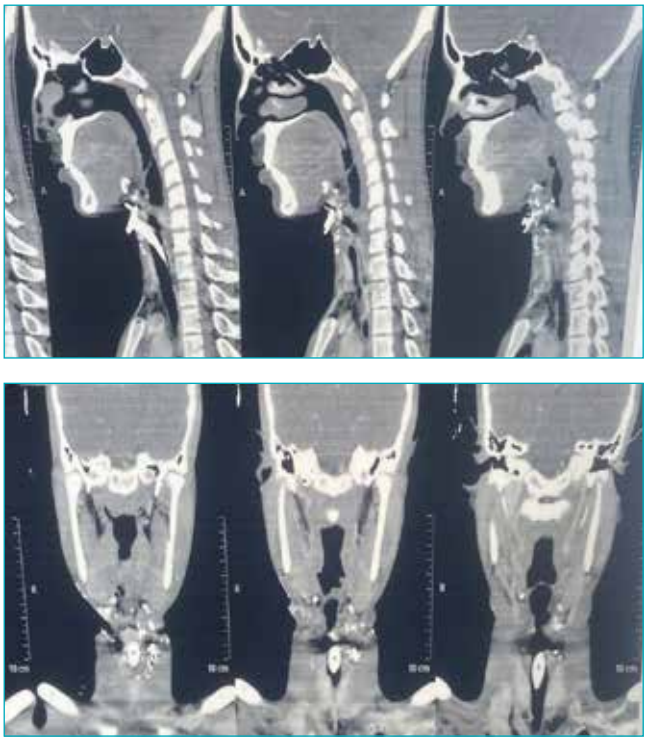

Figure 2: Contrast-enhanced computed tomography (CT) scan of the neck (axial and coronal views) demonstrating a shattered thyroid cartilage with disruption of the cricoid ring and complete distortion of the glottic and subglottic airway.

Surgical management

After multidisciplinary evaluation — including ENT, anaesthesia, and speech pathology, a surgical plan was adopted.

A laryngofissure with anterior midline thyrotomy was performed. Intraoperatively, the larynx was found to be completely shattered, with loss of anterior support and severely displaced cartilage fragments, along with

metallic pellets. Mucosal integrity was partially preserved posteriorly.

The reconstructive strategy included:

- Harvesting autologous costal cartilage to recreate the anterior thyroid lamina and portions of the cricoid arch (Figure 3)
- Placement of an intralaryngeal silicone hood stent, fabricated to match the reconstructed airway contour (Figures 4 and 5)
- Securing the grafts using non-absorbable sutures to provide stability (Figure 6)
- Reinforcement with a strap muscle flap to aid healing and prevent fistula formation

The tracheostomy was retained, and the patient was put on nasogastric feeding.

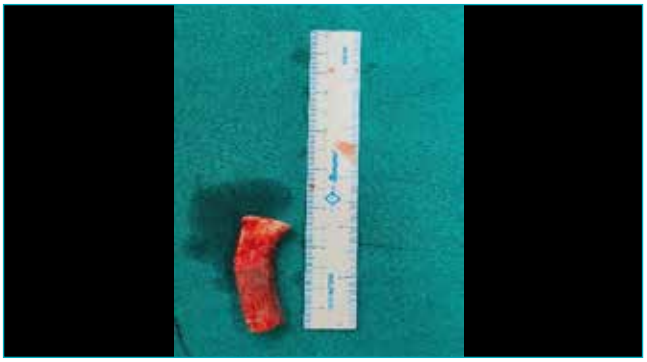

Figure 3: Harvested autologous costal cartilage intralaryngeal shaped to reconstruct the anterior thyroid lamina and cricoid framework.

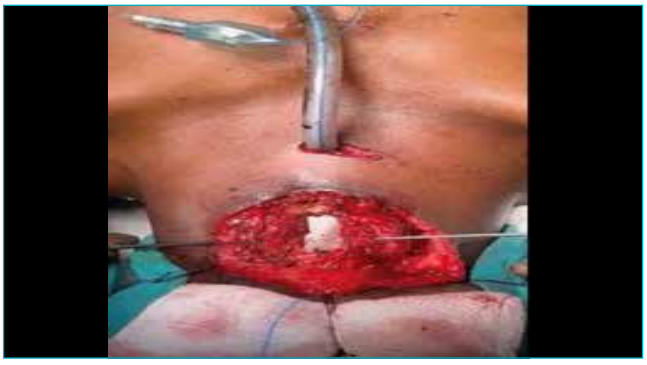

Figure 4: Custom-fabricated silicone hood stent positioned to maintain airway patency and support reconstructed laryngeal framework.

Figure 5: Intralaryngeal silicone hood stent.

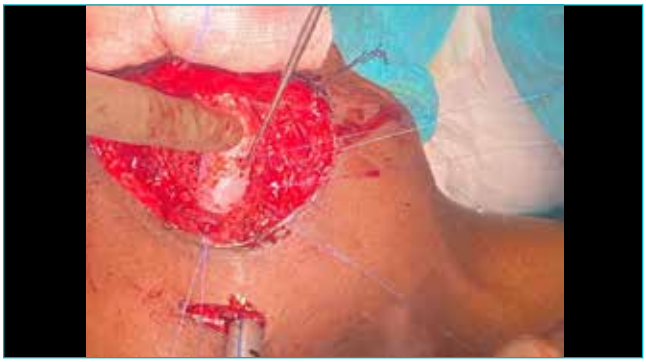

Figure 6: Intraoperative photograph showing fixation of reconstructed cartilage framework using non-absorbable sutures with reinforcement using strap muscle flap.

Postoperative course

The patient recovered well postoperatively without evidence of wound infection or graft extrusion. Endoscopic evaluation at six weeks showed intact grafts and epithelialisation over the stent. Direct laryngoscopy and stent removal were performed at eight weeks, and the tracheostomy and nasogastric tube were removed at ten weeks following confirmation of adequate airway patency (Figure 7) and successful oral challenge.

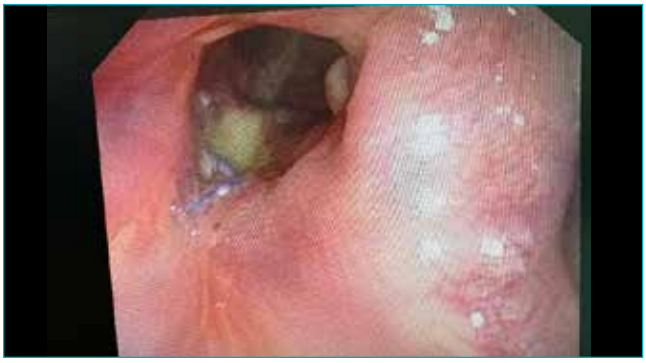

Figure 7: Post stent-removal endoscopic view showing well epithelialised neo-glottic airway with adequate lumen and restored airway continuity.

Speech therapy was initiated early and focused on vocal cord mobilisation and compensatory techniques. At three months, the patient had regained acceptable voice, was able to eat orally, and had returned to daily activities.

Discussion

Laryngeal trauma due to firearms is infrequent but devastating. The functional goals in such injuries include restoration of a stable airway, prevention of aspiration, and re-establishment of intelligible speech. Our case highlights the importance of individualised surgical planning, appropriate timing of intervention, and coordinated multidisciplinary rehabilitation.

Mechanism and extent of injury

Gunshot injuries differ from blunt trauma due to their energy dispersion, resulting in both direct tissue disruption and secondary cavitation. This accounts for the extensive comminution and soft tissue loss observed in our patient. Damage to the laryngeal framework, particularly the cricoid cartilage, compromises the integrity of the entire airway scaffold.[4]

In such scenarios, CT imaging is essential for surgical planning. It allows precise mapping of residual structures and informs the reconstructive approach. However, clinical signs such as subcutaneous emphysema, haemoptysis, and dysphonia should always warrant early airway intervention regardless of imaging findings.

Challenges

Various challenges in achieving desired outcomes in traditional reconstructive surgery following such traumas include:

- Tissue loss
- Risk of infections
- Difficulty in maintaining lumen patency
- Restoration of vocal function

Timing of surgical intervention

A key debate in laryngeal trauma is the optimal timing of surgery. Primary repair during the acute phase (< 24 hours) is ideal in stable clean injuries. However, in contaminated or extensively comminuted cases, delayed reconstruction after stabilisation allows better debridement, reduced infection risk, and clearer tissue planes.[5] Our patient had already undergone emergency tracheostomy immediately after injury and presented to us one year later.

Reconstructive techniques

A variety of grafts and flaps are described for laryngeal reconstruction:

- Costal cartilage is the most favoured autologous graft due to its strength, availability, and resistance to resorption. It has shown promising results in both laryngotracheal stenosis and trauma.[6]
- Silicone stents, especially custom-fitted ones, prevent graft collapse and restenosis.
- We opted for an intraluminal stent, which conforms to the neo-laryngeal framework, a technique adapted from Montgomery T-tube principles.[7]

Endoscopic approach vs open surgery

Effective management of penetrating laryngeal trauma is dependent on accurate recognition of the extent of laryngeal injury. Endoscopic approach, as opposed to open management has been found particularly useful in patients with trauma to the larynx with small, comminuted fragments of fractured cartilage.[8]

In our case, an open surgical approach was planned to evaluate and treat the laryngeal injury to avoid long-term sequelae of untreated cartilaginous or mucosal injury. The decision was made because of the presence of combined stenosis, multiple comminuted fractures of the thyroid lamina and cricoid cartilage, and the inability to clearly define the extent of injury on imaging and endoscopy due to massive distortion of the laryngeal framework.

Airway and voice outcomes

Despite the anatomical success, functional recovery of voice remains variable. In our patient, early involvement of speech therapy was instrumental. Techniques like resonant voice therapy, vocal function exercises, and biofeedback-based phonation were key in restoring glottic closure.

Risk of aspiration is another challenge in postoperative period. In our case, despite the minimal risk of aspiration due to placement of stent, a nasogastric tube was placed and feeding started immediately postoperatively. After

removal of stent at eight weeks, nasogastric tube was retained for a further two weeks to prevent aspiration and oral feeds were commenced at ten weeks.

Studies show that even in extensive trauma, phonatory rehabilitation can achieve acceptable voice quality if mucosal vibration is preserved or re-established.[9] Long-term surveillance is necessary to detect complications such as granulation tissue, restenosis, or vocal fold immobility.

Multidisciplinary role

This case also emphasises the role of a multidisciplinary team in managing complex airway trauma:

- ENT surgeons lead the airway reconstruction
- Speech-language pathologists direct functional voice recovery
- Pulmonologist and anaesthetist assist in respiratory planning and postoperative airway care

Outcomes

The outcomes of this collaborative care model were:

- Successful decannulation
- Restoration of phonation
- Resumption of oral intake

Conclusion

Ballistic injuries to the larynx pose formidable challenges due to their complexity and unpredictability. This case highlights the possibility of achieving near-complete functional restoration through:

- Delayed but definitive surgical reconstruction
- Judicious use of costal cartilage grafts and custom stenting
- Structured speech and swallowing rehabilitation
- A multidisciplinary treatment algorithm

This approach can serve as a framework for managing similar cases of extreme laryngeal trauma.

Richa Saha, Vineet Narula, Sumit Mrig, Sandeep Arora, Amrit Kapoor, Sachin Goel. Reconstruction of a Shattered Larynx Following Gunshot Injury: A Case Report and Comprehensive Review. MMJ. 2026, March. Vol 3 (1).

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Autoimmune Mastitis with Gigantomastia Gravidorum: Report of a Case and Review of Literature

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Abstract:

Breasts can be the target organ for many autoimmune conditions. Pregnancy is a known trigger for flares of autoimmunity. Sometimes, inflammation limited to the breast is the first symptom of a systemic autoimmune disease. However, due to the rarity of this presentation, the diagnosis of a pregnancy-induced autoimmune breast inflammation can be very difficult.

A young woman presented in the 12th week of her pregnancy with persistent symptoms of pain and erythema of the breast. She underwent repeated imaging investigations and received multiple courses of antibiotics without relief. Within a few weeks, she also developed massive enlargement of her breasts. Even though she was evaluated for a possible autoimmune aetiology, the test results could not clinch a diagnosis. In view of the development of gigantomastia by the third trimester, delivery was induced at 30 weeks. Lactation was suppressed with cabergoline. Two weeks after delivery, she started manifesting symptoms of systemic autoimmune disease, and after detailed evaluation, was diagnosed with systemic lupus erythematosus with Sjögren's syndrome. After appropriate medication, her disease went into remission, and the gigantomastia regressed to near-normal size.

A diagnosis of autoimmune mastitis should be kept in mind in patients with persistent inflammation of the breast. An early diagnosis may help detect systemic diseases and initiate a prompt, appropriate therapeutic strategy.

Key words: Autoimmune Mastitis, Gigantomastia Gravidorum, Systemic Lupus Erythematosus, Dopamine Agonists, Reduction Mammoplasty, Case Report.

Introduction

Inflammation of the breast due to infection is a common occurrence. Inflammatory carcinoma of the breast is the next most important diagnosis. Autoimmune mastitis belongs to a third group of aetiology.[1] It includes conditions that are limited to the breast only, such as idiopathic granulomatous mastitis. It may also be part of the presentation of a wide range of autoimmune diseases, such as diabetes, thyroiditis, systemic erythematosus lupus (SLE), Sjögren's syndrome, giant cell arteritis, polyarteritis nodosa, Behçet's disease, sarcoidosis, Crohn's disease, etc.[2,3] However, breast-limited inflammation is sometimes the first symptom of a systemic autoimmune disease. The clinical picture of autoimmune mastitis may vary from being asymptomatic to presenting with severe, recurrent breast inflammation, painful nodules, nipple discharge or retraction, and lymphadenopathy.

Gigantomastia gravidorum (GG) is another rare diagnosis, with a reported incidence of 1:28,000 to 1:100,000 pregnancies.[4] It is characterised by rapid, diffuse, and excessive hypertrophy of the breasts, which requires reduction of more than 1500 g of tissue from each breast for relief of symptoms.[5] It is usually bilateral, presents during the 1st and early 2nd trimesters of pregnancy, and can give rise to a myriad of physical symptoms, such as breast pain, infection, ulceration, postural problems, back pain, and loss of nipple sensation.[6]

The aetiopathogenesis of gigantomastia is still not clearly understood. Theories such as end-organ hypersensitivity, hyperprolactinaemia, impaired liver function or steroid metabolism, autoimmune stimulation antibodies, and high insulin-like growth factor 1 (IGF-1) have been proposed.[3,4] GG has been reported to be associated with various autoimmune disorders, such as SLE, myasthenia gravis, Graves' disease, chronic arthritis, psoriasis, and Hashimoto's thyroiditis.[7,8] In a review of 108 patients with gigantomastia, 9.2% cases had autoimmune conditions.[6]

We present the case of a young woman who developed autoimmune mastitis with GG during her 4th pregnancy, and progressed to full-blown manifestation of SLE with Sjögren's disease in the postpartum period, and discuss the challenges faced in managing this very rare clinical problem.

Case Report

A 28-year-old multigravida (gravida 4, para 1 plus 2 abortions [G4P1+2]) presented at 12 weeks of gestation in her 4th pregnancy with pain and redness of the skin over her left breast. There was no history of fever, prior illness, or medication use. However, her obstetric history was significant. She had to terminate her first pregnancy due to the absence of foetal cardiac activity. For her second pregnancy, she underwent a caesarean section in view of decreased foetal movements due to oligohydramnios. In the postpartum period, she developed a left breast abscess for which incision and drainage (I&D) was done. The third pregnancy was terminated, as it was unplanned.

Her examination showed enlargement of both breasts with an area of erythema and tenderness in the left breast (Figure 1A and B). Skin oedema was present, with no palpable lump or fluctuation. Bilateral enlarged axillary accessory breasts were noted, along with a scar of I&D on the left breast. With a provisional diagnosis of mastitis, she was advised a course of antibiotics (Tab Augmentin 625 mg × thrice a day) for 7 days, without symptomatic relief. She continued to present for follow-up for over a month, with persistent symptoms and no abscess formation.

Laboratory investigations were all within normal limits, and serial ultrasounds showed diffuse enlargement of both breasts without any focal lesion. Given concern for inflammatory carcinoma of the breast, a breast biopsy was performed, which showed mild chronic perivascular inflammation in the dermis, with no evidence of malignancy or granulomas. By the end of 20–22 weeks, she had developed gross enlargement of both breasts. Assessment of hormonal profile was done, and serum prolactin (186 ng/mL, range 10 to 209 ng/mL), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinising hormone, and oestradiol were all found to be within normal limits. She was advised to take tablet cabergoline 0.5 mg twice weekly for about a month; however, breast enlargement continued, and skin showed patchy redness and peau d'orange appearance. With a possible diagnosis of autoimmune mastitis, she was further investigated. Inflammatory markers were raised (erythrocyte sedimentation rate [ESR] 58 mm/h; C-reactive protein [CRP] 9.34 mg/dL [normal < 0.6 mg/dL]). Blood counts showed dimorphic anaemia (normocytic normochromic and microcytic hypochromic with mild anisocytosis), normal white blood cell (WBC) and platelet count. However, tests for autoantibodies (antinuclear antibody [ANA], rheumatoid factor [RF], and direct and indirect Coombs' test) were all negative.

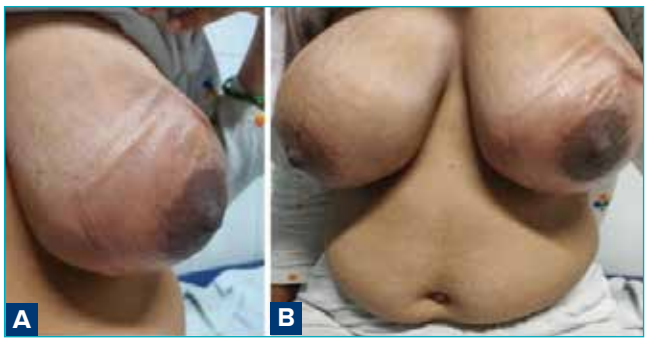

Figure 1A and B: Clinical presentation at 12 weeks of gestation showing pain and erythema of the left breast.

By 28 weeks of pregnancy, the breasts extended to the umbilicus in the sitting position, causing significant physical discomfort due to the excessive weight, without ulceration or necrosis of the skin (Figure 2A and B).

With a diagnosis of GG, the patient was referred to a gynaecologist. After assessment of foetal maturity, a lower-segment caesarean section (LSCS) was performed at 30 weeks of gestation, delivering a healthy baby weighing 1.8 kg. Her lactation was suppressed by cabergoline.

Figure 2: A. Gigantomastia gravidorum at 24 weeks of gestation; **B.** Progressive gigantomastia at 30 weeks of gestation.

At 1 month postpartum, there was some reduction in breast size. However, she developed symptoms of joint pains and stiffness, and red scaly rashes on her face. She also complained of photosensitivity and redness of the eyes. With the clinical picture of an autoimmune disorder more clearly evident, her investigations were repeated. Results showed: haemoglobin (Hb) 12.0 g/dL; total leucocyte count (TLC) 7.9 cu/mm; platelet count 2.12 lakh; ESR 40 mm/hr; urea 26 mg/dL; creatinine 0.9 mg/dL; 24-hr urinary protein 266 mg/day (normal < 140 mg/day); bilirubin 0.5 mg/dL; serum glutamic oxaloacetic transaminase (SGOT) 29 IU/L; serum glutamic pyruvic transaminase (SGPT) 18 IU/L; alkaline phosphatase (ALP) 92 IU/L; CRP 3.13 mg/L (normal 0.3–1.0 mg/dL); procalcitonin 18.0 (normal < 0.1 ng/mL); complement component 3 (C3) 90 mg/dL (90–180 mg/dL); complement component (C4) 39 mg/dL (10-40 mg/dL); anti-thyroid peroxidase antibody (anti-TPO Ab) 65.0 IU/mL (normal < 60 IU/mL); TSH: 2.73 µU/mL (normal 0.35–4.94 µU/mL); RF 2.25 (normal < 20 U/mL), ANA titre > 1:1280 homogeneous and speckled; anti-double-stranded deoxyribonucleic acid antibody (anti-dsDNA) > 5 IU/mL (normal < 10 IU/mL); Ro/Sjögren's syndrome-related antigen A antibody (Ro/SSA) 60 U/mL (normal < 7 U/mL).

Based on clinical and laboratory findings, a diagnosis of SLE with Sjögren syndrome was established, and immunomodulatory therapy (hydroxychloroquine 400 mg/day, prednisolone 20 mg/day, mycophenolate 1 g/day) was initiated. Symptoms started resolving within 2–3 months. At 1-year follow-up, the patient was asymptomatic, and her breasts had reduced to near normal size (Figure 3).

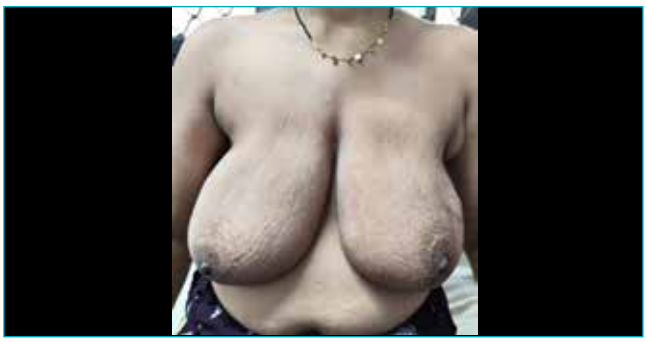

Figure 3: One year after delivery, showing near-complete resolution of gigantomastia following remission of autoimmune disease.

Clinical timeline

The chronological sequence of clinical events, investigations, and outcomes in the present case is summarised in Table 1.

Clinical events	Timeline
Pain and erythema in the left breast	12 weeks of gestation
Investigations, antibiotics, and persistent symptoms	12–20 weeks of gestation
Bilateral gigantomastia gravidorum	20 weeks onwards
Induction of labour	30 weeks
Symptoms of systemic autoimmune disease	2 weeks postpartum
Diagnosis and treatment	4–6 weeks postpartum
Complete resolution of symptoms and gigantomastia	6–8 months after diagnosis

Table 1: Clinical timeline summarising the presentation, investigations, management, and outcome of a patient with autoimmune mastitis and gigantomastia gravidorum progressing to systemic lupus erythematosus with Sjögren's syndrome.

Discussion

The diagnosis of autoimmune mastitis and GG may be difficult in the early stage and may be confused with inflammatory carcinoma of the breast, especially if it is unilateral. Bilateral axillary swelling due to hypertrophy of the accessory axillary breast tissue may be confused with lymphadenopathy of malignancy.[9] However, underlying malignancy should always be considered and excluded first, as there are case reports where patients initially presenting with GG later proved to have underlying malignancy.[10,11] Other differential diagnoses, such as a phyllodes tumour, non-Hodgkin's lymphoma and lymphoblastic lymphoma, can be excluded through biopsy.

Biopsy in autoimmune inflammation of the breast may show pathological changes such as: (i) lymphocytic infiltrates; (ii) ductal ectasia; (iii) granulomatous mastitis; and (iv) vasculitis. Although these patterns are not specifically related to a particular autoimmune disease, they provide an indication for a diagnostic pathway.[1] Histological features of GG include significant lobular hypertrophy, ductal proliferation, periductal fibrosis, and pseudoangiomatous hyperplasia. In the present case, investigations revealed only subtle changes of chronic perivascular inflammation in skin biopsy with raised inflammatory markers, though autoantibody titres were normal.

Pregnancy is known to cause flaring up of autoimmune diseases.[12] This may lead to several pregnancy-related complications such as foetal loss, pre-eclampsia and eclampsia, congenital heart block, and neonatal lupus. Spinillo *et al.* reported that 25% of patients experience a significant rheumatic disease flare during pregnancy.[12] Many changes are known to occur within the immune system during pregnancy, such as stimulation of immune cells and release of inflammatory mediators. Mild titres of ANA in normal pregnancy have been variously reported to range from 1%–53%.[7] The mechanism by which autoimmune diseases cause inflammation in the breast and gigantomastia is based on a hypothesis that ANA causes an inflammation in the breast that leads to an abnormal proliferation of glandular tissue. However, no specific antibody against a breast antigen has been identified so far. In this patient, a poor obstetric history, perivascular dermal inflammation on breast skin biopsy, and inflammatory markers were some clues towards the autoimmune nature of her problem.

There are no clear management guidelines for autoimmune mastitis or GG owing to a huge variability in aetiology and course of the disease. While symptomatic treatment should be offered for autoimmune inflammation, medication with dopamine agonists or surgical intervention are the options for GG, and are employed on a case-by-case basis. A large majority of reports mention the use of surgical procedures in the form of reduction mammoplasties or subcutaneous mastectomies.[6,13] Spontaneous complete resolution is a rarity.[13] Bromocriptine and cabergoline are the most commonly used drugs. Treatment with bromocriptine has been reported to halt breast growth, though it has no apparent effect on reducing breast size. Both bromocriptine and cabergoline have been shown to have a good safety profile when administered during early pregnancy. Data on exposure of the foetus or embryo to cabergoline during the first weeks of pregnancy have now been reported in more than 900 cases, which indicate that cabergoline is safe in this context.[14]

Surgical procedures in the form of reduction mammoplasty or bilateral mastectomy with reconstruction are more often employed in the management of GG.[13] As a patient can have a relapse after breast-conserving surgery in her future pregnancies, mastectomy is recommended for patients who have not completed their families.[15]

In a review of 50 cases of GG, 37 cases (74%) were managed surgically, nine received bromocriptine, while two cases had spontaneous resolution in the postpartum period.[6] Even though literature does not recommend a conservative approach in patients of GG with an underlying autoimmune condition per se, experience with our case provides some evidence that in patients with autoimmune aetiology of GG, a conservative approach may be adopted with the hope of complete resolution once the disease goes into remission.

Declarations

Conflict of interests:

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding:

None.

Consent for publication:

Written informed consent was obtained from the patient for the publication of her case report.

Ethical approval:

Ethical approval is not required to publish an anonymous case report.

Conclusion

Autoimmune mastitis should be considered as a differential diagnosis in patients with persistent inflammation of the breast, while adequately investigating the patient to rule out a malignancy. GG has a chance for complete remission when the autoimmune disease goes into remission.

Navneet Kaur, Virali Savani. Autoimmune Mastitis with Gigantomastia Gravidorum: Report of a Case and Review of Literature. MMJ. 2026, March. Vol 3 (1).

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Symptomatic Heterotopic Ossification in the Plantar Soft Tissue of the Heel: A Rare Cause of Chronic Plantar Heel Pain

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Abstract:

Plantar heel pain is most commonly attributed to plantar fasciitis or calcaneal spurs. Rarely, extra-osseous ossified lesions arising within the plantar soft tissues may present with similar symptoms and pose a diagnostic challenge. We report a rare case of symptomatic heterotopic ossification occurring entirely within the plantar soft tissue of the heel, without any attachment to the calcaneum. Imaging revealed a well-defined ossified lesion within the plantar soft tissue. Surgical excision was performed due to persistent symptoms. Histopathological examination confirmed heterotopic ossification with mature lamellar bone and no evidence of malignancy. This case highlights the importance of considering rare extra-osseous ossified lesions in the differential diagnosis of chronic plantar heel pain.

Key words: Heterotopic Ossification, Plantar Heel Pain, Soft Tissue Ossification, Heel Mass.

Introduction

Plantar heel pain is a frequently encountered orthopaedic complaint, most commonly caused by plantar fasciitis, calcaneal spur, or degenerative soft-tissue pathology.[1] In contrast, ossified lesions arising within the plantar soft tissues are exceedingly rare and often misdiagnosed due to their nonspecific presentation.

Heterotopic ossification (HO) refers to the formation of mature lamellar bone in soft tissues outside the normal skeletal system.[2] While commonly reported around large joints following trauma, surgery, or neurological injury, HO occurring in the plantar soft tissues of the foot is extremely uncommon, with only isolated case reports available in the literature.

We present a rare case of symptomatic HO arising entirely within the plantar soft tissue of the heel, without attachment to the calcaneum, and provide a focused review of similar reported cases.

Case Report

A 66-year-old female presented with pain and swelling over the plantar aspect of the right heel for several months. The pain was insidious in onset, gradually progressive, and aggravated by prolonged standing and walking. The patient described a sensation of “walking on a hard object.” There was no history of trauma, surgery, infection, or systemic illness.

Clinical examination

Local examination revealed a firm, well-defined swelling measuring approximately 2 × 2 cm over the plantar posteromedial aspect of the heel. The lesion was mildly tender and mobile, not fixed to the underlying calcaneum. The overlying skin was normal. Ankle and subtalar joint movements were full and painless. Distal neurovascular status was intact.

Investigations

Plain radiography

Plain radiographs of the right foot demonstrated a well-defined ossified mass located within the plantar soft tissues of the heel, with no cortical continuity or attachment to the calcaneum.

The calcaneal cortex appeared intact (Figure 1).

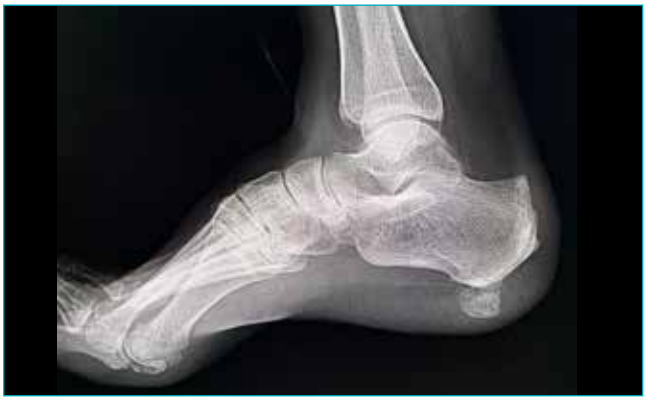

Figure 1: Pre-operative X-ray: Plain radiograph of the right foot showing a well-defined ossified mass in the plantar soft tissues of the heel, without cortical continuity or attachment to the calcaneum.

Magnetic resonance imaging (MRI)

MRI revealed a well-circumscribed ossified lesion measuring approximately 1.9 × 1.3 cm within the plantar soft tissue of the heel. The lesion showed signal characteristics similar to mature bone and was surrounded by fibrous tissue. There was no involvement of the calcaneum, plantar fascia origin, or adjacent musculotendinous structures, and no aggressive features were identified (Figure 2A and B).

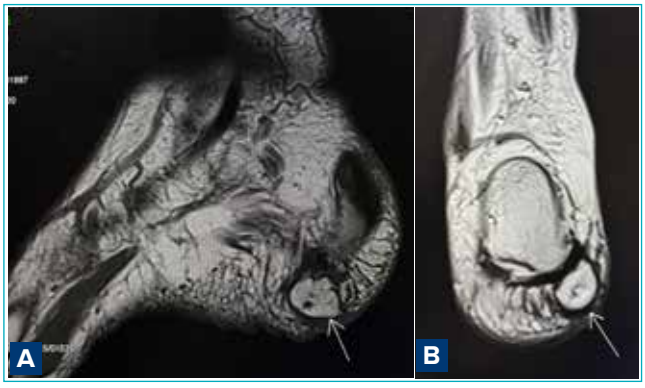

Figure 2A and B: Magnetic resonance imaging (MRI) images: MRI of the right heel showing a well-circumscribed ossified lesion within the plantar soft tissues, without involvement of the calcaneum, plantar fascia, or adjacent structures.

Management

Given the persistent pain and functional limitation despite conservative measures, surgical excision was planned (Figure 3A–G). A medial plantar approach was used. Intraoperatively, a well-encapsulated ossified mass was identified within the plantar soft-tissue plane. The lesion was clearly separate from the calcaneum and plantar fascia and was excised completely (Figure 3E).

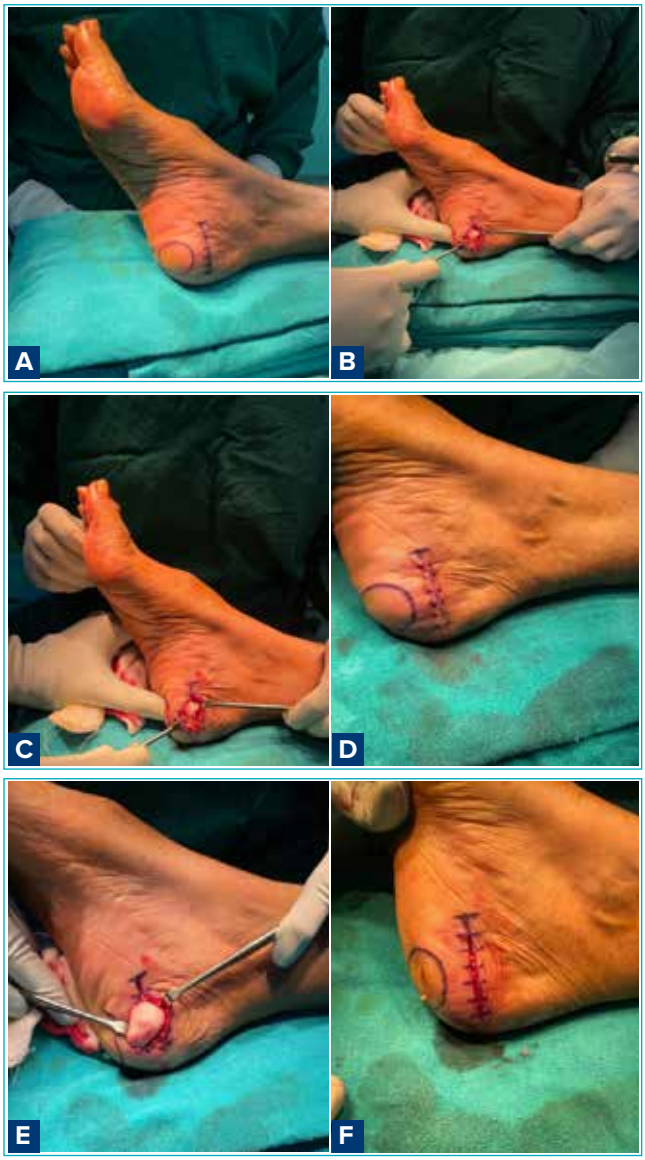

Figure 3A–G: Intraoperative process: Preoperative clinical photograph showing the marked area of maximal tenderness over the plantar heel; intraoperative images demonstrating exposure and complete excision of a well-circumscribed heterotopic ossified mass from the plantar soft tissues without attachment to the calcaneum; excised specimen; and postoperative photographs showing wound closure.

Histopathological examination

Microscopic examination demonstrated a well-circumscribed lesion composed of mature lamellar bone with central fatty marrow spaces, surrounded by fibrous tissue. No cellular atypia or malignant features were identified, confirming the diagnosis of heterotopic ossification (Figure 4).

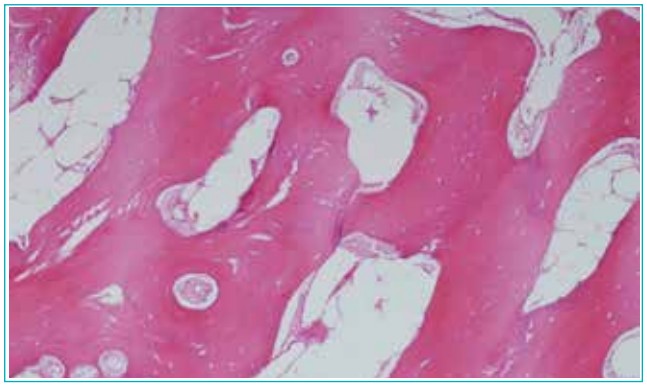

Figure 4: Histopathological examination: Photomicrograph showing mature lamellar bone with fatty marrow spaces, surrounded by fibrous tissue, without atypia, consistent with heterotopic ossification.

Outcome and follow-up

The postoperative period was uneventful. The patient reported complete resolution of heel pain and returned to normal ambulation. No recurrence was noted on follow-up (Figure 5).

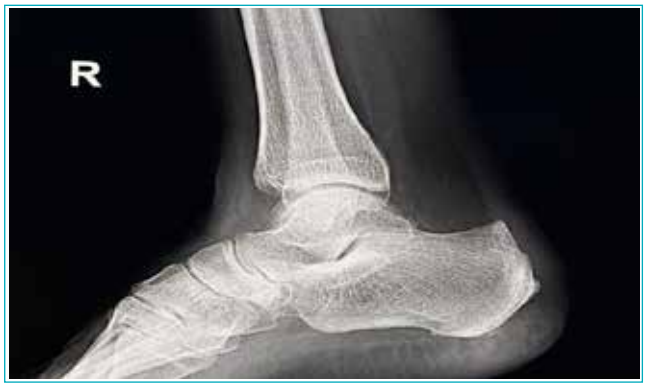

Figure 5: Post-operative X-ray: Postoperative plain radiograph of the right foot demonstrating complete excision of the plantar ossified mass, with no residual lesion visible.

Discussion

Extra-osseous ossified lesions of the plantar heel are rare and can mimic common causes of heel pain, such as plantar fasciitis or calcaneal spurs. The differential diagnosis includes heterotopic ossification, myositis ossificans, extra-osseous osteochondroma, tumoral calcinosis, and malignant soft tissue tumours.[3]

Unlike calcaneal spurs or osteochondromas, which demonstrate continuity with the parent bone, heterotopic ossification is characterised by ossification within soft tissues without skeletal attachment. MRI is particularly valuable in confirming the extra-osseous location and excluding aggressive pathology.

Previously reported rare similar cases

Only a limited number of similar cases involving ossified lesions in the plantar or hindfoot soft tissues have been reported:

- Danya *et al.* reported a case of heterotopic ossification involving the hindfoot soft tissues, completely isolated from the underlying bone and confirmed by histopathology.[4]
- Trankovskiy *et al.* described ossification within the plantar soft tissues in the region of the calcaneus, presenting with pain during ambulation and a palpable plantar mass, similar to the present case.[5]
- Singh *et al.* reported an extra-osseous osteochondroma arising from the superficial fascia of the heel, presenting as a well-defined ossified plantar mass without attachment to the calcaneum.[6]
- Earlier reports have also documented soft tissue osteochondromas of the heel pad, emphasising that well-circumscribed ossified lesions can arise within plantar soft tissues independent of the calcaneum.[7]

These reports, together with the present case, emphasise that extra-osseous ossified lesions of the plantar heel, although rare, are well-documented entities and should be included in the differential diagnosis of chronic plantar heel pain associated with a firm mass.

Declarations

Informed consent:

The patient provided informed written consent for publication of this case report and accompanying images.

Conflict of interest:

The authors declare that they have no conflict of interest.

Funding:

No financial support was received for this study.

Conclusion

Heterotopic ossification occurring entirely within the plantar soft tissue of the heel, without attachment to the calcaneum, is extremely rare. Awareness of this entity is essential to avoid misdiagnosis. Imaging and histopathological evaluation are crucial for accurate diagnosis, and surgical excision offers excellent symptomatic relief with low risk of recurrence.

Heterotopic ossification within the plantar soft tissues of the heel is an extremely rare cause of chronic plantar heel pain and should be considered in patients with persistent symptoms unresponsive to conservative treatment.

Dilveer Brar, Vishal Sharma, Kheman Grover. Symptomatic Heterotopic Ossification in the Plantar Soft Tissue of the Heel: A Rare Cause of Chronic Plantar Heel Pain. MMJ. 2026, March. Vol 3 (1).

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Anaesthetic Considerations in a Paediatric Patient Posted for Left Pericardial Patch Bronchoplasty for Traumatic Left Main Bronchus Fracture: Stricture

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Abstract:

Traumatic tracheobronchial injury often necessitates surgical intervention when complicated by airway disruption. If not managed properly and timely, it can lead to significant morbidity and mortality. Clinical manifestations of tracheobronchial injury include persistent pneumothorax, subcutaneous emphysema, pneumomediastinum, and respiratory insufficiency. Bronchoplasty using a pericardial patch is a rare but crucial surgical technique aimed at restoring bronchial integrity to preserve pulmonary function. This case report discusses the successful anaesthetic management of a patient who underwent left-sided bronchoplasty using a pericardial patch for traumatic bronchial fracture reconstruction. The anaesthetic challenges in this case were the paediatric age group of the patient, compromised gas exchange due to complete left lung collapse, requirement of differential one-lung ventilation (OLV) to provide an optimal surgical field to the surgeon, maintenance of gas exchange and haemodynamic stability intraoperatively, and to ensure bronchial suture integrity to reduce the risk of air leaks postoperatively. A right-sided double-lumen tube (DLT) with pressure-controlled ventilation was used for differential right lung ventilation, strict haemodynamic monitoring, and multimodal analgesia. The patient was extubated postoperatively to avoid barotrauma and bronchial suture disruption. A multidisciplinary approach with vigilant airway management, lung-protective ventilation strategies, and postoperative care is essential for optimal outcomes in these patients.

Key words: Paediatric Anaesthesia, Traumatic Bronchial Injury, Bronchoplasty, One-Lung Ventilation, Double-Lumen Tube, Thoracic Anaesthesia.

Introduction

Tracheobronchial injury (TBI) is a rare incidence following blunt chest trauma and can often be missed. Traumatic bronchial injury is estimated to occur in 2%–3% of patients who succumb to traumatic injury.[1,2] Blunt trauma has a lower incidence of TBI (0.5%–2%) as compared to penetrating trauma (1%–2%).[2]

It requires a high level of suspicion for timely diagnosis and proper treatment, failure of which can lead to significant morbidity and mortality. Diagnosis is confirmed by fibreoptic bronchoscopy or by computed tomography (CT) of the chest. Complex injuries involving bronchial rupture may require pneumonectomy in many cases. Bronchoplasty can be used as a lung-sparing surgical approach for airway reconstruction in these cases and presents unique perioperative anaesthetic challenges,

such as management of perioperative airway, ventilation, perfusion, providing an optimal surgical field to surgeons, and postoperative care. The preferred airway management technique is to intubate the healthy bronchus with either a single-lumen tube or a double-lumen tube (DLT).[3,4]

Deceleration injury resulting from blunt chest trauma commonly occurs at the transition zone between the fixed and mobile bronchus within 2.5 cm of the carina. These injuries are more common on the right side and 10 times more common in adults due to their hard bone contour as compared to the pliable chest wall in children.[4] This case report discusses the successful anaesthetic management of a 14-year-old male child who underwent left thoracotomy and bronchoplasty using a bovine pericardial patch for traumatic left bronchial fracture–stenosis resulting in complete left lung collapse. A right-sided DLT was used for differential lung ventilation.

Case Report

A 14-year-old male patient presented to the emergency department with complaints of difficulty in breathing, left-sided chest pain, and a history of blunt chest trauma 2 weeks earlier. Auscultation revealed absent air entry on the left side, and a left-sided intercostal drain (ICD) in situ. The patient had previously been admitted to another hospital after trauma with the same complaints, where fibreoptic bronchoscopy (FOB) was attempted but had to be abandoned due to the development of tachycardia and hypoxia. ICD was placed on the left side for pneumothorax; however, persistent symptoms prompted referral for definitive treatment.

Preoperative evaluation revealed a heart rate (HR) of 135 beats/min, blood pressure (BP) of 112/78 mmHg, oxygen saturation (SpO_2) of 96% on 2 L of oxygen (0_2) via nasal prongs, respiratory rate (RR) of 20 breaths/min, weight of 45 kg, height of 142 cm, and absent air entry to the left side of the chest on auscultation. Blood investigations were all within normal limits. Chest X-ray revealed a completely collapsed left lung with ipsilateral volume loss and shift, giving clinical suspicion of endobronchial injury (Figure 1A). Contrast-enhanced computed tomography (CECT) of the thorax revealed a complete cut-off of the left main bronchus, indicative of traumatic bronchial disruption (Figure 1B). Flexible bronchoscopy confirmed the absence of a bronchial lumen 2.8 cm from the carina on the left, supporting the diagnosis of complete bronchial transection (Figure 2).

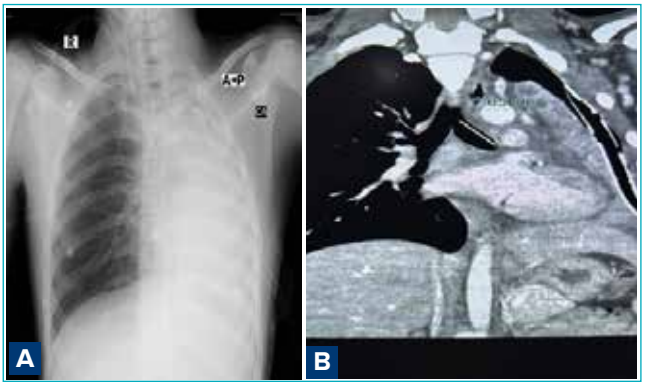

Figure 1: A. Chest radiograph showing complete collapse of the left lung with ipsilateral volume loss and mediastinal shift; **B.** Contrast-enhanced computed tomography (CECT) of the thorax revealing complete cut-off of the left main bronchus, consistent with traumatic bronchial disruption.

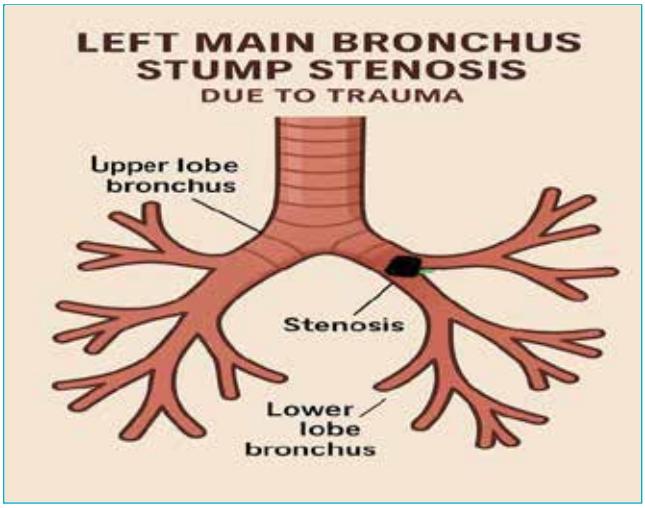

Figure 2: Schematic representation showing complete obliteration of the left main bronchus approximately 2.8 cm distal to the carina, confirming traumatic bronchial transection.

Intraoperative anaesthetic management

In the operating room, monitors were attached, and two wide-bore intravenous cannulae were secured. Patient was preoxygenated and premedicated with glycopyrrolate, midazolam, and fentanyl. Anaesthesia was induced with propofol, and the muscle relaxant atracurium was administered. The patient was intubated with a right-sided 35 Fr DLT, and correct positioning was confirmed through fibreoptic bronchoscopy. One-lung ventilation (OLV) of the right side was achieved after blocking the tracheal lumen. The patient was ventilated on pressure-control mode, keeping peak airway pressures between

25–28 mmHg and positive end-expiratory pressure (PEEP) of 5 cmH_2O, to attain a tidal volume of approximately 350 mL and a respiratory rate of 18 breaths/min. End-tidal carbon dioxide ($ETCO_2$) was maintained between 35–40 mmHg, and SpO_2 remained at 94%–96% on 0.5 FiO_2. The right radial artery was cannulated for continuous blood pressure monitoring and blood gases measurement. Anaesthesia was maintained with sevoflurane, oxygen and air. Paracetamol, diclofenac, and morphine were given as analgesics. Surgery was conducted in the right lateral position. Haemodynamics were maintained throughout the surgery within normal limits.

Intraoperatively, the left main bronchus was found to be fractured, fibrosed, and stenosed, causing obliteration of the distal bronchial segment with total lung collapse, which was repaired with a bovine pericardial patch.

After bronchoplasty, the tracheal lumen was declamped to allow both lungs to inflate and check for leaks from the anastomotic site. No air leak was found, and the left lung was slowly inflated. The patient maintained saturation of 98% on pressure-control ventilation. The thoracotomy was closed after insertion of an ICD.

The patient was reversed and extubated after confirming adequate respiratory efforts. Postoperatively, he was kept on spontaneous ventilation to avoid barotrauma and prevent suture disruption.

Postoperative care

The patient was shifted to the Intensive Care Unit (ICU) for further observation. Vital parameters were maintained, with SpO_2 of 98% on 4 L/min of 0_2 via mask. Multimodal analgesia was used with paracetamol, non-steroidal anti-inflammatory drugs (NSAIDS), and morphine. On postoperative Day 1, the patient was ambulated, deep breathing exercises were encouraged, and spirometry was done thrice a day. There were no postoperative complications. By the postoperative Day 7, chest X-ray revealed re-expansion of the left lung, mediastinal normalisation, and no evidence of anastomotic leak or stricture (Figure 3). ICD was removed, and the patient was discharged in a stable condition with good pulmonary function.

Figure 3: Postoperative chest radiograph demonstrating re-expansion of the left lung with normalisation of mediastinal position and no evidence of air leak, anastomotic disruption, or residual bronchial stenosis.

Discussion

Anaesthetic management in thoracic trauma with bronchial injury is complex and multifaceted. Traumatic tracheobronchial injury often necessitates surgical intervention when complicated by airway disruption. If not managed properly and timely, it can lead to significant morbidity and mortality.[3] Diagnosis in these patients can be difficult, which may cause a delay in treatment.[5] Presentation of unexplained dyspnoea, recurrent pneumonia and unresolved pneumothorax, even with ICD in a patient with a previous history of trauma, should raise suspicion of missed bronchial injury.[6] Bronchoplasty using a pericardial patch is a rare but crucial surgical technique aimed at restoring bronchial integrity to preserve pulmonary function.

The key challenge in these patients is achieving adequate oxygenation and ventilation during OLV. Maintaining low airway pressures is vital to protect suture lines and pericardial patch integrity. Recommended methods for securing the airway in patients with tracheobronchial injury include DLT, bronchial blockers, single-lumen endotracheale tube (ETT).

Bronchial blockers are easier to displace and provide limited suction and drainage to the isolated lung, leading to accumulation of pus, blood or secretions. It can also interfere with the surgical field since they are placed in the operative bronchus. Management with a single-lumen ETT with positive pressure ventilation is likely to cause air leakage and produce further deterioration of pulmonary function.[4]

The use of a DLT confirmed by bronchoscopy is the gold standard for OLV. Previous studies have also supported the use of high-frequency jet ventilation if OLV fails. A right-sided DLT with pressure-control mode was used for differential right lung ventilation. Strict haemodynamic monitoring was done, multimodal analgesia was used intraoperatively, and the patient was extubated postoperatively to avoid any barotrauma and bronchial suture disruption by elective ventilation.

Protective ventilation strategies are crucial in avoiding further lung damage. Injury from OLV can cause re-expansion pulmonary oedema (REPE), acute lung injury (ALI), or acute respiratory distress syndrome (ARDS). Early ALI is predicted by high intraoperative ventilation pressures. Reduction of tidal volumes during OLV to 5 mL/kg has been shown to reduce alveolar concentration of tumour necrosis factor (TNF) and soluble intercellular adhesion molecule-1 (sICAM-1). However, fixed volumes of 9 mL/kg with the addition of 5 cmH_2O PEEP was associated with better oxygenation and earlier extubation.[5]

Pain control promotes pulmonary recovery. Postoperative ICU care is essential for the timely diagnosis and management of complications such as bronchopleural fistula, ARDS, and persistent air leak. If the patient is haemodynamically unstable and requires postoperative ventilation, it should be done with low tidal volume.

Multidisciplinary coordination among anaesthesiologists, thoracic surgeons, and intensivists significantly improves outcomes in such high-risk procedures.

Conclusion

Anaesthesia for thoracotomy with bronchoplasty in a patient with bronchial injury demands meticulous airway planning, lung-protective ventilation, and vigilant perioperative monitoring. Personalised ventilation strategies and adequate analgesia play pivotal roles in reducing morbidity. A well-orchestrated team of a surgeon, anaesthesiologist and pulmonologist enhances safety and facilitates recovery.

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Saving the Sight: Expanding the Therapeutic Horizon in Ophthalmic Tumours and Successful Introduction of Plaque Brachytherapy

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Abstract:

Plaque brachytherapy is a well-established, eye-preserving treatment for selected intraocular tumours. It delivers a high radiation dose directly to the tumour with rapid dose fall-off, thereby minimising exposure to adjacent critical ocular structures. We report the successful introduction of ruthenium-106 (^{106}Ru) plaque brachytherapy at Max Super Speciality Hospital, Saket, New Delhi and describe our initial experience.

A 41-year-old male diagnosed with choroidal melanoma on clinico-radiological evaluation was planned for ocular brachytherapy. The procedure was performed under general anaesthesia with strict radiation safety protocols and multidisciplinary coordination. Radiation dose and other parameters were decided based on clinico-radiological parameters. Plaque insertion and removal were uneventful.

Published literature supports high local control rates and acceptable toxicity profiles with ^{106}Ru plaque therapy, despite high scleral surface doses. Our experience demonstrates that plaque brachytherapy is a feasible, effective, and vision-sparing modality. Establishing such a programme requires institutional commitment, trained personnel, and close collaboration among ophthalmology, radiation oncology, medical physics, and radiation safety teams.

Key words: Plaque Brachytherapy, Ruthenium-106, Uveal Melanoma, Choroidal Melanoma, Ocular Oncology.

Introduction

Plaque brachytherapy is a specialised form of brachytherapy used for treating certain intraocular tumours. It refers to the process of using a low-energy radioactive source (plaque) as a temporary interstitial implant and suturing it to the scleral surface of the eye overlying the tumour. This allows for high doses of radiation to be delivered directly to the tumour, with rapid dose fall-off to surrounding normal tissues, resulting in minimal radiation-induced damage to nearby sensitive normal structures.[1]

Indications

Its role in uveal melanoma is evolving as it serves as an alternative to enucleation. It is especially indicated

for medium-sized tumours (e.g., 2.5–10 mm height). Other indications include retinoblastoma, conjunctival melanomas, iris melanomas, choroidal haemangiomas, and ocular surface tumours like conjunctival squamous cell carcinoma. Plaque brachytherapy is of interest in these tumours as it is an effective, globe-sparing, and consequently vision-preserving treatment that provides good tumour control and a high rate of survival.[2]

Radioisotopes used for plaque treatment[3]

- **Iodine-125 (^{125}I) –** Emits low-energy gamma rays; widely used due to predictable dosimetry and suitable penetration for medium and thicker tumours.
- **Ruthenium-106 (^{106}Ru) –** A beta emitter with a steep dose fall-off, particularly useful for thinner lesions.
- **Palladium-103 (^{103}Pd) –** A photon emitter with a short half-life that may reduce radiation exposure to non-target tissues.[3]

Each radionuclide has distinct dosimetric properties that influence dose distribution, penetration depth, and duration of treatment. The choice of radionuclide depends on tumour size, thickness, and proximity to critical structures such as the macula and optic nerve.[4]

Plaque brachytherapy requires a multidisciplinary team consisting of radiation oncologists, ophthalmologists, medical physicists, and radiation safety officers for the successful application and implementation of treatment (Figure 1). Treatment planning is guided by detailed imaging (ultrasound, fundus photography) to define various tumour characteristics like tumour dimensions, location, and depth.

Figure 1: The "Ocular Brachytherapy Team" at Max Super Speciality Hospital, Saket, New Delhi.

Case Report

A 41-year-old gentleman presented to the ophthalmology outpatient department (OPD) with complaints of decreased vision in the right eye. He was evaluated for his complaints and underwent further testing. On detailed clinical examination, his right-sided visual acuity was 6/12. Fundoscopy revealed a large mass in the superotemporal quadrant with exudative retinal detachment. Based on the clinico-radiological assessment, the diagnosis of right choroidal melanoma was established. Further treatment options, including plaque brachytherapy, particle beam therapy, and enucleation, were discussed in detail. The patient was keen on preserving vision, and he was planned for right eye plaque brachytherapy procedure with a ^{106}Ru source. The tumour specifications were assessed with ultrasound, and the tumour thickness was found to be 13.5 mm with an apical height of 9.5 mm. The dosimetric planning was performed prior to the procedure. A dose of 100 Gy at 7 mm depth was prescribed after calculating the dose rate according to the current activity of the source. The scleral dose was 929 Gy. The duration of the application was 166.7 hours (almost 7 days).

After taking necessary consent and ensuring sterility and radiation safety, the patient was posted for the procedure under general anaesthesia. The eyelid was retracted, and a tunnel was made to position the dummy source, on the scleral surface above the tumour (Figure 2). Indirect fundoscopy was done to confirm the tumour location. The dummy source was then removed. The radioactive plaque was gently applied over the area of bare sclera adjacent to the limbus and sutured (Figure 3). The final position of the plaque was again confirmed with indirect fundoscopy (Figure 4). During the entire treatment, lubricants and other eye drops were used as needed. Radiation safety during the entire procedure was ensured with the use of handheld radiation counters and wipe tests for all surgical instruments to rule out leakage of radiation. All healthcare personnel were required to wear thermoluminescent dosimeter (TLD) badges during the procedure. After the plaque placement, the eye was patched, and the patient was shifted to an isolation room. The attendants were advised to maintain a distance of at least 6 feet from the patient as a precautionary measure. The plaque was removed under local anaesthesia after the completion of the

calculated time. There was mild conjunctival and scleral congestion with no other major problems. The patient was discharged, and his first follow-up after 3 months is awaited.

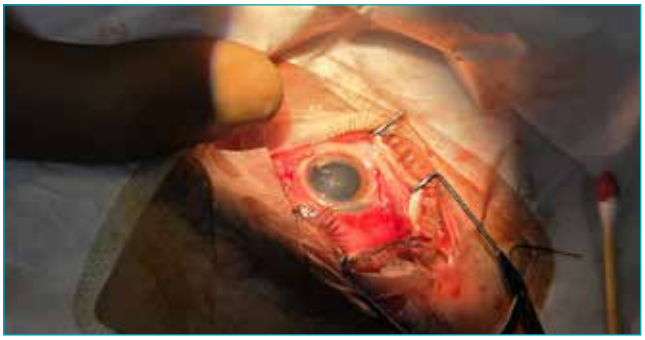

Figure 2: Retraction of the eyelid for the placement of the plaque.

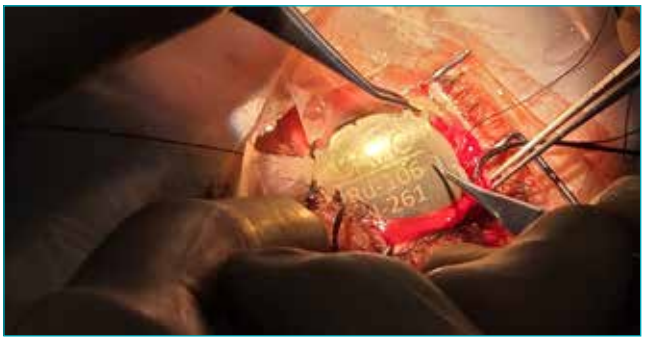

Figure 3: Placement of the radioactive plaque.

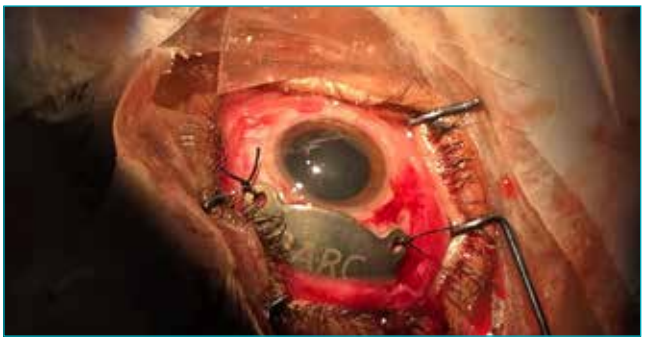

Figure 4: Final positioning of the plaque.

Discussion

Plaque brachytherapy is a form of localised internal radiation therapy widely used in ophthalmic oncology to treat intraocular tumours such as uveal melanoma, retinoblastoma, and certain benign tumours (e.g., circumscribed choroidal haemangioma). Among various radionuclide plaques, ^{106}Ru has become a commonly employed isotope due to its favourable dosimetric and clinical properties. Unlike external beam radiation, plaque brachytherapy provides high doses to the tumour while sparing adjacent critical structures like the optic nerve and macula.[5]

In India, the Bhabha Atomic Research Centre (BARC) has developed indigenous plaques, making them more cost-effective. Two types of plaques are commercially available – notch and round. They vary slightly in their dose distribution parameters, while the basic principle for both remains the same. Round plaques can be used for treating slightly larger tumours, while notch plaque is used for smaller or posteriorly located tumours where optic nerve shielding is needed. Essentially, the plaque is made up of three silver layers: a 15.8 mm diameter and 0.9 mm thick backing plate, a 13.3 mm diameter and 0.2 mm thick silver substrate that contains ^{106}Ru, and a 0.1 mm thick silver window. Both these plaques are available for treatment with our department. Considering the larger tumour size, our patient was treated with the round plaque.[6]

Over decades, retrospective studies and meta-analyses have provided data on efficacy, local control, survival, and toxicity profiles of ^{106}Ru plaques. ^{106}Ru is a pure beta emitter with a maximum energy of approximately 3.5 MeV. Its emissions result in a steep dose fall-off beyond a few millimetres, delivering a high radiation dose at the plaque surface but quickly reducing energy deposition in deeper tissues. This characteristic is advantageous for treating superficial or moderately deep tumours while limiting exposure to deeper ocular structures such as the retina and lens. However, its limited penetration makes it less effective for thicker tumours (> 7–8 mm), where other isotopes like ^{125}I may be preferred. For treatment purposes, tumour thickness is calculated as the height of the tumour along with the scleral thickness. The tumour thickness calculated in this case was 9 mm. We plan to assess the response to therapy at 3–6 months from completion of treatment and plan further local therapy in case of any residual disease. This is a widely accepted treatment technique considering the logistics related to radioactive plaque availability.[4]

Plaque brachytherapy with ruthenium involves scleral fixation of a plaque directly adjacent to the tumour base. The desired delivered radiation dose to the tumour apex usually ranges from 70 Gy to > 140 Gy, depending on tumour characteristics and institutional protocols. We treated our patient with a total dose of 100 Gy as per the

recommendation for the primary treatment of choroidal melanomas.[5]

The shorter range of beta emission translates to lower radiation exposure of nearby normal tissues compared with gamma-emitting sources and subsequently easier handling of the radioactive source. The closest nearby normal tissue of concern in our patient was the sclera. The tumour was away from the optic nerve. The decision regarding total treatment dose is guided by acceptable scleral doses to prevent related toxicity. In ^{106}Ru plaque brachytherapy, the sclera inevitably receives very high radiation doses because the plaque is sutured directly onto the episcleral surface and ^{106}Ru is a beta emitter with a steep dose fall-off. The sclera is a radio-resistant structure, and scleral surface doses typically range from 400 to 1500 Gy, and in some series may exceed 2000 Gy, particularly for thicker tumours where a therapeutic apex dose (70–100 Gy) is prescribed. The spectrum of scleral toxicity can vary from scleritis to necrosis and subsequent vision loss. Despite these high doses, clinically significant scleral necrosis is uncommon, with reported rates generally below 5% in large series.[7]

Uveal melanoma is the most common primary intraocular malignant tumour in adults. In terms of survival with plaque treatment, an institutional report from MD Anderson showed extremely high 5-year control (97%) and overall survival (92%) in 40 uveal melanoma patients treated with ^{106}Ru plaques, with low rates of enucleation and acceptable toxicity.[7]

A meta-analysis of 21 studies involving nearly 4000 patients with uveal melanoma treated with plaque brachytherapy showed local control rates ranging from approximately 59% to 98%. Larger tumours had lower local control rates. The most commonly reported complications were cataract and radiation-related retinopathy. This meta-analysis established that ^{106}Ru brachytherapy seems to be successful in achieving local control of uveal melanoma.[5]

Studies comparing ^{106}Ru brachytherapy with enucleation in thicker tumours (apex ≥ 8 mm) reported similar melanoma-related mortality between plaque therapy and enucleation, with eye preservation achieved in over 70% of cases.[8]

Conclusion

Plaque brachytherapy is an established first-line curative treatment modality in multiple ocular tumours. Establishing a plaque brachytherapy facility is challenging and time- and resource-consuming. It also needs a motivated multidisciplinary team to make it a successful programme. There is a learning curve to it, and adequately trained manpower is one of the cornerstones in having a successful plaque brachytherapy service.

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Steroid-Responsive Encephalopathy Associated with Autoimmune Thyroiditis: A Case Report – Significance of History, Suspicion, and Imaging

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Abstract:

Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) is a rare but potentially reversible autoimmune neurological disorder characterised by a wide spectrum of neuropsychiatric manifestations, seizures, and encephalopathy. Owing to its protean clinical presentation and frequently nonspecific conventional investigations, SREAT is often misdiagnosed as a primary psychiatric illness or cryptogenic epilepsy. We report a case of a young male presenting with acute psychosis in whom multimodal neuroimaging using contrast-enhanced magnetic resonance imaging (MRI) of the brain and ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET)/computed tomography (CT) revealed limbic and functional cerebral involvement, respectively. Early recognition and prompt immunotherapy resulted in significant clinical improvement. This case highlights the complementary role of structural and functional neuroimaging in establishing the diagnosis of SREAT. The patient was initially misdiagnosed as schizophrenia due to predominant hallucinations and cognitive decline in the absence of overt seizures, highlighting the diagnostic challenge posed by autoimmune encephalopathies with psychiatric presentations.

Key words: Steroid-Responsive Encephalopathy, Autoimmune Thyroiditis, Hashimoto Encephalopathy, FDG-PET/CT, Limbic Encephalitis, Psychosis, Seizures.

Introduction

Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), also referred to as Hashimoto's encephalopathy, is an uncommon immune-mediated encephalopathy associated with elevated thyroid autoantibodies, independent of thyroid hormone status.[1,2] Since its initial description, SREAT has remained a diagnostic challenge due to its heterogeneous clinical manifestations and lack of disease-specific biomarkers. Patients may present with cognitive decline, altered behaviour, psychosis, seizures, movement disorders, stroke-like episodes, or fluctuating consciousness.[1-3]

The diagnosis of SREAT is largely one of exclusion. Cerebrospinal fluid (CSF) analysis is often normal or shows mild protein elevation, while magnetic resonance imaging (MRI) findings range from normal to subtle, nonspecific abnormalities. Electroencephalography (EEG) commonly demonstrates diffuse slowing with or without epileptiform discharges, reflecting underlying encephalopathy. In recent years, functional neuroimaging using ^{18}F-fluorodeoxyglucose positron emission

tomography/computed tomography (FDG-PET/CT) has gained importance in demonstrating cerebral metabolic dysfunction in autoimmune encephalopathies, particularly when structural imaging is inconclusive.[3,4]

We describe a case of SREAT in a young male presenting with acute psychosis and refractory seizures, where combined MRI brain and FDG-PET/CT findings played a pivotal role in diagnosis and management.

Case Report

A 24-year-old male with no prior history of psychiatric illness, epilepsy, or systemic disease presented with acute psychosis. The patient had initially been evaluated by a psychiatrist and was diagnosed with schizophrenia based on prominent neuropsychiatric manifestations, including persistent visual and auditory hallucinations, behavioural disorganisation, and progressive cognitive decline. He had been receiving antipsychotic treatment for several months with minimal clinical improvement. Notably, there was no history of overt seizures, convulsive episodes, or loss of consciousness, which initially reduced suspicion for an underlying epileptic or organic encephalopathic process.

However, the subacute onset of fluctuating confusion, worsening cognitive impairment, and prominent hallucinations in a young male, along with poor response to standard antipsychotic therapy, raised concern for a possible organic and autoimmune aetiology rather than a primary psychotic disorder. The absence of classical seizure activity did not exclude the diagnosis, as autoimmune encephalopathies, particularly SREAT, are well known to present predominantly with psychiatric symptoms, altered mental status, and cognitive decline, sometimes in the absence of seizures.

This diagnostic reconsideration prompted further neurological evaluation, including neuroimaging, EEG, metabolic work-up, and autoimmune testing, ultimately leading to the diagnosis of SREAT and subsequent dramatic response to corticosteroid therapy.

On examination, the patient was conscious but confused, with markedly altered behaviour. He responded intermittently to verbal commands and exhibited no focal motor deficits. Vital parameters were stable. Routine laboratory investigations, including metabolic and infectious work-up, were normal.

EEG revealed diffuse background slowing with intermittent epileptiform discharges, suggestive of an underlying encephalopathic process with cortical irritability. CSF analysis showed normal cell counts and biochemistry, effectively excluding infectious encephalitis.

Autoimmune evaluation revealed markedly elevated anti-thyroglobulin antibody titres, while anti-thyroid peroxidase antibodies and thyroid function tests were within normal limits.

In view of the clinical presentation and EEG findings, autoimmune encephalopathy was suspected, and neuroimaging was pursued.

Neuroimaging findings

MRI of the brain demonstrated subtle bilateral hippocampal and mesial temporal T2-fluid-attenuated inversion recovery (FLAIR) hyperintensities with mild patchy post-contrast enhancement (Figure 1). There was no associated mass effect, diffusion restriction, or haemorrhage. These findings were suggestive of limbic involvement, a pattern commonly seen in autoimmune encephalopathies. The subtlety of MRI abnormalities underscored the limitations of relying solely on structural imaging in such cases.

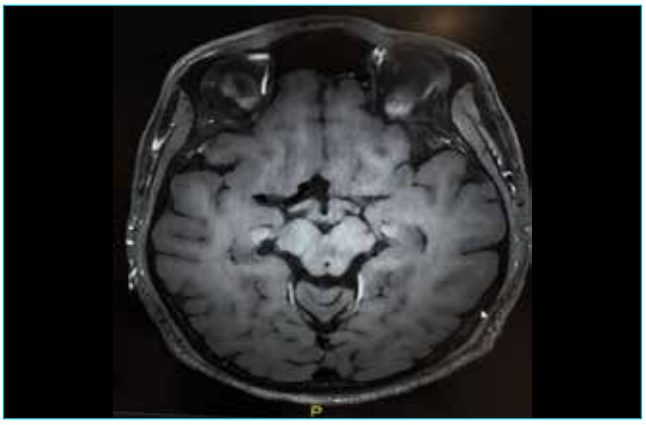

Figure 1: Magnetic resonance imaging (MRI) of the brain (contrast-enhanced): Subtle T2-fluid-attenuated inversion recovery (FLAIR) hyperintensities seen in bilateral hippocampi with patchy contrast enhancement.

Whole-body FDG-PET/CT was performed to evaluate cerebral metabolism and to exclude occult malignancy. PET imaging revealed diffuse hypometabolism of the cerebral cortex, with relative preservation and hypermetabolism of the bilateral basal ganglia and

occipital cortex (Figure 2A and B). Fused PET-CT images demonstrated no corresponding structural abnormality on CT. No hypermetabolic lesion suggestive of malignancy was identified elsewhere in the body.

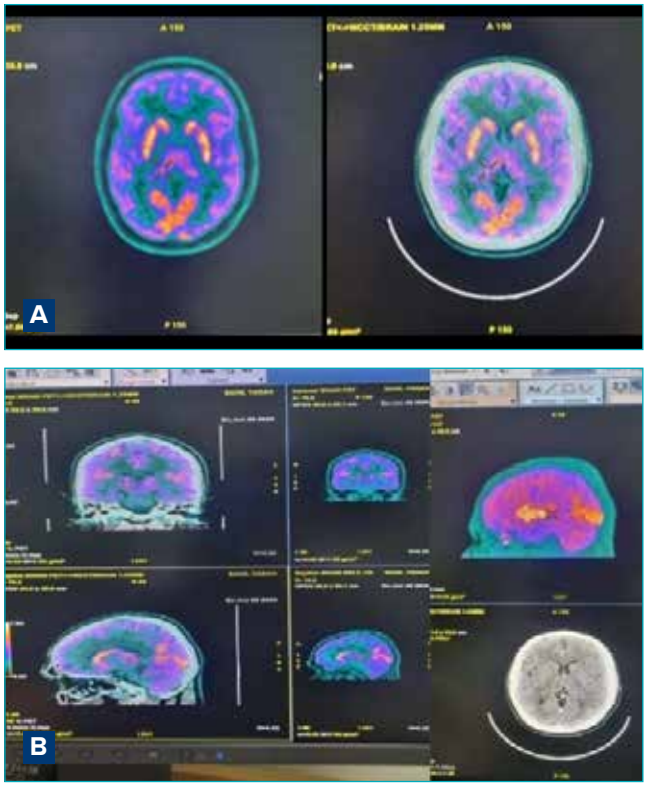

Figure 2A and B: Whole-body ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET)/computed tomography (CT) scan: Diffuse relatively increased/preserved FDG uptake in bilateral basal ganglia and occipital lobe (visual cortex), relative to suppressed FDG uptake in the rest of the cerebral cortex. No other significant focal hypermetabolic lesions in the FDG-PET/CT of the brain were identified.

This metabolic pattern strongly supported an immune-mediated encephalopathy and effectively excluded paraneoplastic encephalitis. The occipital cortical involvement correlated with the patient's visual hallucinations, while basal ganglia hypermetabolism explained the prominent behavioural disturbance and seizure propensity.

Management and outcome

Based on the clinical features, EEG abnormalities, elevated thyroid autoantibodies, limbic MRI changes, and characteristic FDG-PET/CT findings, a diagnosis of SREAT was established.

The patient was initiated on intravenous methylprednisolone (1 g/day for 5 days). Although partial improvement was observed, given the severity of symptoms and PET evidence of widespread functional involvement, intravenous immunoglobulin (IVIG) was administered. Following immunotherapy, the patient showed marked and sustained clinical improvement, with resolution of hallucinations, normalisation of behaviour, and improved seizure control. He was discharged on tapering oral steroids and maintenance antiepileptic medications.

Discussion

SREAT is a rare but important differential diagnosis in patients presenting with acute psychosis and refractory seizures, particularly when routine investigations are unrevealing.[1,2] Misdiagnosis as schizophrenia or functional psychiatric illness is common, leading to delays in appropriate therapy and prolonged morbidity.[2]

Thyroid autoantibodies in SREAT are considered markers of immune dysregulation rather than direct pathogenic agents, and antibody titres do not correlate with disease severity.[2,5] Normal thyroid function tests, as seen in our patient, do not exclude the diagnosis.[1,5]

MRI findings in SREAT are often subtle or nonspecific, as demonstrated in this case.[2] EEG abnormalities, though nonspecific, provide an important clue to the encephalopathic nature of the illness.[1] FDG-PET/CT plays a crucial complementary role by demonstrating functional cerebral abnormalities that may precede or exceed structural changes.[4] The pattern of diffuse cortical hypometabolism with basal ganglia and occipital hypermetabolism has been described in autoimmune encephalopathies and correlates well with neuropsychiatric manifestations.[3,4]

Importantly, whole-body PET/CT also aids in excluding paraneoplastic aetiologies, thereby guiding appropriate immunotherapy.[3]

Conclusion

This case highlights SREAT as a reversible cause of acute psychosis and refractory seizures in young adults. A high index of suspicion, combined with multimodal neuroimaging using MRI of the brain and FDG-PET/CT, is essential for early diagnosis. Prompt immunotherapy can result in dramatic clinical recovery and prevent long-term neurological and psychiatric sequelae.[1,3]

Anand Kumar Saxena. Steroid-Responsive Encephalopathy Associated with Autoimmune Thyroiditis: A Case Report – Significance of History, Suspicion, and Imaging. MMJ. 2026, March. Vol 3 (1).
DOI: https://doi.org/10.62830/mmj3-01-34

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Ante-Mortem Lower-Segment Caesarean Section: A Saviour of Four Lives — A Case Report of Maternal Survival Following Triplet Gestation Complicated by Severe Pre-Eclampsia with Pulmonary Oedema Requiring Ventilatory Support

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Abstract:

Ante-mortem caesarean section (AMCS) is a rare but life-saving intervention performed during maternal cardiac arrest or impending arrest to improve both maternal and neonatal outcomes. Triplet gestation significantly heightens maternal haemodynamic and respiratory demands. Coexisting severe pregnancy-induced hypertension (PIH) with pulmonary oedema creates a high-risk scenario for rapid clinical deterioration. We report a case of a 32-year-old primigravida with a triplet pregnancy complicated by severe pulmonary embolism (PE) and acute pulmonary oedema, who progressed to respiratory failure requiring urgent intubation and ventilatory support. Rapid multidisciplinary intervention culminated in an ante-mortem lower-segment caesarean section (LSCS), resulting in maternal survival and favourable postoperative stabilisation. This case highlights the importance of early recognition of clinical decompensation, prompt airway management, and coordinated obstetric-critical care, intensivist and neonatologist response in managing high-risk multiple gestations.

Key words: Triplets, Severe Pre-Eclampsia, Pulmonary Oedema, Ante-Mortem Caesarean Section (AMCS).

Introduction

A 32-year-old patient conceived triplets through intrauterine insemination (IUI) at a private nursing home. She refused a reduction and wanted to continue all three pregnancies. She was attending regular antenatal care (ANC) visits with her gynaecologist. Suddenly, she developed hypertension and became very breathless at 34 weeks of pregnancy, with oxygen saturation (SpO_2) dropping to 85%; hence, she was transferred under our care at Nanavati Max Super Speciality Hospital, Mumbai.

Triplet gestations are associated with significantly increased maternal complications, including hypertensive disorders, cardiopulmonary compromise, and preterm labour.[1] Severe pregnancy-induced hypertension (PIH) can precipitate pulmonary oedema due to increased systemic vascular resistance, endothelial dysfunction, and reduced colloid osmotic pressure.[2] In acute decompensation, timely airway support and expedited delivery are essential.[3]

Reports of ante-mortem caesarean section (AMCS) in triplet pregnancies are exceedingly rare.[4] We present a case illustrating successful maternal resuscitation and

survival following AMCS in the setting of triplet gestation complicated by severe PIH and pulmonary oedema.

Case Report

A 32-year-old primigravida with IUI-conceived triplet gestation presented at 33 weeks and 5 days with severe hypertension (blood pressure [BP] 150/100 mmHg), dyspnoea, and orthopnoea. She demonstrated tachycardia (118 beats per minute [bpm]), tachypnoea (32 breaths per min), oxygen saturation of 84% on room air, and bilateral basal crepitations. Chest radiography confirmed florid pulmonary oedema. Laboratory investigations revealed proteinuria (2+), elevated uric acid, and marginally deranged liver enzymes.

Despite administration of intravenous antihypertensives and high-flow oxygen, the patient rapidly deteriorated and became severely hypoxic. She underwent urgent endotracheal intubation for respiratory failure. Immediately post-intubation, her vital parameters improved; however, pulmonary oedema persisted. Hence, a decision to initiate diuretics was taken after consultation with the intensivist and obstetric consultants.

Given the critical condition and the presence of a viable triplet gestation, the decision for ante-mortem lower-segment caesarean section (LSCS) was taken to improve maternal survival and optimise foetal outcomes. Accordingly, counselling of the patient's husband and relatives was undertaken, and high-risk consent was obtained. Under continued advanced cardiac life support (ACLS) measures, she was shifted to the operation theatre. A Pfannenstiel incision was made, and rapid LSCS was performed. The foetuses were delivered within three minutes of incision. The three preterm neonates were subsequently transferred to the neonatal intensive care unit for further care.

Following uterine evacuation, maternal haemodynamics improved significantly. However, the uterus remained atonic despite administration of routine uterotonics, and B-Lynch sutures were placed to maintain uterine tone. The patient was stabilised with mechanical ventilation, aggressive BP control, diuresis, and supportive critical-care management. Extubation was achieved on postoperative Day 2; however, she developed persistent abdominal distension due to paralytic ileus, which was managed conservatively over the next 48 hours. She was discharged in stable condition on Day 10 with normalising BP and no neurological deficit.

All three neonates required intubation for 48 hours, and surfactant therapy was administered. Airway support was gradually tapered, and the neonates subsequently tolerated feeds. They were discharged after two weeks with appropriate weight gain. All three neonates are alive and healthy.

Discussion

This case underscores several critical clinical principles:

1. Triplet gestation as an amplified risk state

Multiple gestations impose increased cardiovascular and respiratory demands, predisposing patients to rapid decompensation when complicated by severe PIH.[1,5]

2. Pathophysiology of pulmonary oedema in PIH

Severe hypertension produces endothelial dysfunction, capillary leakage, and reduced colloid oncotic pressure,[2] making patients vulnerable to acute pulmonary oedema, particularly in the third trimester.

3. Need for early airway intervention

Rapid deterioration in respiratory function necessitated early intubation. Maternal hypoxia is the primary driver of foetal compromise in these settings.[3]

4. Life-saving value of AMCS

AMCS was initiated promptly at the onset of maternal circulatory collapse.[3,4] Uterine decompression improves maternal venous return and cardiac output, enhancing resuscitation success. In this case, maternal haemodynamics improved immediately following delivery.

5. Multidisciplinary coordination

Successful outcomes require synchronised efforts among obstetricians, anaesthesiologists, intensivists, pulmonologists and neonatologists. Rapid decision-making and well-practised protocols contribute strongly to maternal recovery.

Acknowledgements

We sincerely acknowledge the support from Dr. Tejaswini Ranade and her team (Intensivist), Dr. Uday Bapat and his team (Anaesthesia), Dr. Nitin Rathod (Pulmonologist), and Dr. Hiren Doshi (Neonatologist).

Conclusion

Ante-mortem LSCS remains a vital intervention in cases of maternal cardiopulmonary collapse, even in complex scenarios such as triplet gestation with severe PIH and pulmonary oedema. Early recognition of respiratory compromise, timely intubation, and rapid operative delivery were instrumental in achieving a favourable maternal outcome. This case reinforces the need for robust obstetric-critical care preparedness and rapid multidisciplinary response in high-risk pregnancies.

'A stitch in time saves nine.'

Rajendra Saraogi, Rekha Ambegaokar, Prajakta Mehendale, Hetal Mistry. Ante-Mortem Lower-Segment Caesarean Section: A Saviour of Four Lives — A Case Report of Maternal Survival Following Triplet Gestation Complicated by Severe Pre-Eclampsia with Pulmonary Oedema Requiring Ventilatory Support. MMJ. 2026, March. Vol 3 (1).

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THE IMAGES

Smile Makeover with Ceramic Restorations without Orthodontic Intervention: A Case Series

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Abstract:

When we meet any individual, the first feature we tend to notice is their smile. An aesthetically pleasing smile plays a pivotal role in a person's self-esteem and confidence. We can state that when an aesthetic dentist performs smile makeover procedures, they aim to improve dental aesthetics and patient confidence. There are many techniques to perform a smile makeover, from composite bonding, orthodontic treatments, dental implants and ceramic restorations. This article explains the steps involved in a smile makeover with ceramic restoration, including veneers, crowns and partial crowns. It also explains which individuals can opt for a smile makeover procedure, along with multiple case presentations. A smile makeover with ceramic restoration is an efficient treatment option to improve the shape, shade, alignment and orientation of an individual's teeth in a relatively short time span.

Key words: Ceramic/e.max Veneers and Crowns, 3D Smile Design, Smile Makeover, Orthodontics, Composite Bonding.

Introduction

What does a smile makeover mean?

A smile makeover can be defined as a procedure that enables the transformation of an imperfect and unattractive smile into a beautiful, aesthetically pleasing smile by means of various dental interventions.[1–3]

These procedures could include the use of composite or ceramic veneers, metal-free crowns, dental implants, teeth whitening, gum contouring and orthodontics.

Who could need a smile makeover?

A smile makeover may be indicated for individuals who are dissatisfied with the appearance of their smile and seek improvement in dental aesthetics and function. Patients commonly present with concerns such as tooth discolouration, enamel wear, chipped or fractured teeth, spacing between teeth, mild-to-moderate malalignment, protrusion, or missing teeth. Additionally, uneven gingival architecture, gingival pigmentation, and teeth that are disproportionate to facial features may adversely affect smile harmony and warrant aesthetic intervention. Smile makeover procedures are also beneficial for patients with altered tooth form or orientation due to parafunctional habits, erosion, or previous dental treatments. Appropriate case selection, based on clinical examination, patient expectations, and periodontal and occlusal health, is essential to determine the most suitable treatment approach and to achieve predictable and satisfactory outcomes.[1,2,4]

What are the procedures involved for a smile makeover?

The procedures involved in a smile makeover include orthodontic treatment for the correction of tooth alignment, teeth whitening to improve dental shade, and dental implants for the replacement of missing teeth. Composite bonding may be used for minor aesthetic corrections, such as closing small spaces or repairing chipped teeth, while periodontal procedures, such as gum contouring or depigmentation, help enhance gingival symmetry and appearance. Fixed prosthetic options, including crowns and bridges, are employed to restore tooth form, function, and aesthetics, whereas ceramic veneers are commonly used to modify tooth colour, shape, size, and alignment to achieve an overall harmonious smile.[5–7] In this article, we will be emphasising on ceramic veneers.

Ceramic veneers are thin layers of porcelain cemented onto the outer surface of the tooth enamel to achieve the desired aesthetic and functional result (Figure 1). This may involve minimal preparation or trimming of the tooth enamel.[1,4,6] These shells are bonded to the front of the teeth, thereby changing their colour, shape, size, or length.

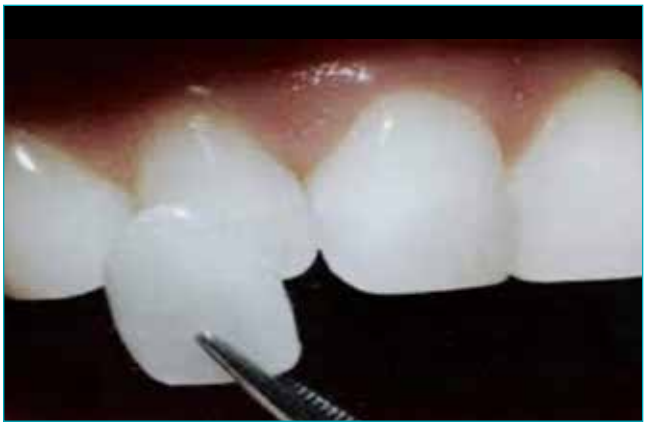

Figure 1: Representative clinical image illustrating a ceramic veneer bonded to the labial surface of anterior teeth to enhance aesthetics.

Why ceramic veneers?

The advantages and limitations of orthodontic treatment, composite bonding, and ceramic veneers are summarised in Table 1.[1,6,7]

Orthodontics	Composite bonding	Ceramic veneers
Advantages 1. Highly conservative, with no tooth reduction 2. Predictable correction of tooth alignment and occlusion 3. Maintains natural tooth structure 4. Provides long-term stability when appropriate retention protocols are followed	**Advantages** 1. Conservative and minimally invasive 2. More economical than ceramic restorations 3. Can be completed in a single-visit or over a short treatment period 4. Easy to repair and modify	**Advantages** 1. Superior aesthetics and translucency 2. Can improve tooth shape, shade, alignment, and proportions 3. Long-lasting with colour stability 4. Better gingival adaptation and biocompatibility 5. Reduced plaque accumulation and staining 6. Can improve occlusion and tooth anatomy
Disadvantages 1. Time-consuming treatment duration 2. Requires high patient compliance 3. Aesthetic improvement is gradual 4. Does not improve tooth shape or shade 5. Risk of relapse if retention is inadequate 6. Extractions or interproximal stripping may be required	**Disadvantages** 1. Inferior aesthetics compared to ceramics 2. Opaque appearance in some cases 3. Prone to staining and discolouration over time 4. Bulky contours may compromise gingival health 5. Increased plaque accumulation 6. Limited longevity	**Disadvantages** 1. More expensive than composite bonding 2. Requires enamel reduction in most cases 3. Irreversible procedure 4. Increased chair time and laboratory involvement

Table 1: Advantages and limitations of orthodontic treatment, composite bonding, and ceramic veneers.

Steps for Smile Makeover

1. Pictures, videos, and impressions or scans
2. Three-dimensional (3D) smile design
3. Mock-up
4. Teeth preparation or veneer preparation
5. Temporisation or trial smile
6. Review to check the trial smile and make changes in the temporaries, if needed
7. Trials and cementation
8. Follow-up

Where do we start?

Smile makeover treatment begins with comprehensive data collection to accurately assess the patient's existing dental and facial parameters before formulating a definitive treatment plan. Diagnostic records include intraoral impressions using elastomeric materials or digital intraoral scans to document the patient's pre-treatment dental condition and occlusion (Figure 2). Standardised extraoral and intraoral photographs and videos are recorded[8,9] using a digital single-lens reflex (DSLR) camera to evaluate smile dynamics, tooth display, facial symmetry, and lip mobility, and to facilitate effective communication between the clinician and the laboratory technician (Figure 3, Figure 4A and B). When indicated, a face-bow transfer is performed to record the maxillomandibular relationship and to accurately transfer functional and aesthetic parameters to the articulator for precise treatment planning (Figure 5A and B). In addition to clinical records, understanding patient expectations is a critical component of smile design, as it helps align the proposed aesthetic outcome with the patient's concerns and desired improvements, thereby enhancing acceptance and predictability of the final result.

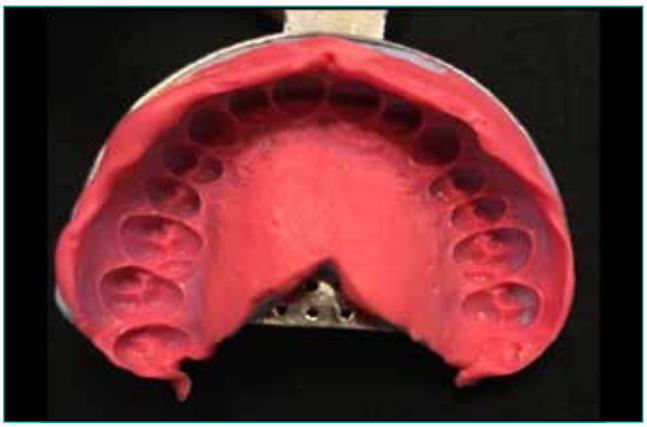

Figure 2: Intraoral impressions or digital scans recorded as part of pre-treatment diagnostic data collection.

Figure 3: Digital single-lens reflex (DSLR) camera for pre-treatment smile analysis and documentation.

Figure 4A and B: Standardised frontal and lateral extraoral facial photographs used for smile analysis and digital smile design.

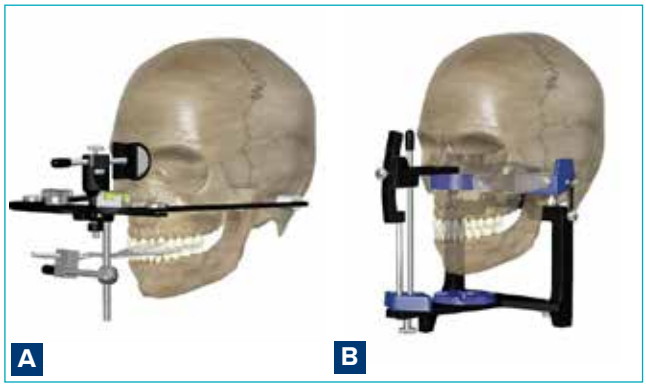

Figure 5A and B: Face-bow transfer procedure used to record maxillomandibular relationships and to transfer them accurately to the articulator.

3D smile design

This is a technique used to envision the final result before beginning the case. By utilising the patient's pictures, impressions, or scans, a digital smile design software like Digital Smile Design (DSD) and Exocad Dental Computer-Aided Design (CAD) is used to create the design of an individual's future smile on a 3D model with facial simulation. This helps the patient understand and accept the treatment plan better.[8,9]

Figure 6A and B: Digital smile design workflow demonstrating the integration of patient photographs and dental scans for virtual smile planning.

Figure 7A and B: Three-dimensional (3D) digital smile design model illustrating proposed teeth dimensions, contours, and smile harmony.

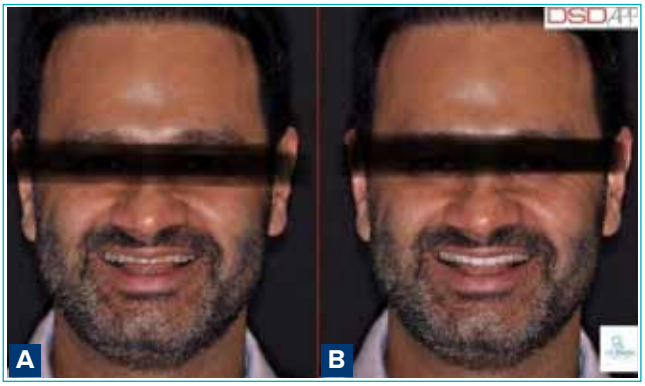

Figure 8A and B: Facial simulation depicting pre-treatment and post-treatment smile outcomes using digital smile design software.

Mock-up

This is a technique used to transfer the new 3D smile onto the patient's existing teeth without altering the patient's original teeth. This mock-up acts as a test drive for the patient, allowing them to see what their future smile would look like even before any tooth preparation begins.[4]

Figure 9A and B: Intraoral mock-up transferred from the digital smile design to the patient's existing dentition without tooth preparation.

Tooth preparation

After the patient is anaesthetised, selective trimming of tooth enamel is performed to make space for the ceramic e.max veneer. The amount of tooth preparation needed is guided by the 3D smile design model.[1,7] Incisal and labial guides are fabricated from the 3D model.

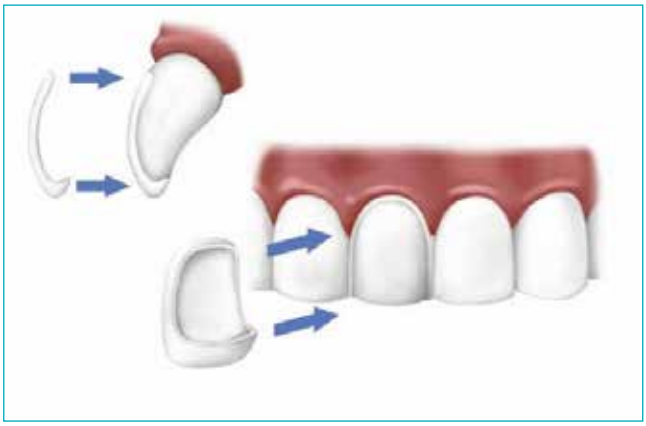

Figure 10: Tooth preparation design for ceramic veneers demonstrating minimal reduction confined to the labial surface with an incisal butt-joint configuration.

Figure 11: Pre-operative view of anterior teeth before veneer tooth preparation.

Figure 12: Post-preparation view showing minimal enamel reduction following guided veneer preparation.

Figure 13: Incisal reduction guide (incisal index) used to verify adequate and controlled tooth preparation.

Temporisation

Once tooth preparation is complete, the patient is fitted with temporary veneers or restorations crafted intraorally from a putty index derived from the 3D smile design model. These temporaries utilise bis-acryl composite materials, such as Protemp or Luxatemp, ensuring optimal fit, aesthetics, and comfort during the interim period.

Figure 14: Putty index derived from the digital smile design used for the fabrication of provisional restorations.

Veneer cementation

The dental laboratory typically requires about one week to fabricate the final veneers,[6,7] most commonly using e.max lithium disilicate or feldspathic porcelain for their strength, aesthetics, and biocompatibility.

Prior to cementation, a trial fitting is performed to confirm the fit, shape, and shade with the patient. Upon approval, the veneers are bonded using a meticulous protocol tailored to the material, ensuring long-term durability and natural results.

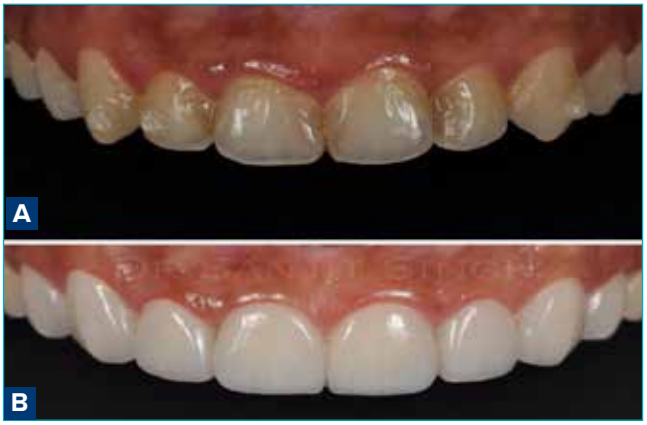

Figure 15A and B: Comparison of anterior teeth before and after cementation of lithium disilicate (e.max) ceramic veneers.

Follow-up

A follow-up appointment is scheduled a few days post-cementation to verify optimal bite, occlusion, and overall comfort. This step ensures that any minor adjustments are addressed promptly, maximising patient satisfaction and the longevity of the veneers.

Case Reports

To illustrate the transformative results of our protocol, we present selected clinical cases below. These feature before-and-after comparisons of patients who received ceramic restorations and veneers,[10] highlighting enhanced aesthetics, function, and patient satisfaction.

Case report 1

A female patient in her mid-30s presented with severe erosion and tooth wear caused by long-standing gastric reflux and bruxism. Loss of anterior tooth length not only compromises masticatory efficiency but also contributes to a prematurely aged appearance. The patient's primary objective was to restore a youthful smile using ceramic restorations. As the patient was travelling from London specifically for dental treatment, comprehensive digital planning was performed in advance, including a 3D smile design prior to her arrival in India. The treatment was completed within 10 days using lithium disilicate (e.max) veneers and partial crowns, achieving both functional and aesthetic rehabilitation.

Figure 16: A. Pre-treatment extraoral and intraoral views showing severe erosion and wear of the anterior teeth due to gastric reflux and bruxism; **B.** Post-treatment views demonstrating restoration of tooth length and smile aesthetics using ceramic restorations.

Figure 17: A. Pre-treatment smile view illustrating reduced incisal display and an aged appearance; **B.** Post-treatment smile view showing improved incisal display, tooth proportions, and overall facial harmony.

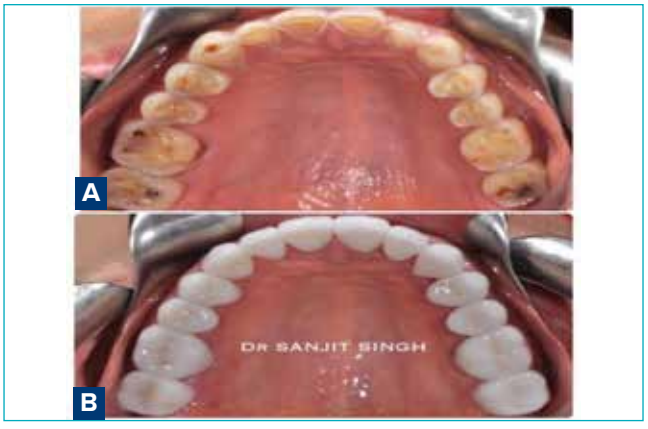

Figure 18A and B: Occlusal view demonstrating severe anterior tooth wear pre-treatment and rehabilitation with ceramic restorations post-treatment.

Case report 2

The patient in this case presented with concerns of spacing between the teeth, excessive gingival display, protrusion, and dissatisfaction with tooth shade. Although orthodontic treatment was a viable option, it was declined by the patient due to its longer treatment duration and its inability to significantly alter tooth shape and shade. Ceramic veneers were therefore selected as the treatment modality. The final outcome demonstrated a wider and more harmonious smile, reduced gingival display, improved tooth shade with a natural appearance, enhanced tooth morphology, and complete closure of interdental spaces.

Figure 19: A. Pre-treatment extraoral and intraoral views showing anterior spacing, protrusion, and excessive gingival display; **B.** Post-treatment views demonstrating space closure, reduced gingival display, and improved smile aesthetics.

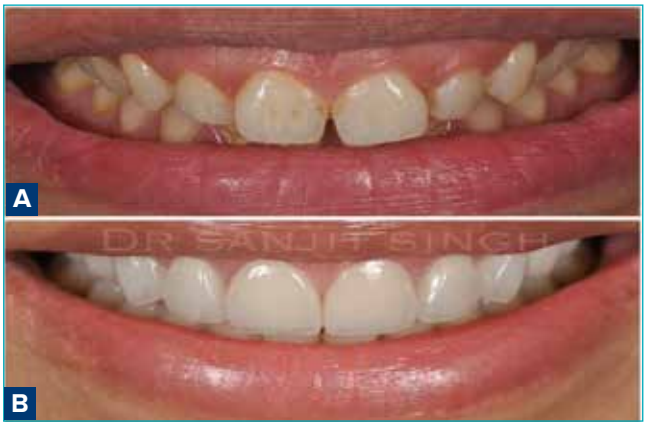

Figure 20: A. Pre-treatment digital smile analysis; **B.** Post-treatment digital smile design illustrating proposed tooth proportions and gingival correction.

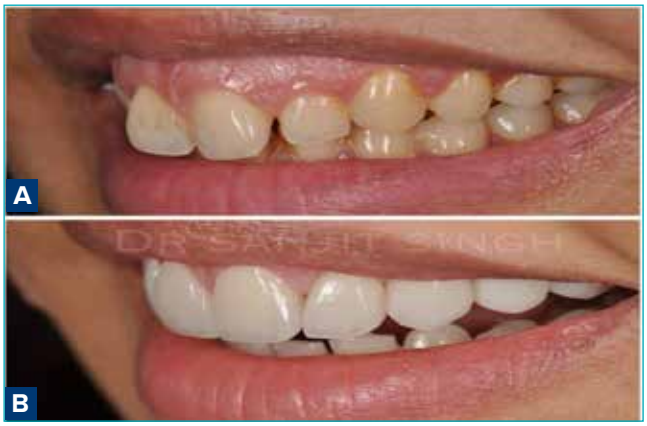

Figure 21: A. Pre-treatment intraoral view prior to veneer preparation; **B.** Post-preparation view following guided minimal tooth reduction.

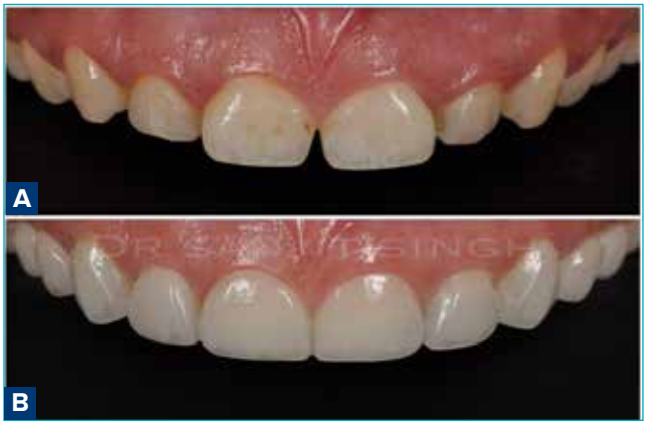

Figure 22: A. Pre-treatment smile view showing spacing and shade discrepancies; **B.** Post-treatment smile view demonstrating improved tooth shade, form, and harmonious smile design.

Case report 3

This case involved a patient residing in the United States who presented with crowded and discoloured anterior teeth. Ideally, such cases are best managed with orthodontic treatment. However, due to the patient's psychological distress, including depression and lack of self-confidence, a restorative approach was selected at the insistence of his family. In cases requiring significant alteration of tooth position and appearance, a 3D smile design is essential to accurately visualise the final outcome prior to initiating treatment. After achieving a satisfactory digital simulation, the treatment plan was approved. Although increased tooth preparation was anticipated and posed a concern, careful planning allowed completion of treatment without the need for endodontic intervention, resulting in a successful aesthetic outcome.

Figure 23: A. Pre-treatment intraoral views showing crowded and discoloured anterior teeth; **B.** Post-treatment views demonstrating correction of crowding and improved tooth shade with ceramic restorations.

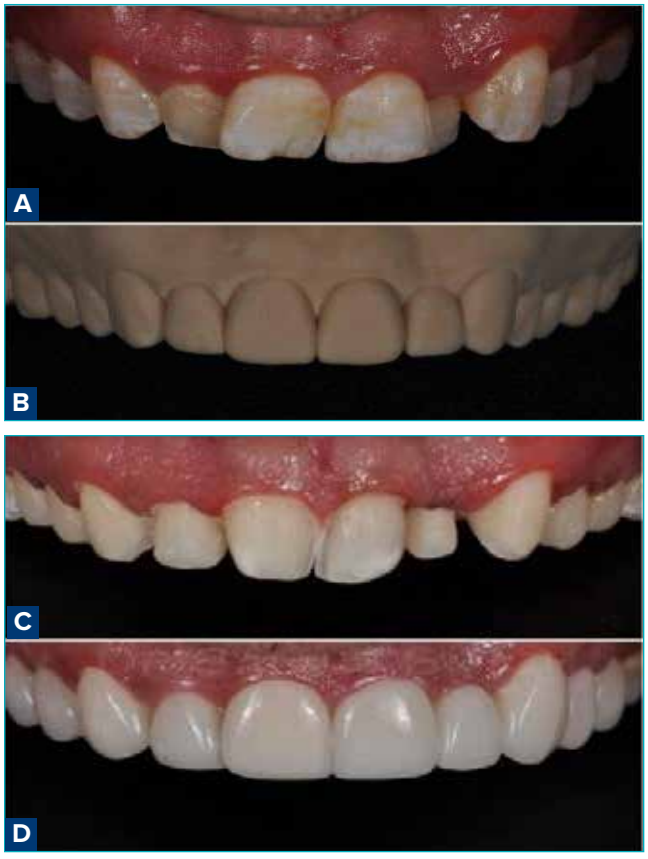

Figure 24: Sequential views illustrating: **A.** Pre-treatment condition; **B.** Digital smile design; **C.** Tooth preparation; **D.** Final restorative outcome.

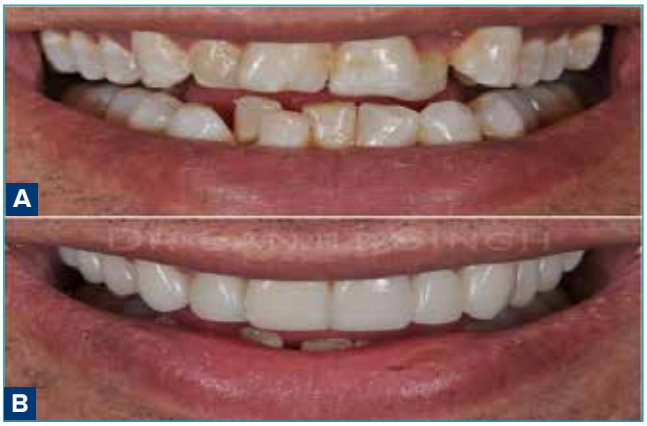

Figure 25: A Pre-treatment frontal smile view showing irregular alignment; **B.** Post-treatment frontal smile view demonstrating improved smile symmetry.

Figure 26: A. Pre-treatment lateral smile view; **B.** Post-treatment lateral smile view showing improved facial harmony.

Figure 27: A. Pre-treatment intraoral frontal view showing crowding and discolouration; **B.** Post-treatment intraoral frontal view demonstrating improved alignment, shade, and symmetry following ceramic restorations.

Case report 4

This patient had previously undergone orthodontic treatment; however, residual spacing remained, resulting in compromised smile aesthetics. A restorative approach using ceramic veneers and partial restorations was employed to correct the spacing and enhance overall dental harmony. The case was managed using an interdisciplinary approach involving a periodontist and an orthodontist to ensure optimal aesthetics, function, and long-term stability.

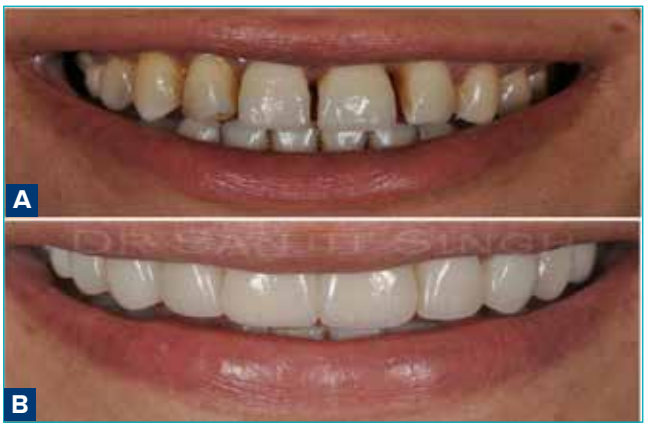

Figure 28: **A.** Pre-treatment intraoral view showing residual spacing following orthodontic treatment; **B.** Post-treatment views after correction with ceramic veneers and partial restorations.

Figure 29: **A.** Pre-treatment smile view with residual spacing and compromised aesthetics; **B.** Post-treatment smile view demonstrating improved dental harmony and proportions.

Case report 5

This case involved a young patient who had lost her maxillary anterior teeth and required placement of two dental implants along with guided bone regeneration. Additional procedures included gingival crown lengthening performed using a diode laser to achieve optimal soft-tissue aesthetics. A multidisciplinary treatment approach was adopted to create a harmonious and natural-looking smile. The total treatment duration was approximately one year, allowing sufficient time for implant osseointegration prior to veneer placement. Final rehabilitation included a combination of implant-supported crowns, endodontic treatment, and lithium disilicate (e.max) veneers.

Figure 30: **A.** Pre-treatment views showing missing maxillary anterior teeth; **B.** Post-treatment view demonstrating restored smile aesthetics following multidisciplinary rehabilitation.

Figure 31: Sequential images showing implant placement and guided bone regeneration in the maxillary anterior region.

Abbreviation: GBR: Guided Bone Regeneration.

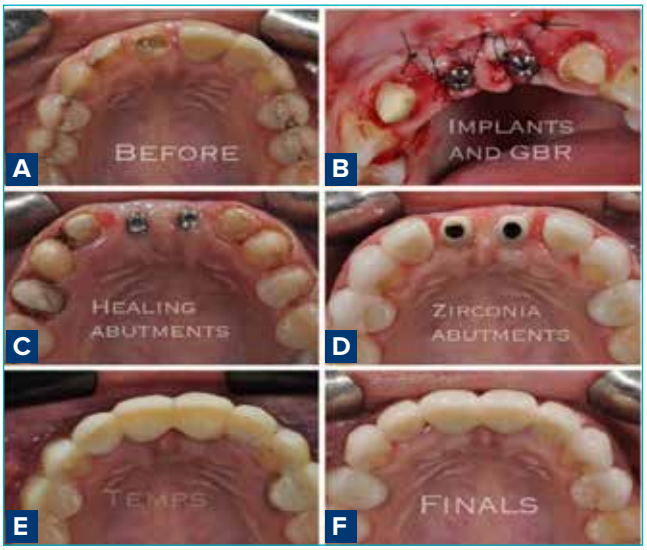

Figure 32: A. Pre-treatment soft-tissue condition; **B-F.** Healing, provisionalisation, and soft-tissue contouring prior to final restoration.

Abbreviation: GBR: Guided Bone Regeneration.

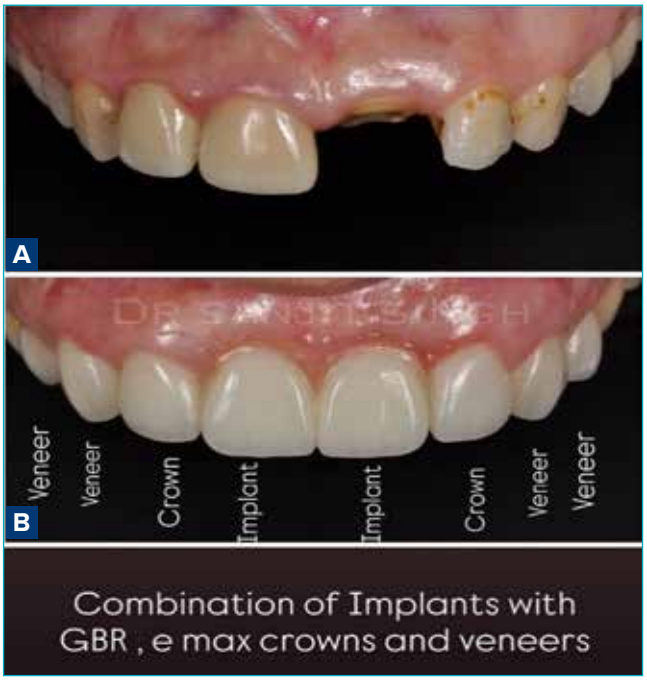

Figure 33: A. Pre-treatment smile view with missing anterior teeth; **B.** Post-treatment smile view showing implant-supported restorations combined with ceramic veneers and crowns.

Abbreviation: GBR: Guided Bone Regeneration.

Case report 6

This patient presented with discoloured teeth caused by dental fluorosis, characterised by dark, patchy enamel discolouration that negatively impacted her self-esteem. The patient desired a brighter and more uniform smile. Ceramic lithium disilicate (e.max) veneers were used to mask the discolouration effectively and restore an aesthetically pleasing smile.

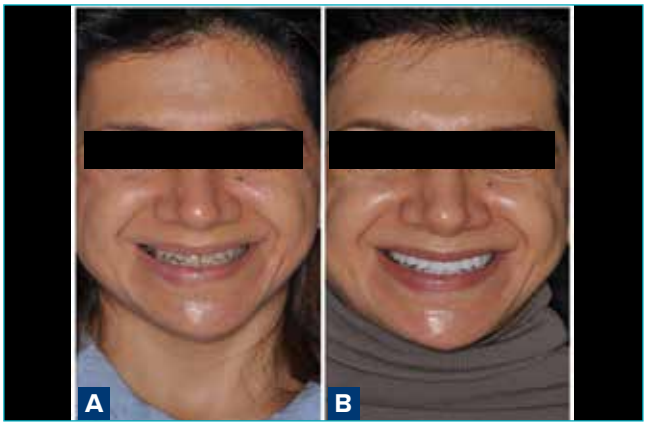

Figure 34: A. Pre-treatment intraoral views showing enamel discolouration due to fluorosis; **B.** Post-treatment views demonstrating masking of discolouration with ceramic veneers.

Figure 35: A. Pre-treatment smile view with uneven tooth shade; **B.** Post-treatment smile view showing a brighter and more uniform smile.

Case report 7

This case involved a patient who presented with an anterior diastema and dissatisfaction with tooth shade and shape. A restorative treatment plan using ceramic veneers and partial crowns was implemented to close the spaces and improve tooth proportions, resulting in a balanced and aesthetically pleasing smile.

Figure 36: **A.** Pre-treatment intraoral views showing anterior diastema; **B.** Post-treatment view demonstrating diastema closure with ceramic restorations.

Figure 37: **A.** Pre-treatment smile view with spacing and shape discrepancies; **B.** Post-treatment smile view showing improved aesthetics with ceramic veneers and partial crowns.

Case report 8

This patient presented with multiple carious lesions accompanied by pain and significant concern regarding her smile appearance. Initial management included comprehensive caries removal, composite restorations, and necessary endodontic treatment. Subsequently, a combination of lithium disilicate (e.max) veneers and crowns was used to achieve functional rehabilitation and a complete aesthetic transformation.

Figure 38: **A.** Pre-treatment intraoral views showing multiple carious lesions; **B.** Post-treatment views following caries management and aesthetic rehabilitation.

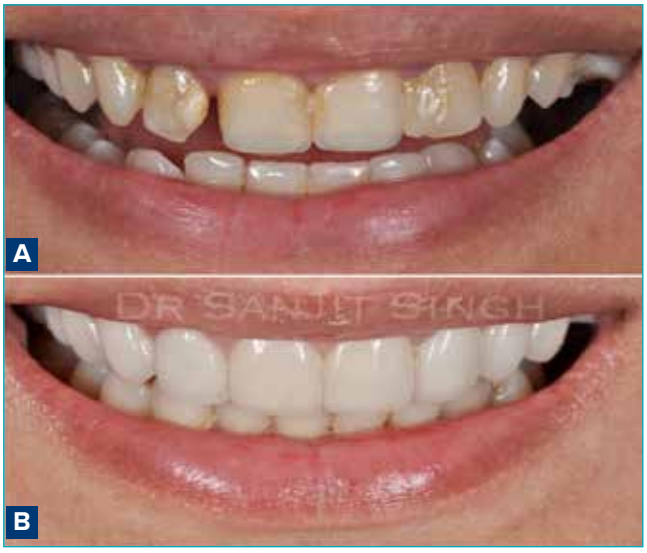

Figure 39: **A.** Pre-treatment view prior to definitive restorations; **B.** Post-treatment view after placement of ceramic veneers and crowns.

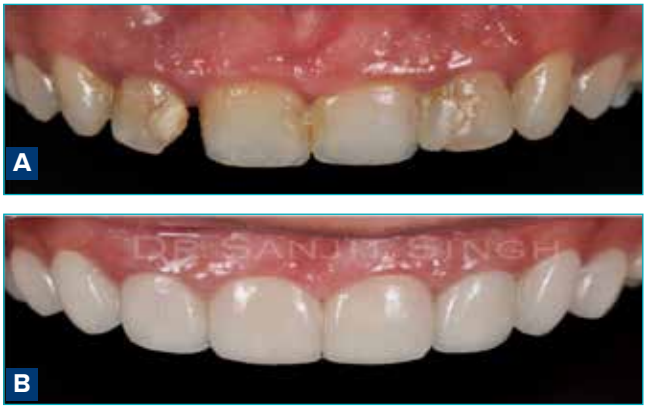

Figure 40: **A.** Pre-treatment smile view with compromised aesthetics; **B.** Post-treatment smile view demonstrating complete functional and aesthetic rehabilitation.

Conclusion

Smile makeovers using ceramic veneers and partial crowns provide a predictable and efficient solution for improving dental aesthetics and function in appropriately selected patients. With careful diagnosis, structured treatment planning, and the use of digital tools such as 3D smile design, clinicians can accurately visualise outcomes, enhance patient communication, and achieve high levels of satisfaction.

Ceramic restorations offer excellent aesthetics, durability, and favourable gingival response, making them a reliable alternative to orthodontic treatment in patients seeking immediate aesthetic improvement. When performed by a trained aesthetic dentist, smile makeover procedures not only enhance dental appearance but also significantly improve patient confidence and overall quality of life.

Sanjit Singh, Ritika Pan. Smile Makeover with Ceramic Restorations without Orthodontic Intervention: A Case Series. MMJ. 2026, March. Vol 3 (1).
DOI: https://doi.org/10.62830/mmj3-01-26

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Implant-Based Breast Reconstruction Following Nipple-Sparing Mastectomy: A Case Series of Immediate and Interval Reconstruction in a Dedicated Breast Unit

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Abstract:

Implant-based breast reconstruction following nipple-sparing mastectomy (NSM) has gained increasing acceptance due to its oncological safety and favourable aesthetic outcomes. It can be performed in immediate or delayed settings depending on disease biology and patient factors. We present a two-patient case series from a dedicated breast unit. The first patient underwent bilateral NSM with immediate implant-based reconstruction for synchronous bilateral breast carcinoma. The second patient, with Li-Fraumeni syndrome, underwent interval NSM and reconstruction following prior breast-conserving surgery and chemotherapy. Surgical technique, perioperative outcomes, and early aesthetic results were evaluated. Both patients underwent successful subpectoral silicone implant placement with native acellular dermal matrix (ADM) support. No intraoperative or postoperative complications were observed. Nipple–areola complex (NAC) viability was preserved in both cases. Patients demonstrated satisfactory wound healing, early mobilisation, and favourable aesthetic outcomes at follow-up. Implant-based reconstruction following NSM is a safe and effective option in carefully selected patients. Both immediate and interval reconstructions can be performed with excellent clinical and aesthetic outcomes in a multidisciplinary setting.

Key words: Breast Cancer, Implant-Based Reconstruction, Nipple-Sparing Mastectomy, Immediate Reconstruction, Interval Reconstruction, Acellular Dermal Matrix.

Introduction

Breast reconstruction has become an essential component of comprehensive breast cancer care, with a significant impact on psychological well-being, body image, and quality of life. Implant-based reconstruction is currently the most performed reconstructive modality worldwide, owing to its shorter operative time, reduced donor site morbidity, and predictable outcomes compared to autologous reconstruction.[1]

Nipple-sparing mastectomy (NSM) represents an evolution in surgical management, preserving the nipple–areola complex (NAC) while achieving oncological safety in appropriately selected patients. Multiple studies have demonstrated that NSM does not compromise oncological outcomes when careful patient selection criteria are followed, including tumour size, location, and absence of NAC involvement.[2,3]

Immediate breast reconstruction offers psychological benefits and reduces the number of surgical procedures, while delayed or interval reconstruction remains valuable in patients requiring staged oncologic treatment, genetic risk evaluation, or contraindications to immediate reconstruction.[4]

The use of acellular dermal matrix (ADM) has further improved implant-based reconstruction by providing additional soft tissue support, improved implant positioning, and enhanced aesthetic outcomes.[5]

This case series aims to highlight the feasibility and safety of implant-based reconstruction following NSM in two distinct clinical scenarios — immediate bilateral reconstruction and interval unilateral reconstruction in a patient with Li-Fraumeni syndrome — demonstrating versatility across varied oncological contexts.

Methods

This is a retrospective case series of two patients undergoing implant-based breast reconstruction following NSM at a tertiary care breast unit. Both patients were evaluated in a multidisciplinary tumour board. Surgical planning was individualised based on tumour characteristics, genetic profile, and patient preference.

Outcomes assessed included:

- Operative details
- Postoperative recovery
- Complications
- Early aesthetic outcomes

Case Reports

Case report 1: Immediate bilateral implant-based reconstruction

A 44-year-old female presented with synchronous bilateral breast malignancy. Clinical examination revealed a 3 × 2 cm lesion in the left breast and a 1.5 × 1.5 cm lesion in the right axillary tail. Imaging, including mammography, magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT), confirmed localised disease without distant metastasis.

Histopathology demonstrated invasive breast carcinoma of no special type (IBC-NST) — Grade 1, luminal A subtype; oestrogen receptor/progesterone receptor (ER/PR) positive, human epidermal growth factor receptor 2 (HER2) negative, Ki-67 4%–5%. Genetic testing was negative for breast cancer gene (BRCA) mutations.

The patient underwent bilateral NSM with a sentinel lymph node biopsy. The left sentinel lymph node was positive (1/4 nodes), necessitating complete axillary lymph node dissection (levels I–II). Important neurovascular structures, including the thoracodorsal pedicle and long thoracic nerve, were preserved.

Reconstruction was performed immediately using subpectoral silicone implants (320 cc with a moderate profile) with native ADM support. A hockey-stick incision was used bilaterally, and well-vascularised skin flaps were raised while preserving NAC vascularity. The mastectomy specimen weights were 318 g (left) and 354 g (right).

A subpectoral pocket was created, and ADM was sutured inferolaterally to create a sling. Closed suction drains were placed, and wounds were closed in layers.

The postoperative course was uneventful. The patient was mobilised on the same day and discharged on postoperative Day 2 with healthy wounds and preserved NAC viability.

Case report 2: Interval unilateral implant-based reconstruction

A 27-year-old female with carcinoma of the left breast in the background of Li-Fraumeni syndrome (TP53 mutation positive) had previously undergone breast-conserving surgery, sentinel lymph node biopsy, and chemotherapy.

Initial histopathology revealed invasive carcinoma (Grade III) with ductal carcinoma in situ (DCIS) — ER 2/8, PR 4/8, HER2 negative, Ki-67 55%. Final staging was pT1cN0.

Given the genetic predisposition and contraindication to radiotherapy, definitive surgical management with mastectomy was planned.

The patient underwent left NSM via a lateral mammary crease incision. A well-vascularised skin flap was raised while preserving NAC. The mastectomy specimen weighed 460 g.

Reconstruction was performed using a 390 cc moderate profile silicone implant placed in a subpectoral pocket with native ADM support. The ADM was secured inferolaterally to create a sling, and a closed suction drain was placed.

The postoperative course was uneventful, with early mobilisation and good wound healing. The patient was discharged on postoperative Day 1 with a satisfactory aesthetic outcome and preserved NAC viability.

Results

Both patients underwent successful implant-based reconstruction without intraoperative complications (Table 1).

- No surgical site infection, haematoma, or seroma was observed
- NAC viability was preserved in both cases
- Hospital stay was 1–2 days
- Early mobilisation was achieved
- Aesthetic outcomes were satisfactory at 3-month follow-up

Parameter	Case report 1	Case report 2
Age	44	27
Laterality	Bilateral	Unilateral (Left)
Reconstruction timing	Immediate	Interval
Genetic syndrome	No	Li-Fraumeni
Implant volume	320 cc	390 cc
Outcome	Uneventful	Uneventful

Table 1: Comparison of both reconstructive surgeries.

Discussion

Implant-based breast reconstruction following NSM is increasingly recognised as a safe and effective approach in selected breast cancer patients. Preservation of the NAC significantly enhances aesthetic outcomes and patient satisfaction without compromising oncologic safety when appropriate criteria are met.[2,3]

Immediate reconstruction, as demonstrated in case report 1, offers several advantages, including reduced psychological distress, improved body image, and avoidance of additional surgeries. In contrast, interval reconstruction, as in case report 2, is particularly valuable in patients requiring prior oncologic treatment or in those with genetic syndromes such as Li-Fraumeni, where radiotherapy is contraindicated due to increased risk of secondary malignancies.[6]

The use of ADM in implant-based reconstruction has revolutionised surgical outcomes by providing inferolateral support, improving implant positioning, and reducing capsular contracture rates. Subpectoral implant placement remains a widely used technique, offering additional soft tissue coverage and reduced complication rates.[5]

Both cases in this series highlight the importance of meticulous surgical technique, including preservation of flap vascularity, careful patient selection, and multidisciplinary planning. The absence of complications in our patients aligns with reported literature demonstrating low complication rates in NSM with implant-based reconstruction.

Although limited by a small sample size, this case series demonstrates the feasibility of implant-based reconstruction across diverse clinical scenarios, including bilateral disease and hereditary cancer syndromes.

Perioperative Figures 1–8

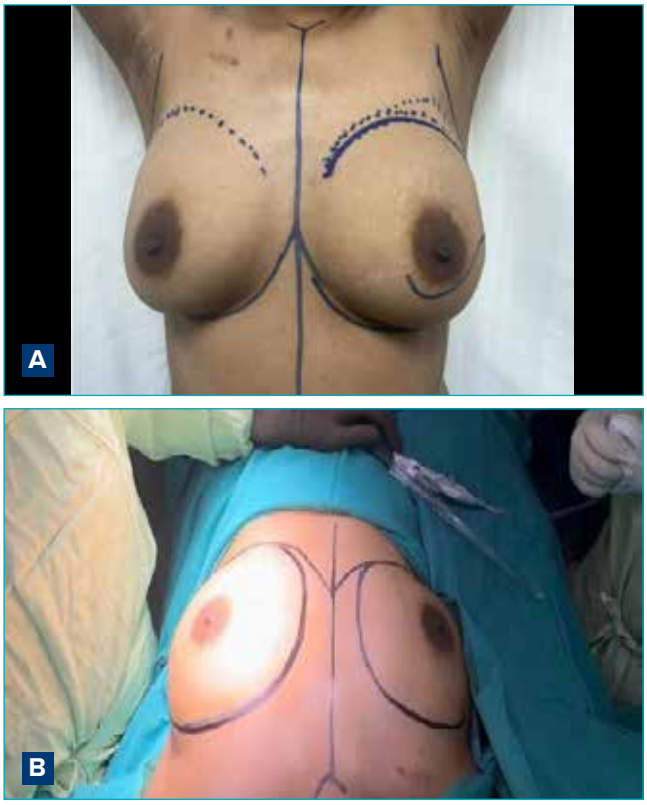

Figure 1A and B: Preoperative markings for nipple-sparing mastectomy.

Figure 2: Intraoperative image showing mastectomy specimen.

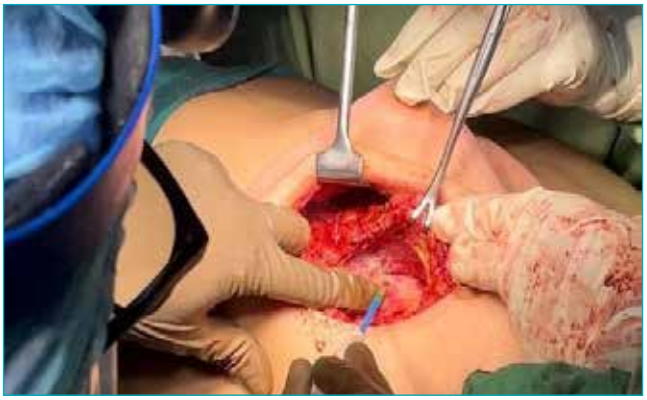

Figure 3: Creation of subpectoral pocket.

Figure 4: Acellular dermal matrix (ADM) placement and sling creation.

Figure 5: Implant positioning.

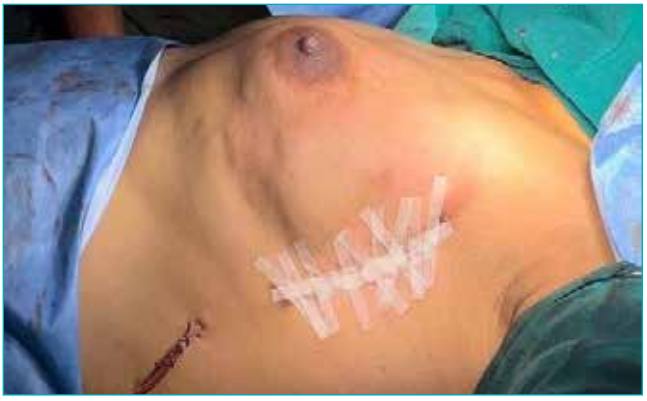

Figure 6: Immediate postoperative outcome.

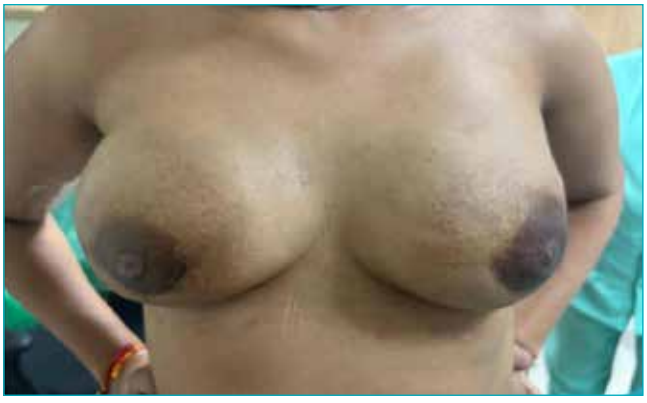

Figure 7: Bilateral reconstruction at 3 months follow-up.

Figure 8: Unilateral reconstruction at 3 months follow-up.

Declarations

Ethics and consent

Written informed consent was obtained from both patients for publication. Institutional ethical guidelines were followed.

Artificial intelligence (AI) disclosure

The authors declare that artificial intelligence-assisted tools were used solely for language editing and manuscript structuring. All clinical content, data interpretation, and final manuscript approval were performed by the authors.

Conclusion

Implant-based breast reconstruction following NSM is a safe, reproducible, and effective technique in both immediate and interval settings. Careful patient selection, adherence to oncologic principles, and multidisciplinary management are critical to achieving optimal outcomes. This approach provides excellent aesthetic results with minimal morbidity and high patient satisfaction.

Rajinder Kaur Saggu, Sneha Galande, Shreya Thakur, Riya Agrawal. Implant-Based Breast Reconstruction Following Nipple-Sparing Mastectomy: A Case Series of Immediate and Interval Reconstruction in a Dedicated Breast Unit. MMJ. 2026, March. Vol 3 (1).
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STUDENTS' CORNER

Clinical Signs – The Forgotten Art! A Review for Postgraduate Medical Students

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Abstract:

Clinical medicine has undergone a paradigm shift over the past few decades, with diagnostic imaging and laboratory investigations increasingly dominating clinical decision-making. While these advances have undoubtedly improved diagnostic precision, they have also contributed to a gradual erosion of bedside examination skills. Many classical clinical signs — once central to diagnosis — are now rarely sought or taught in routine practice. This review revisits the relevance of physical signs in modern medicine, explores why they have been neglected, and highlights nine important but underutilised clinical signs across multiple systems. Each sign is discussed with respect to its historical origins, method of elicitation, pathophysiological basis, and current clinical relevance. Two newly described signs—the 'Pruritic polished nail sign' and the 'Hepatic scratch transmission sign' — are also introduced as original contributions to contemporary clinical semiology.

Key words: Clinical Signs, Bedside Medicine, Physical Diagnosis, Forgotten Signs, Medical Education.

Introduction

The foundation of clinical medicine lies in careful observation. For centuries, physicians relied almost exclusively on history-taking and physical examination to arrive at a diagnosis. The great clinicians of the past — Hippocrates, Sydenham, Laennec, and Osler — emphasised that "the patient is the textbook," and that disease reveals itself through patterns of symptoms and signs.[1,2]

The invention of the stethoscope by René Laennec in 1816 marked the beginning of systematic physical diagnosis. Over the next century, numerous clinical signs were described, each representing an attempt to correlate external physical findings with internal pathology. These signs formed the backbone of bedside medicine well into the mid-20th century.[1,2]

However, the last five decades have witnessed a dramatic transformation. Modern clinicians now have immediate access to ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), echocardiography, endoscopy, and molecular diagnostics. While these tools have revolutionised care, they have also subtly displaced bedside skills from the centre of clinical practice.[1,2]

Why Have Clinical Signs Been Forgotten?

Several factors have contributed to the decline of physical diagnosis:[1,2]

Technological dependence

The availability of imaging and laboratory tests has reduced reliance on clinical reasoning. Diagnosis is often investigation-first rather than examination-first.

Time constraints

High patient volumes and administrative burdens leave little time for detailed bedside examination.

Educational shifts

Medical training increasingly prioritises protocols, algorithms, and test interpretation over physical signs.

Perceived inferiority

Some signs lack high sensitivity or specificity and are therefore considered inferior to imaging.

Defensive medicine

Clinicians rely on investigations for medico-legal documentation rather than clinical judgment.

Why Clinical Signs Still Matter

Despite these challenges, clinical signs remain indispensable:[1,2]

- They provide immediate diagnostic clues
- They are cost-free and universally available
- They enhance clinical reasoning and pattern recognition
- They reduce unnecessary investigations
- They strengthen the doctor–patient relationship
- They are critical in resource-limited settings

Clinical signs should not compete with technology; rather, they should guide the intelligent use of technology.

Nine Important but Underappreciated Clinical Signs

1. Hutchinson's sign (Dermatology/Neurology)

First described: Sir Jonathan Hutchinson, 1864.

Description: Vesicular lesions on the tip of the nose in herpes zoster.

Pathophysiology: Involvement of the nasociliary branch of the ophthalmic division of the trigeminal nerve.

Clinical significance: Strong predictor of herpes zoster ophthalmicus and corneal involvement.[3]

Modern relevance: A simple inspection sign that determines the urgency of ophthalmology referral (Figure 1).

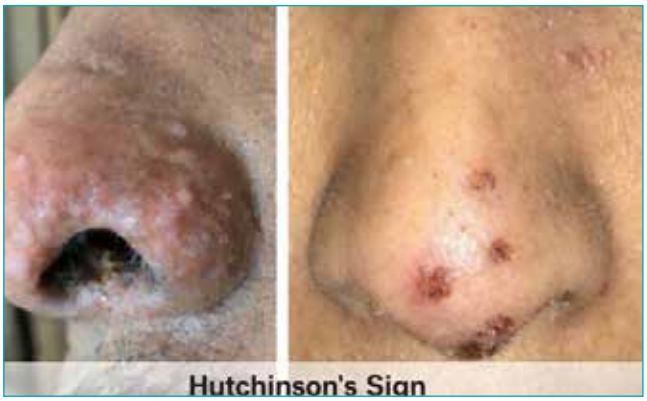

Figure 1: Hutchinson's sign.

2. Coin test for pneumothorax (Respiratory medicine)

First described: Late 19th-century European clinical practice, pre-radiography era.

Method: Two coins are tapped on one side of the chest while auscultating the opposite side.

Positive sign: Metallic "ringing" resonance.

Pathophysiology: Air in the pleural space conducts sound efficiently.

Clinical significance: Suggests pneumothorax, especially in trauma settings (Figure 2).[1,2]

Figure 2: Coin test for pneumothorax.

3. Cruveilhier–Baumgarten sign (Gastroenterology)

First described: Jean Cruveilhier (1835); elaborated by Paul Baumgarten (1907).

Description: Venous hum heard over the epigastrium or umbilicus.

Pathophysiology: Recanalisation of the umbilical vein in portal hypertension.

Clinical significance: Indicates portal hypertension with portosystemic shunting (Figure 3).[4]

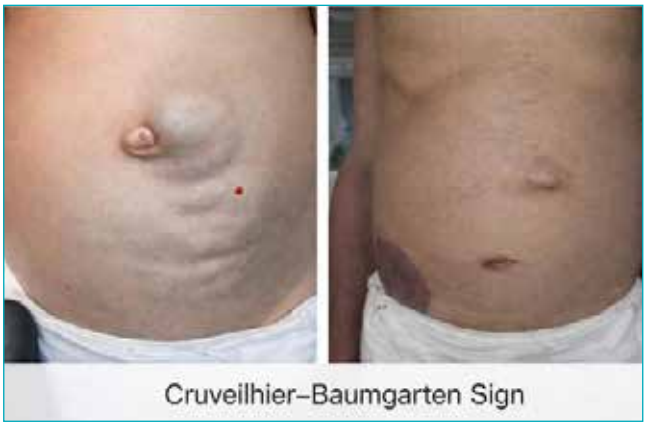

Figure 3: Cruveilhier–Baumgarten sign.

4. Renal bruit (Nephrology)

First correlated with disease: Goldblatt experiments, 1934.

Description: Systolic bruit over flanks or epigastrium.

Pathophysiology: Turbulent flow in renal artery stenosis.

Clinical significance: Suggests renovascular hypertension (Figure 4).[5]

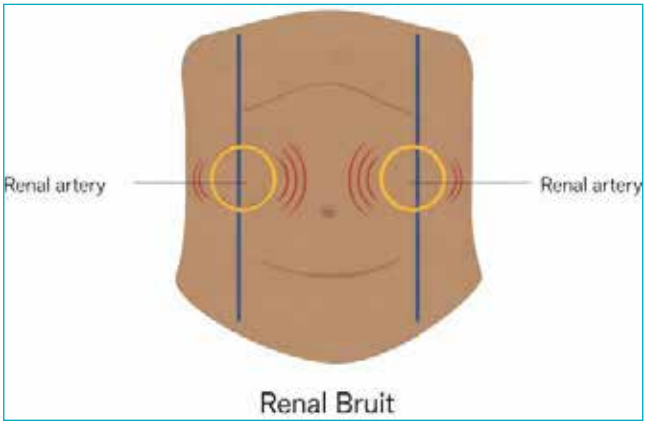

Figure 4: Auscultation over the flank and epigastrium to detect renal bruit suggestive of renal artery stenosis.

5. Plummer's nails (Endocrinology)

First described: Henry Stanley Plummer, 1912.

Description: Onycholysis — distal separation of nail from nail bed.

Seen in: Graves' disease, psoriasis, trauma.

Clinical significance: Subtle but classic sign of thyrotoxicosis (Figure 5).[6]

Figure 5: Plummer's nails.

6. Ewart's sign (Cardiology)

First described: William Ewart, 1896.

Description: Dullness and bronchial breathing in the left infrascapular region.

Pathophysiology: Compression of the lung by a large pericardial effusion.

Clinical significance: Suggests massive pericardial effusion (Figure 6).[7]

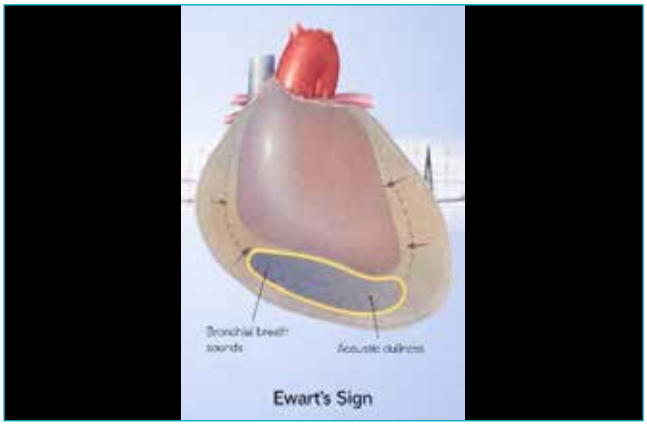

Figure 6: Ewart's sign.

7. Auscultatory signs of aortic regurgitation (Cardiology)

First systematically described: Austin Flint, mid-19th century.

Key auscultatory signs include:

- **Early diastolic decrescendo murmur** (best heard at left sternal border).
- **Austin Flint murmur:** Mid-diastolic rumble at the apex due to regurgitant jet hitting the anterior mitral leaflet.
- **Duroziez sign:** To-and-fro murmur over the femoral artery.
- **Traube's sign:** Pistol-shot sounds over the femoral artery.

Pathophysiology: High stroke volume with rapid diastolic runoff.

Clinical significance: Together, these signs indicate severe aortic regurgitation.[8]

8. Caput medusae (Gastroenterology)

First described: Ancient Greek medicine; formalised in the 18th century.

Description: Dilated periumbilical veins radiating outwards.

Pathophysiology: Portal hypertension with collateral flow.

Clinical significance: Suggests advanced chronic liver disease (Figure 7).

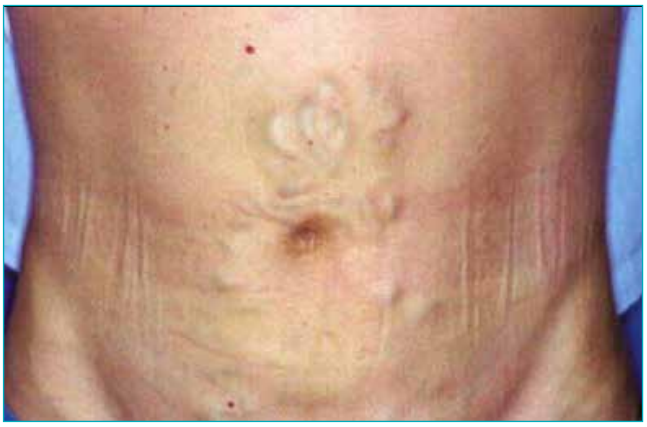

Figure 7: Caput medusae.

9. Plantar reflex variants (Neurology)

First systematically described: Joseph Babinski, 1896.

Variants include:

- **Babinski:** Upgoing great toe
- **Chaddock (1911):** Stroking the lateral malleolus
- **Oppenheim (1902):** Stroking tibial crest
- **Gordon (1904):** Squeezing the calf muscle
- **Schaefer:** Achilles compression

Clinical significance: Upper motor neuron lesion.

Modern relevance: Still the most reliable bedside sign of corticospinal tract dysfunction.[8]

Novel Clinical Signs Described by Prof. Narinder Pal Singh

1. Shiny nail sign (Pruritus nail sign) in obstructive jaundice

Definition: In patients with chronic cholestasis and obstructive jaundice, persistent generalised pruritus leads to repeated rubbing and scratching of the nails against clothing, skin, or bed linen. Over time, this results in abnormally smooth, glossy, and polished nails.

Clinical significance: The presence of unnaturally shiny nails in a jaundiced patient is an indirect marker of severe, long-standing cholestatic pruritus and suggests obstructive pathology rather than hepatocellular jaundice (Figure 8).

Proposed name: Pruritic polished nail sign (or cholestatic shiny nail sign). This sign was originally described by the author based on over 35 years of clinical experience in Internal Medicine.

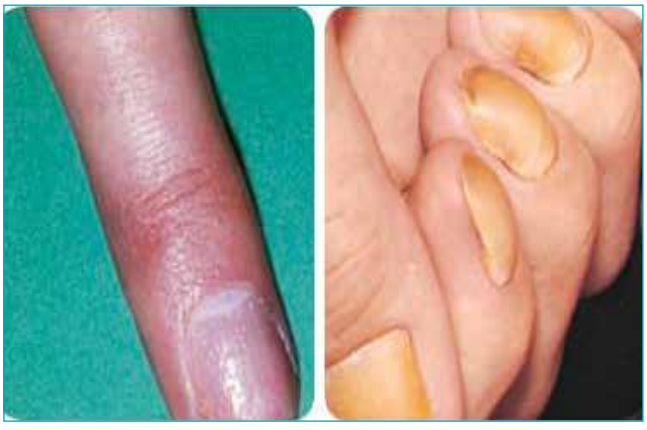

Figure 8: Shiny nail sign.

2. Scratch auscultation sign for liver span

Definition: This is a bedside method to estimate liver size by sound transmission.

Method: Place the diaphragm of the stethoscope over the right upper quadrant, just below the costal margin (over the presumed liver area).

- Using a fingernail, gently scratch the abdominal wall starting from the right lower abdomen and move upward towards the costal margin.
- A sudden change in sound intensity and clarity is heard when the scratching reaches the surface of the liver, because sound is transmitted better through solid organ tissue than through bowel and air.

Clinical significance: This helps identify the inferior border of the liver when percussion is difficult (obesity, tense abdomen, ascites).

Proposed name: Hepatic scratch transmission sign (commonly referred to as scratch test for liver span).

This bedside sign was conceptualised and refined by the author through extensive clinical observation over more than three decades of medical practice.

Discussion

These signs span neurology, cardiology, hepatology, nephrology, endocrinology, and respiratory medicine. None of these signs replace investigations, but all precede them intelligently. They transform clinicians from test interpreters into clinical thinkers.

Physical diagnosis trains:

- Pattern recognition
- Hypothesis formation
- Anatomical reasoning
- Bedside empathy

Conclusion

Clinical signs represent the intellectual heritage of medicine. They are not relics but living tools that connect modern clinicians to centuries of observational wisdom. Technology should confirm, not replace, the bedside examination. Reviving clinical signs restores balance between science and art, ensuring that medicine remains a human discipline rather than a purely technological one.

Narinder Pal Singh. Clinical Signs – The Forgotten Art! A Review for Postgraduate Medical Students. MMJ. 2026, March. Vol 3 (1).
DOI: https://doi.org/10.62830/mmj3-01-33

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Max Institute of Medical Education Announcements

March – 2026

Max Institute of Medical Education (MIME), the educational division of Max Healthcare Institute Ltd., serves as a dedicated centre for the comprehensive education and training of medical professionals, including doctors, nurses, paramedics, allied health professionals, and non-medical healthcare staff.

With meticulous attention to detail, MIME has honed its capabilities in designing well-crafted programs that instil confidence in trainees and students, enabling them to apply their skills with utmost proficiency, adhere to the highest standards, and create a safe environment for patients.

MIME's mission is to build a unique institution where patient care is at the forefront, driven by a committed and highly skilled workforce, with excellence in healthcare delivery. This, in turn, is intended to result in providing ready access to a highly skilled and industry-ready workforce, translating to superior patient care. In addition, it will be a traction factor and retention tool for all cadres of the healthcare workforce.

Creating the Next Generation Of Leaders In Healthcare

12,000
Healthcare Professionals Trained Annually

5,000+
Doctors Trained Annually

800
Faculty Members

170
In-Person and Online Courses

Core Elements of Our Training

- Extensive Practical Training
- Central Academic Council
- World-Class Faculty
- Simulation Lab
- Online Library - Elsevier Clinical Key
- Integrated Healthcare Network
- Learning Management System

Delivering Unparalleled Quality in Medical Education

Diplomate Of National Board (DNB)

Since 2009, Max Healthcare has been officially recognised by the National Board of Examinations (NBE) to provide practical training to students pursuing courses of DNB. This comprehensive DNB training is offered at various locations in Delhi/National Capital Region (NCR), Mumbai, Punjab, and Uttarakhand. Under the guidance of highly qualified, experienced and distinguished faculty who possess extensive experience from various institutions, students undergo their training in accordance with the guidelines laid out by the NBE. At present, MIME has 618 DNB residents in its group of network hospitals.

International Affiliated Programmes

Internal Medicine Training – Imt (MRCP-UK)

Internal Medicine Training (IMT) is a 3-year structured, full-time training programme under the partnership between Max Healthcare and the Federation of Royal Colleges of Physicians of the United Kingdom (UK). The goal of this partnership is to sustainably develop and maintain the standard of a locally run programme, aspiring to provide training equivalent to IMT in the UK from speciality training (ST) 1 to ST 3. Implementing the IMT stage 1 curriculum, the initial stage of ST for most physician specialties in the UK is taken upon completion of the Bachelor of Medicine, Bachelor of Surgery (MBBS) degree. Training, supervision, and assessments are done by the Max Healthcare pool of consultants who are fully trained by the Royal College of Physicians, UK. Trainees gain exposure to a wide range

of internal medicine sub-specialities, like acute medicine, nephrology, gastroenterology, pulmonology, cardiology, and others. Access to the ePortfolio and workplace-based assessment tools offers assessment of various competencies in the curriculum.

External support is provided for trainee reviews to ensure consistent and high-quality feedback by an annual review of competence progression (ARCP). The Max Healthcare, New Delhi IMT programme is a level 3 accredited programme, the highest level of UK-equivalent accreditation. Building on the success of the initial implementation, Max Healthcare expanded the programme to Nanavati Max Super Speciality Hospital (NMSSH) Mumbai in 2024, further solidifying the commitment to high-quality medical education. Currently, over 60 residents are training under this programme.

TRAINING LOCATION:

- Max Super Specialty Hospitals – Delhi and Mumbai

Admission is open for New Session FY 2026

Rcog-Mhc Obstetrics And Gynaecology Programme (Rcog)

This joint postgraduate programme in Obstetrics and Gynaecology is delivered in collaboration with the Royal College of Obstetricians and Gynaecologists (RCOG) in the UK. This programme aims to bring world-class training to the medical fraternity in India, offering an equivalent level of education and expertise as provided in the UK.

This training is equivalent to the Basic (ST 1-2) and Intermediate training (ST 3-5) in the UK. The training programme is underpinned by the RCOG curriculum, membership of the RCOG (MRCOG) examinations, the use of RCOG e-Portfolio, and an ARCP process with UK externality. Max Healthcare is only the second Indian site to be accredited for this programme.

MIME currently has 10 residents enrolled in its RCOG training programme.

KEY HIGHLIGHTS: RCOG-MHC Obstetrics and Gynaecology Programme (RCOG) was recently launched at Max Super Speciality Hospital, Lucknow, UP.

TRAINING LOCATION:

- Max Super Specialty Hospitals – Delhi and Lucknow

Admission is open for New Session FY 2026

Mem–Gwu International

The Max Emergency Medicine–George Washington University (MEM–GWU) is a postgraduate training programme conducted by the MIME in collaboration with the Ronald Reagan Institute of Emergency Medicine, United States of America (USA), George Washington University Medical Centre. This course aims to enrich the knowledge, skills and compassion of Max Healthcare residents, which is needed for effective and efficient emergency medical care.

MEM is a post-MBBS 3-year course comprising 36 modules in Emergency Medicine with the support of faculty from GWU and Max Healthcare. This programme was started in 2008 and has been running successfully with alumni placed in India and worldwide. MIME currently has 90 residents in the MEM–GWU programme.

Admission is open for New Session FY 2026

Fellowship Courses (Non-NBE)

We offer medical training in various specialities to build the competency of physicians through our fellowship courses. The duration of the fellowship ranges from 6 months to 2 years.

- Abdominal and Transplant Imaging Aesthetic Medicine and Surgery
- Bariatric Anaesthesia
- Breast Imaging
- Critical Care Medicine
- Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)
- Emergency Department
- Dialysis
- Orthopaedic Oncology and Reconstruction Foot and Ankle
- Gastroenterology
- General Nephrology
- Gynaecological Onco-Surgery
- Gastrointestinal (GI) Endoscopy
- Head and Neck Surgery
- Hip and Knee
- Pulmonology
- Radiology
- In Vitro Fertilisation (IVF)
- Robotic and Renal Transplant
- Neuro Imaging
- Non-Invasive Cardiology
- Pain Management
- Rheumatology
- Robotics
- Spine Surgery
- Surgical Oncology
- Transplant Hepatology
- Ultrasound-Guided Regional Anaesthesia (UGRA)
- Uro-Oncology and Robotic Surgery
- Women's Imaging and more

Doctor of Philosophy (Ph.D.)

Max Healthcare, through the Max Society of Medical Academics Innovation and Research (MSMAIR), offers a Doctor of Philosophy (Ph.D. – Biological Sciences and Medical Research) programme in collaboration with the Academy of Scientific and Innovative Research (AcSIR). This distinguished programme is designed to provide students with an in-depth understanding of public health challenges, fostering the acquisition of advanced knowledge and skills. It aims to empower graduates to effect sustainable improvements in healthcare through rigorous research, exemplary teaching, and dedicated community health projects.

Post-Graduate (PG) Diploma and Master of Science (M.Sc.) Course

MIME is offering 2-year full-time Master's courses at Max Healthcare Institute Ltd. These programmes are a post-graduate-level degree that allows students to acquire knowledge and skills. In addition, the course will prepare them to work with specific populations and communities to improve health through education, awareness, policy, and real time exposure. Provide career advancement and placement opportunities through these Master's programmes:

- **PG Diploma and Master of Public Health** certified by AcSIR
- **PG Diploma and Master of Healthcare Quality Management** certified by AcSIR
- **PG Diploma and M.Sc. in Clinical Research** certified by Regional Centre for Biotechnology (RCB)
- **PG Diploma in Artificial Intelligence (AI) in Healthcare** in collaboration with Bennett University

  Minimum Eligibility: Bachelor's degree/Graduation in science.

  Duration: 1 year for PG Diploma and 2 years for M.Sc.

Admission is open for New Session FY 2026

Observerships

Medical Observership Programmes are provided in various clinical departments, wherein the Head of the Department shall review the applications from Indian and international students and accept candidates based on the criteria set by the department. Observerships are customised training programmes to develop the skills and knowledge of the medical graduates, where they learn as an observer.

Internships

Internships are provided to expose the students to the industry and give them hands-on expertise to enhance their skills and knowledge. Internship duration can be 1–6 months.

Allied:

- Physiotherapy
- Dietetics
- Psychology

Support Services:

- Biomedical Engineering
- Service Excellence
- Human Resource
- Finance
- Medical Records Department
- Information Technology (IT)
- Fire and Safety
- Healthcare Supply Chain Management

Upcoming Courses Announcement

Life Saver Training Programmes and Bespoke/ Workshop

Max Healthcare Institute is certified as an International Training Centre for the American Heart Association and offers short courses in emergency/resuscitation.

Basic Life Support Provider Course (BLS) - Provider and Instructor

Advanced Cardiac Life Support Provider Course (ACLS) - Provider and Instructor

Paediatric Advanced Life Support Course (PALS) - Provider and Instructor

Upcoming BLS and ACLS training: March 2026

- **Max Super Speciality Hospital, Saket**

  16th Mar: Heartsaver First-aid Cardiopulmonary Resuscitation (CPR) Automated External Defibrillator (AED) Provider

  17th Mar: BLS Provider (HeartCode)

  17th–18th Mar: ACLS Provider Course with Video Prework

  19th Mar: BLS Instructor

  20th Mar: ACLS Instructor

- **Max Super Speciality Hospital, Patparganj**

  19th Mar: BLS Provider (HeartCode)

  19th–20th Mar: ACLS Provider Course with Video Prework

- **Max Super Speciality Hospital, Lucknow**

  21st Mar: BLS Provider (HeartCode)

  21st–22nd Mar: ACLS Provider Course with Video Prework

Bespoke/Certificate Courses

Max Healthcare has been at the forefront of advancing medical education by offering a diverse range of specialised training programmes tailored to cater to the unique needs of healthcare professionals. The institution has implemented simulation training for Emergency Medicine, Internal Medicine, and MBBS students, providing them with valuable hands-on experience to enhance their clinical skills.

Short-term training programmes scheduled in March 2026:

Name of the Course	Duration	Eligibility
Certification Course in Infection Prevention and Control for Nurses	3 months	General nursing and midwifery (GNM)/B.Sc. Nursing
Paediatric Cardiac Computed Tomography (CT)	8 weeks	Doctor of medicine (MD)/DNB in Radiodiagnosis or Diploma in Medical Radiodiagnosis (DMRD)
Mammography Reporting	8 weeks	MD/DNB/DMRD in Radiodiagnosis
Liver Transplant Donor Evaluation Imaging	3 days	MD/DNB/DMRD in Radiodiagnosis
Advanced Course in Endoscopic Gynaecological Surgery	3 days	MD, MRCOG, or DNB qualification, along with mandatory Delhi Medical Council (DMC) registration

Foreign Medical Graduate (Fmg)–Clinical Skills Courses (Csc)

The FMG–CSC Programme is a specialised training initiative designed for FMGs, whether currently pursuing their medical education or having recently completed it. The primary goal of this program is to strengthen core clinical skills, build familiarity with the Indian healthcare system, and ensure that returning FMGs are well-prepared for clinical practice in India.

This programme bridges the gap between the theoretical medical training received abroad and the practical, hands-on experience required in India.

Eligibility: Foreign Medical Graduates

Duration:

- **Basic –** 15 Days
- **Advanced –** 20 Days
- **Batch Commencement –** April 2026

MIME Online Courses

MIME's online learning management system offers flexible, self-paced courses for doctors, nurses, allied health professionals, and non-medical staff, enabling continuous skill development and knowledge enhancement. The platform provides easy access to industry-relevant content while fostering collaboration and knowledge-sharing among healthcare professionals.

Mode: Self-paced online learning (Hybrid)

Successful candidates will be awarded a certificate by MIME.

Online Fellowship Courses

- Diabetes Management
- Infectious Disease
- Emergency Medicine
- Critical Care
- Clinical Cardiology
- Obstetrics and Gynaecology
- Bariatric Anaesthesia
- Management of Liver Disorder

Online Certificate Courses

- Aesthetic Medicine and Surgery
- Healthcare Quality Management
- Public Health
- Clinical Research
- Bariatric Nutrition
- Acute Liver Failure (ALF)
- Geriatrics Care
- Difficult Airway Management

Collaborations

MIME's prestigious accreditations ensure our programmes meet rigorous international standards set by overseeing bodies, equipping healthcare professionals with qualifications that bolster clinical competency and global recognition. As an accredited DNB centre, it provides comprehensive training in Internal Medicine, ensuring eligibility for the DNB examinations and recognition across India as specialists in the field. It holds level 3 accreditation from the Federation of Royal Colleges of Physicians of the UK — attesting to the highest UK training standards — and is the first institution in North India and Mumbai to host the Practical Assessment of Clinical Examination Skills (PACES)-MRCP examination for Internal Medicine trainees worldwide. In partnership with Max Healthcare, it is one of only two centres in India (and the third globally) authorised to offer the RCOG-accredited Obstetrics and Gynaecology postgraduate programme, providing qualifications equivalent to both basic and intermediate UK standards. Its Master's in Emergency Medicine (MEM) programme, delivered in collaboration with George Washington University, USA, combines world-class academic content with hands-on clinical exposure in high-acuity settings. Additionally, it is an accredited AHA training centre for all life support programmes, further extending its commitment to excellence in clinical education and patient care.

Furthermore, its accreditation by the AcSIR and RCB facilitates the delivery of advanced PG diplomas, Master's in Public Health, Healthcare Quality Management, and Clinical Research, and Ph.D. courses in Biological Sciences and Medical Research. Since its establishment in 2008, its training initiatives have consistently enabled professionals to secure specialist roles and leadership positions both in India and on the global stage.

Office of Research

At Max Healthcare, the Office of Research (OOR) serves as a cornerstone of support, fostering a dynamic research culture. Since its inception in 2005, the OOR has been backed by its five core pillars: Clinical Trials Support Unit, Regulatory Office, Grants and Collaborations Unit, Biostatistics and Clinical Data Analytics Cell, and Health-tech Incubation Unit.

OOR's Core Functions

- Grant-funded population and epidemiological studies
- Large-scale clinical trials
- Artificial intelligence (AI) and digital health investigations
- Biosample curation and storage
- Regulatory compliance support
- Publication support
- Molecular and genomic studies
- Capacity building in research

Our Milestones

675+
Drug and device trials

$2.4M
Awarded in grants

2200
Investigator-initiated studies

30
Grant-funded public health studies

2950+
Publications in indexed journal over the last 9 years

30+
International and national partners

16
-80°C deep freezers

150K
Individuals screened

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Scan for more details

About Max Healthcare

Max Healthcare Institute Limited (Max Healthcare) is one of the largest integrated healthcare providers in the country. We own, operate and provide medical services to facilities in Delhi NCR, Mumbai, Punjab, Uttar Pradesh and Uttarakhand. Max Lab supplements our commitment towards patient care by providing accurate testing and diagnostics. We are also revolutionising the care-continuum through Max@Home, ensuring treatment options are available to our patients in the comfort of their homes. Our continued emphasis on patient-centric care accompanied by our patients' trust has strengthened our position to become one of India's top private healthcare providers.

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BED CAPACITY - **5,200+**

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Phone: +91-11-6611 5050

Max Smart Super Speciality Hospital, Saket

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Max Institute of Cancer Care, Lajpat Nagar

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Phone: +91-11-4720 3000

Max MedCentre, Lajpat Nagar

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Phone: +91-11-4720 3030

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Max Super Speciality Hospital, Noida

Wish Town, Sector-128, Noida - 201 303
Phone: +91-120-4122 222

Max Multi Speciality Centre, Noida

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MAHARASHTRA

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Mumbai - 400 056
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Max Super Speciality Hospital, Nagpur

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Max Super Speciality Hospital, Mohali

(A Unit of Hometrail Buildtech Pvt. Ltd.)
Near Civil Hospital, Phase - 6, Mohali,
Punjab - 160 055
Phone: +91-172-521 2000

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Plot No - A-19, Industrial Area Phase VI,
S.A.S Nagar, Mohali - 160 055
Phone: +91-172 521 2000

Max Super Speciality Hospital, Bathinda

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Submit your articles for the June 2026 edition by 30th April 2026.
Email us at **mmjeditorialboard@maxhealthcare.com**