CASE REPORT

JIACM 2023; 24 (1): 74-77

Thrombotic Thrombocytopenic Purpura does not Always Present with a Classical Pentad

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder characterised by thrombosis in microvasculature, microangiopathic haemolysis and thrombocytopenia[1]. This condition is described by a classical pentad; Microangiopathic haemolytic anaemia, Thrombocytopenia, Neurological abnormalities, Fever, and Renal impairment. However, the entire pentad may not be seen in all the patients[1,2]. TTP can affect any organ system, but involvement of peripheral blood, central nervous system and kidneys causes the clinical manifestations. The classic histologic lesion is thrombi in the microvasculature of affected organs. These thrombi consist predominantly of platelets, with little fibrin and red blood cells compared with thrombi that occurs secondary to intravascular coagulation. The ultimate cause of TTP is unknown. Patients with TTP have unusually large multimers of Von Willebrand Factor (vWF) present in their plasma, and lack a plasma protease that is responsible for breakdown of these ultra large vWF multimers. In the congenital form of TTP, mutations in the gene coding this protease have been described. In the more common sporadic form, an antibody inhibitor can be isolated in most patients. This protease has been isolated, cloned and is designated as ADAMTS13 (A Desintegrin like and Metalloprotease with ThromboSpodin type 1 motif 13)[2]. The activity of this protease is normal in most patients with classic HUS, suggesting differing pathogenesis of these closely related entities[3]. Untreated TTP has mortality rate of as high as 90%. With plasma exchange, the mortality rate is reduced to 10 - 20%. Acute morbidities due to TTP include ischaemic events such as stroke, transient ischaemic attack, myocardial infarction and cardiac arrhythmia, bleeding and azotemia[1-4]. TTP during pregnancy may precipitate fetal loss[5]. In general, survivors have no long-term sequelae, with the exception of residual neurologic deficits in a minority of patients. However, relapses are not uncommon.

Case report

A 35-year-old female, presented with complaints of menorrhagia for last 2 cycles, one episode of hematuria, purpura over right thigh and generalised body ache for 40 - 45 days. No other complaints were there. Patient had a past history of seizure disorder (absence seizure) since 12 years of age and was on Carbamazepine. Patient did not have any other significant past history and co-morbidities. Patient was married and had two children, both were normal vaginal hospital delivery. Patient did not have any history of abortion. Patient also had history of multiple RBC and platelets transfusions in last 40 - 45 days before admission, but still had persistent thrombocytopenia and anemia. Patient was vegetarian and did not have any history of any substance abuse.

On physical examination patient was conscious, oriented, comfortable and was vitally stable. Pallor was present on examination. Patient had purpura on right thigh. No other skin pigmentations were present. Abdomen was soft and non-tender without hepatomegaly and splenomegaly. Neurological, Respiratory and Cardiovascular systems were normal on examination. Patient did not have any active bleed from mouth, vagina or rectum at the time of presentation.

On investigation, complete blood count showed the picture bicytopenia despite multiple transfusions, haemoglobin was 7.2 g/dl and platelet count was 15,000/microl. Peripheral blood film suggested anisopoikilocytosis, schistocytes and microspherocytes. Patient's LDH was 2,329 U/L, and reticulocyte count was 5%. Her serum creatinine was 0.6 mg/dl, indirect bilirubin was 1.2 mg/dl. Urine output was adequate, 1,800 - 2,000 ml/day durning her hospital stay and urine routine analysis was also normal.

Patient's direct/indirect Coomb's tests were negative. ANA profile was negative. PF4-H (IgG antiplatelet factor 4) was 0.77 (normal range < 1.00), which ruled-out Heparin induced thrombocytopenia, along with vaccine induced thrombocytopenia as patient also had history of COVID-19 vaccination . Patient's bone marrow aspiration and biopsy was done, which showed marrow was normocellular for age with trilineage hematopoiesis . ADAMTS13 activity was

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done by chemiluminescence immunoassay method, which was 0.40%, less than the normal range of 60.6 - 130.6 and confirmed the diagnosis of TTP.

Differential diagnosis

Idiopathic thrombocytopenic purpura, microangiopathic haemolytic anaemia, vaccine induced thrombocytopenia, carbamazepine induced thrombocytopenia, haemolytic uraemic syndrome (HUS), Evan's syndrome and heparin induced thrombocytopenia were the major differential diagnoses in our case.

Low ADAMTS-13 activity can be observed, primarily in idiopathic TTP, and in a congenital condition with low ADMATS13 (Upshaw-Schumann syndrome) but as our patient developed symptoms in her middle-age, Upshaw-Schumann Syndrome was unlikely. Other secondary clinical conditions are ITP, HUS, DIC, sepsis, pregnancy and post-solid organ or bone marrow transplant.

HUS generally presents with diarrhoea (usually bloody), which was absent in our case. Endotoxins are the culprit causing endothelial damage in HUS. The most common toxin is Shiga toxin from *E. Coli* strain. It is usually associated with a history of eating undercooked/spoiled food. Culture/sensitivity and ADAMTS-13 activity are done to distinguish between the two.

Evan's syndrome is an autoimmune condition that presents with autoimmune haemolytic anaemia (AIHA) and immune thrombocytopenia (ITP), with or without immune neutropenia. The type of AIHA present in Evan's syndrome is warm AIHA. In our case Coomb's tests were negative. Further, there is no reduction in ADAMTS-13 activity in Evan's syndrome.

Our patient did not have any history of heparin use, and PF4-H (IgG antiplatelet factor 4) was 0.77 (normal range < 1.00) so heparin induced thrombocytopenia was also unlikely.

As our patient was on carbamazepine since her childhood, for absence seizures, there could be a possibility of carbamazepine induced bone marrow suppression, as the drug carbamazepine can cause bone marrow suppression, but this drug does not cause a decreased activity of ADAMTS-13, which was seen in our case.

Idiopathic thrombocytopenia is a diagnosis of exclusion.

Haematological malignancies were excluded after an unremarkable bone marrow biopsy, and sepsis too was ruled-out with routine blood tests.

Our patient was not taking any drug except carbamazepine for a long time and this was stopped, so the condition was not drug-induced.

Discussion and Review of literature

This 35-year-old female, a known case of seizure disorder on Carbamazepine for 23 years presented, with complaints of generalised weakness, menorrhagia for last 2 cycles and hematuria. CBC showed bicytopenia, not improving even after multiple blood transfusions. Carbamazepine was thought to be the cause of thrombocytopenia and was stopped; later patient was started on levetiracetam after overlapping for three days but patient did not improve. After ruling-out other possible diagnoses like micro angiopathic haemolytic anaemia, and vaccine-induced thrombocytopenia with routine investigations and Bone marrow aspiration/biopsy, she was started on pulse therapy of methylprednisolone for 5 days, for possible diagnosis of idiopathic thrombocytopenic purpura but she did not improve. Plasma exchange along with IVIG were then started, to which she responded well. Diagnosis of TTP was confirmed by low ADAMTS-13 activity, which was ordered before starting IVIG. A low level of ADAMTS-13 (< 5% of normal) can be interpreted as the patient having TTP[6-8]. In some other pathological conditions unrelated to TTP, ADAMTS-13 levels are low or undetectable[9-12]. Patients with both localised and disseminated malignancies have been reported to have reduced levels of ADAMTS-13[11,12]. The effect of inflammation on ADAMTS-13 was studied in pediatric patients with severe sepsis, and ADAMTS-13 activity was reduced[13]. The expression of ADAMTS-13 in acute myeloid leukaemia (AML) patients was decreased and the level of ADAMTS-13 was also related to infections and risk stratification of AML patients[14].

TTP has a high mortality rate, up to 90%, which can be reduced to 10 - 20% with plasma exchange[4]. Along with plasma exchange, IVIG is also used in the treatment of TTP. Therapeutic plasma exchange (TPE) is the most effective therapy; about one-third of TTP patients will relapse, A subset of patients with TTP have antibodies to ADAMTS13 and may become resistant to conventional treatments. It has been observed that adding adjuvant treatment with IVIG helps in achieving remission and may sustain remission in some patients with chronic, relapsing TTP[15]. ADAMTS-13 is an enzyme that specifically cleaves large vWF multimers. If activity of ADAMTS13 is decreased,

either because of an inherited mutation within ADAMTS-13 gene, or because of the development of autoantibody, the accumulation of ultra large vWF multimers may cause microvasculature thrombosis due to platelet aggregation and produce syndrome of TTP. ADAMTS-13 activity assay is performed to confirm TTP diagnosis and may also be used in prediction of TTP relapse, though measurement of ADAMTS-13 activity is not necessary for taking decisions and for diagnosis and initial management. Its severe deficiency is associated with increased risk of relapse.

TTP presents with a classic pentad, mainly involving peripheral blood (Haemolysis and Thrombocytopenia), CNS and kidneys. As our patient's urine output, serum potassium and serum creatinine were normal and she did not have fever, throughout the illness, the possibility of TTP was less likely initially as fever, neurological symptoms and renal impairment were not there. Classical PENTAD may be absent in cases of TTP, and high degree of suspicion is required and a positive ADAMTS-13 test can confirm the diagnosis.

Joly *et al* reported that the first-line therapy for acute TTP is based on daily TPE supplying deficient ADAMTS-13, with or without steroids. Additional immune modulators targeting ADAMTS-13 autoantibodies are steroids and the humanised anti-CD20 monoclonal antibody rituximab. In refractory or unresponsive TTP, more intensive therapies including twice-daily plasma exchange; adding IVIG, pulses of cyclophosphamide, vincristine, or cyclosporine A; or salvage splenectomy are considered[1].

Vesely *et al* pointed out severe ADAMTS-13 deficiency does not detect all patients of TTP-HUS who may respond to TPE[2].

Miller *et al* reported that the incidence of TTP and HUS was higher among women than men. Most cases of HUS occurred before 20 years of age. They confirmed several known risk factors for TTP and HUS like cancer, bone marrow transplantation, and pregnancy[4].

Scully *et al* reported that pregnancies have been successfully managed, guided by ADAMTS-13 levels. Congenital TTP presents more frequently than acquired TTP during pregnancy and must be differentiated by ADAMTS 13 analysis. Careful diagnosis, monitoring, and treatment in congenital and acquired TTP have resulted in excellent pregnancy outcomes[5].

Oleksowicz *et al* found unusually large vWf multimers in patients with metastatic tumours, probably resulting from deficient vWf-cleaving protease activity and may represent a novel mechanism regulating primary platelet-tumour adhesive interactions involved in the metastatic process[6].

Sarode mentions that atypical TTP can be diagnosed by the presence of microangiopathic haemolytic anaemia and thrombocytopenia in a patient who frequently presents with central nervous system involvement and, to a lesser extent, renal dysfunction. Recent understanding of the pathophysiology of TTP due to severe deficiency of ADAMTS-13, has improved diagnosis of TTP. Once the diagnosis is suspected, life-saving TPE is initiated. Occasionally, an unusual clinical presentation makes TTP diagnosis difficult, thus resulting in a delay in management. This review highlights an atypical TTP case. It is intended to bring unusual scenarios to the clinician's awareness, so that timely treatment can be instituted[16].

Conclusion

TTP is a rare disorder and confirmation of diagnosis poses a challenge to the clinician, as the classical pentad of clinical presentation may be absent in some patients and costly ADAMTS-13 test may not be available everywhere. A high degree of suspicion for TTP is required in such patients, after ruling-out other causes. Early diagnosis and management can be life-saving.

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