Rituximab for Thrombotic Thrombocytopenic Purpura: A Case Report

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DOI: https://doi.org/10.62830/mmj2-02-26c

Abstract:

Thrombotic thrombocytopenic purpura (TTP) is a rare thrombotic microangiopathy (TMA). The diagnosis is difficult and can be easily missed. TTP is an emergency condition, and its treatment must not be delayed once a diagnosis is established. Delays in treatment may result in significant morbidity and mortality. There has been a significant reduction in the mortality rate following the emergence of plasma exchange therapy. However, a high rate of recurrence has been noted in those who have achieved remission. Patients who fail to respond to plasma exchange therapy may respond to various other drugs. One such drug is rituximab, which is an anti-CD20 antibody that depletes B cells.

We present a case of a 38-year-old man with anaemia, thrombocytopenia, elevated creatinine, increased lactate dehydrogenase (LDH), seizures, and schistocytes in the peripheral smear, which favoured TTP. The absence of a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13) levels confirmed TTP. The patient responded to rituximab therapy and was cured of TTP.

TTP is a relatively uncommon condition with the potential to develop serious consequences leading to mortality. Early diagnosis and treatment are essential to avoid this. In our case, due to the early diagnosis and therapy, the patient was cured of the dreadful disease.

Key words: Thrombotic Thrombocytopenic Purpura (TTP), ADAMTS13 Deficiency, Rituximab, Plasma Exchange Therapy, Microangiopathic Haemolytic Anaemia (MAHA), PLASMIC Score.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare thrombotic microangiopathy (TMA) characterised by von Willebrand factor (VWF)-platelet-rich hyaline thrombi that develop in the arterioles and capillaries of the affected individual. It is a relatively uncommon condition with the potential to develop serious consequences affecting the brain, pancreas, kidney, and heart, amongst other organs.[1] The diagnosis of TTP is confirmed when the patient presents with at least three of the following symptoms: microangiopathic haemolytic anaemia (MAHA), thrombocytopenia, neurological phenomena (stroke or seizures), fever, and end-organ damage.[2,3] The most common triggers for TTP include viral or bacterial infections, malignancy, and autoimmune diseases.[4] Complications arising from cardiac or neurological abnormalities are the most common cause of mortality in these patients. The mortality rate from TTP has decreased drastically from > 90% to < 10%-30% after the emergence of plasma exchange therapy.[5] However, a high rate of recurrence has been noted in those who have achieved remission.[6,7] A few patients may even present with multiple relapses requiring numerous sessions of plasma exchange therapy, which can be costly and may even lead to complications such as thrombosis, infections, and other reactions to transfusion.

A few patients fail to respond and achieve remission on plasma exchange therapy. These patients may show a response to corticosteroids, cyclophosphamide, azathioprine, vincristine, high-dose intravenous immunoglobulin, staphylococcal protein A immunoadsorption, cyclosporine A, and/or splenectomy.[8-11]

TTP results from the inhibition of the VWF-cleaving protease, a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13), a member of a family of proteases with a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs.[12]

Studies in the past have reported an association between the subset of thrombotic MAHA with the deficiency of ADAMTS13. The pathogenesis of TTP may involve a deficiency of ADAMTS13.[13-16] In adults, immunoglobulin (Ig) autoantibody against the ADAMTS13 enzyme is usually the cause of ADAMTS13 deficiency.[15,16] Immunosuppressive therapy may be useful in these cases due to this autoimmune cause.

Rituximab is an anti-CD20 antibody that depletes B cells in the lymphoid tissue as well as in the circulation. It is known to be effective in the treatment of numerous antibody-mediated autoimmune diseases, including autoimmune thrombocytopenia.[17,18]

Case Report

A 38-year-old man presented with fatigue, lethargy, and headache. A detailed blood work-up revealed very low vitamin B12 levels of < 50 ng/mL. He was prescribed intramuscular injections of vitamin B12 1000 mcg on alternate days. After the 3rd injection, he developed a haematoma at the injection site. His injections were immediately stopped, and he was started on sublingual vitamin B12. After 4 months, he presented with a severe headache for the last 10-15 days. While he was being evaluated for a headache, after 2 weeks, he had an episode of recurrent vomiting associated with weakness over the left half of his body with motor power of 3/5. His blood reports revealed a low platelet count of 11,000/mm^3, elevated serum creatinine of 1.8 mg/dL, and low haemoglobin of 9 gm/dL. He refused a magnetic resonance imaging (MRI) of the brain because of severe claustrophobia. The haematologist advised a change in treatment strategy in view of anaemia, thrombocytopenia, elevated creatinine, increased lactate dehydrogenase (LDH), seizures, and schistocytes in the peripheral smear, which favoured TTP. The absence of ADAMTS13 levels confirmed TTP. The high-risk nature of the disease was explained to the relatives. The patient underwent three plasmapheresis sessions on alternate days along with intravenous methylprednisolone and rituximab. The patient responded with a satisfactory complete blood count (CBC) and no further requirement of packed cells and platelet transfusion. The patient was extubated and discharged in a very stable condition with normal laboratory tests. He was given two more doses of rituximab and steroids weekly. TTP is a dreadful disease with a poor outcome, but if diagnosed and treated early, it can also be cured.

Discussion

The incidence of TTP is estimated to be around 2 per million per year.[19] The most commonly affected age group is the fourth decade of life, and women are more likely to be affected compared to men.[20] TTP usually occurs in its secondary form in association with various predisposing factors, including malignancy, infection (e.g. human immunodeficiency virus [HIV]), autoimmune diseases (e.g. systemic lupus erythematosus), certain drugs, and pregnancy. Primary TTP without any predisposing factors is usually rare, which makes it extremely difficult to diagnose.

Diagnosis of TTP

TTP must be suspected in any patient who presents with MAHA and thrombocytopenia, as these are the hallmarks of TTP.[19,21] This is a form of haemolytic anaemia that presents with schistocytes or red blood cell fragments on peripheral blood smear. In healthy individuals, schistocytes are reported within the range of 2 to 3 per 1000 red blood cells.[22,23] The mechanical shearing of these red blood cells while they traverse through microvascular thrombi results in the formation of these schistocytes in patients with TTP. Thus, the presence of schistocytes is most suggestive of TTP when they are present as the dominant abnormality on red blood cell smear.[24] Patients with TTP report a higher percentage of schistocytes on average compared to other forms of TMAs (4% to 8% schistocytes in TTP vs 0.2% to 2% schistocytes in transplant-associated TMA, preeclampsia, and haemolytic-uremic syndrome).[22,23] Previous studies demonstrate that signs and symptoms of abnormal bleeding, such as petechiae, ecchymoses, and menorrhagia have been reported in about 46% of cases.[25] A high platelet count of > 30 × 10^9/L is usually suggestive of other forms of TMA but does not rule out TTP.

The nervous system is usually the most affected organ, involved in 40% to 80% of TTP cases, with symptoms ranging from minor headache to severe seizure, stroke, or coma.[19,21] A nine-fold increase in mortality was noted in patients with a Glasgow Coma Scale (GCS) score of 14 or less compared to those with a normal GCS score.[26] Another organ commonly affected in cases with TTP is the gastrointestinal tract (35% to 40% of cases). They may present with symptoms such as abdominal pain, nausea, vomiting, or diarrhoea. The kidneys may also be affected, with a median creatinine at presentation being 0.9 to 1.4 mg/dL. Only about 4% to 15% of the patients present with acute renal failure requiring dialysis, and renal dysfunction is more common in the older age group.[27]

With regards to the evaluation of a patient with TMA, the primary goal of a physician is to promptly initiate plasma exchange therapy in those who may have TTP. This decision is, however, extremely challenging due to the rarity of TTP and the variations and overlap in clinical presentation with other TMAs. Laboratory detection of ADAMTS13 activity is of immense help in these cases, but due to their unavailability at most centres, clinical prediction scores have been developed.[28] The most recently developed is the PLASMIC score, which has proved to be robust and cost-effective.[29-32] The PLASMIC score categorises patients into low-risk, intermediate-risk, and high-risk. Immediate plasma exchange therapy is suggested in high-probability PLASMIC scores, while in cases with a low-probability PLASMIC score, plasma exchange therapy may be withheld, and the physician must search for an alternative diagnosis.[33]

The presence of ADAMTSI 3 deficiency on laboratory testing strongly supports the diagnosis with high specificity and sensitivity. Severe deficiency (< 10%) of ADAMTS13 activity further confirms the diagnosis. Thus, diagnosing a patient with TTP is a multistep process involving careful interpretation of the clinical presentation, clinical prediction scores, and laboratory findings.

Treatment of TTP

TTP is an emergency condition, and its treatment must not be delayed after a diagnosis is established. Delay in treatment may result in significant morbidity and mortality. A severe deficiency of the ADAMTS13 activity is required to confirm the diagnosis, but one must not wait for the report before initiating therapy.

The first-line treatment for TTP is therapeutic plasma exchange (TPE).[5] The therapy must be continued until a clinical response has been obtained and maintained for an additional two days. Glucocorticoids are also used along with TPE from the time of initiation of the therapy. Most standard practices recommend the use of oral prednisone (dose 1 mg/kg/day) daily untill a clinical response has been achieved.[34] These may later be tapered off over a period of 3-4 weeks.

In our case, the use of rituximab proved to be highly effective in treating the patient. Rituximab is usually prescribed within the first few days of hospitalisation in cases of acute TTP. A prospective phase 2 trial has proved the efficacy of rituximab when used in conjunction with the standard therapy in acute TTP.[35] Trials conducted in the past have also demonstrated that rituximab given in cases of acute TTP results in fewer relapses.[19,35-38] A recent meta-analysis has also proved that administration of rituximab in the acute stage further reduces the mortality rate.[39] A few previous studies have also demonstrated the efficacy of rituximab in cases of refractory TTP as well as in cases non-responsive to TPE.[37,38,40]

Declaration

The author certifies that he has obtained appropriate patient consent form. In the form, the patient has given his consent for his clinical information to be reported in the journal. The patient understands that name and initials will not be published, and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

Conclusion

TTP is a rare condition which can be easily missed by the primary physician. However, it is an emergency and requires immediate management. Thus, it is important to be on the lookout for this condition and initiate therapy immediately. TPE and corticosteroids are the first-line therapies. Rituximab has proven to be highly effective in both acute as well as refractory TTP.

Ashutosh Shukla. Rituximab for Thrombotic Thrombocytopenic Purpura: A Case Report. MMJ. 2025, June. Vol 2 (2).

DOI: https://doi.org/10.62830/mmj2-02-26c

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