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Thrombotic Thrombocytopenic Purpura- Approach To Diagnosis And Management

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Abstract

Thrombocytopenic thrombotic purpura (TTP) is a rare ,but severe hemorrhagic syndrome characterized by the classical pentad of thrombocytopenia, microangiopathic hemolytic anemia and microvascular occlusion, fever, neurological and renal impairment, although the confluence of all elements of the pentad is rarely seen in one patient. The pathophysiology involves the autoimmune or genetic deficiency of a metalloproteinases activity (ADAMTS-13), responsible for the cleavage of von Willebrand Factor multimers. The treatment is plasmapheresis; and in acute or recurrent cases, corticosteroids and immunosuppressants . In this article, we present a classical case report about this disease, treated in the medical ICU of a tertiary care hospital in Thiruvananthapuram, Kerala. The report evidences that rapid diagnosis and intervention entails a good prognosis.

Keywords: purpura thrombotic thrombocytopenic; anemia hemolytic; plasmapheresis

Introduction

Microangiopathic hemolytic anemia, represented by hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), is characterized by the triad findings: microangiopathic hemolytic anemia, microvascular occlusion and thrombocytopenia.[1]

TTP is associated with fever and neurological signs, although both are clinically indistinguishable. The clinical suspicion favouring TTP or HUS is the presence of neurological changes or acute kidney injury, respectively. Differential diagnosis includes disseminated intravascular coagulation (DIC) and consumptive thrombohemorrhagic diseases. [2]Despite the clinical and histological similarity between TTP and HUS, the diagnosis must be accurate, as both require different treatment and follow up. [3]

TABLE – Diagnostic criteria

Diagnostic criteria	Confirmation
1. Microangiopathic hemolytic anemia	1.1. Hemoglobin < 12 g/dl + reticulocytosis 1.2. Negative test 1.3. Histology with two or more schistocytes per field 1.4. Increase of LDH
2. Thrombocytopenia	2.1. Platelet count < 100 × 10^9/l
3. Variable organic dysfunction	3.1. Neurologic and renal changes with no signs of DIC

LDH: lactate dehydrogenase; DIC: disseminated intravascular coagulation.

Moschowitz first described Thrombotic thrombocytopenic purpura (TTP) in 1925 as a disease characterized by the pathological findings of hyaline thrombi in blood vessels of multiple organs. [4]Typically, it consists of the pentad including thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, fever, and renal impairment. Currently unexplained thrombocytopenia and microangiopathic hemolytic anemia are the two criteria required to diagnose TTP. [5,6]

The etiopathogenesis of TTP is the deficiency or inhibition, congenital or acquired, of a metalloproteinase that degrades the von Willebrand factor (vWF) polymers, called multimers. The acquired form can be explained by the presence of immunoglobulin class G anti- metalloproteinase antibodies; the congenital form is due to mutation in the ADAMTS-13 gene (a disintegrin and metalloproteinase with eight thrombospondin-1-like), leading to enzymatic deficiency. [7]Endothelial dysfunction is the key pathophysiological reason for the occurrence of microangiopathy, resulting in microvascular thrombosis with formation of fibrin and inhibition of fibrinolysis.[8] Several etiologic agents such as viruses, bacterias, drugs like antiplatelet agents and cyclosporine may cause TTP.[9]The laboratory profile shows hemolytic anemia with hemoglobin values between 7-9 g/dl, platelet count below 30,000/ mm3 , elevated indirect hyperbilirubinemia and a significant rise in lactate dehydrogenase (LDH); clotting tests are usually within normal range. The identification of schistocytes in the peripheral blood smear along with the compatible clinical-laboratory finding is fundamental for the diagnosis of TTP, in addition to being strongly suggestive. [10] TTP can be classified according to the presentation as primary – acute, chronic recurring, plasmapheresis resistant, familial; and secondary – pregnancy-related, drugs, human immunodeficiency virus (HIV), autoimmune diseases, neoplasia or chemotherapy or immunosuppression. The neurological condition may manifest as confusional states, visual field changes, sensory and motor deficits, seizures, and lowered level of consciousness. Renal dysfunction presents as proteinuria, microscopic hematuria and transient acute kidney injury. , 4]TTP treatment strategy consists of plasmapheresis, by removing pathogenic autoantibodies and cytokines with endothelial action.(11) The mortality improves from 90% to 10%- 30% with plasmapheresis.(12) In severe or recurrent cases, corticosteroids, immunosuppressants and splenectomy may be indicated. Recently, rituximab has been reported as a treatment option for cases of TTP resistant to plasmapheresis.(13, 14) Plasmapheresis is crucial for all patients with TTP, but the number of sessions necessary for clinical-laboratory remission varies.(12) The guidelines found in the literature for acute cases suggests daily plasmapheresis until normalization of markers of the therapeutic response which is platelet count and LDH level.(15)

Case Report

A 46-year-old female , known hypothyroid on replacement thyroxine, presented with fever, right sided neck pain, headache and dizziness for approximately 10 days prior to admission. She was initially taken to a local hospital where laboratory reports showed anemia, thrombocytopenia and mildly elevated blood urea and creatinine along with proteinuria and she was referred here after an episode of GTCS. There was no history of autoimmune diseases in the family. Her surgical, family and social

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history was insignificant. Vital signs were normal. Conjunctivae showed pallor. No hepatosplenomegaly , malar rash or other type of rash , tenderness or deformities in the joints, active oral, vaginal or rectal bleeding were found . Neurological examination was altered during seizures and post ictal phase. Our differential diagnosis included cerebrovascular attack, meningo-encephalitis, sepsis with MODS, Tropical fever .The possibility of MIS-A, Vaccine Induced Thrombocytopenic thrombosis (VITT) was also considered given the context of the pandemic and post vaccination status of the patient .MRI with MRV and MRA was done which was unremarkable.CSF study was normal. She was electively ventilated for airway protection during frequent seizure episodes. Multiple polychromasia and schistocytes were found on peripheral blood smear suggestive of microangiopathic haemolytic anaemia with thrombocytopenia. Tropical fever work up was found negative. In light of microangiopathic haemolytic anemia, thrombocytopenia, fever, seizures and altered RFT the possibility of TTP and APLA were considered and ADAMTS 13 LEVELS and APLA workup were sent ,out of which ADAMTS13 LEVELS came as very low. APLA workup was negative. She was started on plasma exchange and steroids .By the 5thplasma exchange, her GCS improved, she was gradually weaned off mechanical ventilation and platelet count also started to climb with decrease in LDH levels indicating that she was responding to treatment. By 8th plasma exchange , her platelet counts was static and the decision was taken to start her on rituximab. Plasma exchange was continued for a total of 10 days. Gradually her condition improved, was shifted out of ICU by day 24 and eventually discharged on day 30 with strict follow up.

Discussion

Microangiopathic hemolytic anemia (TTP and HUS) is a rare and potentially fatal condition, but present a recognized effective treatment.(16) However, the therapeutic success is directly related to the rapid diagnosis enabled by the simplification of its criteria for diagnosis.(12, 16)The recent diagnostic criteria includes the presence of thrombocytopenia and microangiopathic hemolytic anemia confirmed by the presence of schistocytes in the peripheral blood,(12, 16) initially disregarding a probable etiology(12) and the presence of organ dysfunction and fever, since the pentad classic is quite unusual. (16)

In our case report, the clinical diagnostic findings of TTP were all present . The specific therapy – plasmapheresis, FFP transfusion and immunosuppression with steroid – was initiated on the third day after diagnostic confirmation. Therapeutic plasma exchange is the association between plasmapheresis and FFP transfusion, since plasmapheresis removes the vWF multimers, ADAMTS-13 antimetalloproteinase antibodies(4, 12) and endothelial cytokines(11). FFP transfusion restores the ADAMTS-13 deficiency with donor enzymes(4, 12). The use of immunosuppressive agents offers additional benefit in the treatment of TTP, especially in severe acute or the plasmapheresis-resistant cases(13, 14, 17) or when autoimmune disease is suspected.(18) In a prospective study, prednisone at a dose of 200 mg/day was shown to induce complete remission in 55% of cases of microangiopathic hemolytic anemia associated with mild neurological dysfunction.(19) There is no definitive treatment duration in the literature, but studies indicate that treatment should be continued until the platelet count reaches 100,000/mm3 and the LDH levels are below 400 UI/l, and these are the most sensitive markers to evaluate the therapeutic response.(20) In this case, hemoglobin and LDH values improved significantly after 72 hours from the start of Plasma Exchange (hemoglobin:

4.9 g/dl to 10.7 g/dl and LDH: 3,325 UI/l to 699 UI/l), but the platelet count only reached acceptable values after 12 days of treatment.

There is a consensual doubt in the literature about the complete remission of the disease in the long term(21) but continuing corticosteroids administration may aid in complete remission of the disease. The patient was discharged from hospital with laboratory parameters within normal range(platelets 163,000/mm3 and LDH 232 UI/l) and was asked to be on strict outpatient followup to monitor remission or detect recurrent chronic form. (22)

Conclusion

TTP is a life threatening disease, where prompt diagnosis and the early management can improve the

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prognosis. The possibility of the wide differential diagnosis, such as consumption coagulopathy and intravascular hemolysis, need to be considered. Since patients may not present with the pentad of HUS/TTP, identifying atypical cases of TTP and prompt initiation of the management of TTP is important. Prior to plasma exchange, the mortality rate approached 90% whereas now improved to twenty percent. Plasma exchange therapy removes the autoantibodies to ADAMTS13 and very high molecular weight von Willebrand factor (VWF) multimers along with replacement of the patients missing protease. Patients with a severe course of TTP responding to plasma exchange may benefit from rituximab.

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