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Case Report

Peri-partum Thrombotic Thrombocytopenic Purpura - A 29 years old Pregnant Lady presented with Convulsion and Thrombocytopenia

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Abstract:

Thrombotic thrombocytopenic purpura associated with pregnancy is a rare antibody-mediated thrombotic microangiopathy with high maternal and fetal mortality. We present a 29-year-old Bangladeshi pregnant lady of 32 weeks of gestation who presented to a tertiary care hospital with multiples episodes of generalized convulsion. She was immediately transferred to the operation theatre and after delivery of her baby, she was transferred to ICU. Her reports revealed features of hemolytic anemia, thrombocytopenia and renal failure. She was suspected as a case of Thrombotic thrombocytopenic purpura and received therapeutic plasma exchange. Her condition gradually improved and she was discharged to home in stable condition.

Key words: *ADAMTS 13, Convulsion, Fresh Frozen Plasma, Thrombotic thrombocytopenic purpura,Therapeutic Plasma exchange.*

Introduction:

Thrombotic thrombocytopenic purpura is a severe and life-threatening disease with an untreated mortality rate of 90%. Given its heterogenous clinical presentation the phenotype of TTP during pregnancy and its management have not been well documented.[1]

TTP is characterized by extensive platelet thrombus in the microvasculature, thrombocytopenia, mechanical hemolysis, injury and dysfunction of involved tissues and organs. The classic diagnosis of TTP includes the pentad of Coombs' negative hemolytic anaemia, thrombocytopenia, neurological symptoms, renal dysfunction and fever.[2] TTP occurs in one out of 25000-100000 pregnancies, mostly in the late third trimester or during the puerperium.[1]

Pregnancy induced TTP maybe associated with autoimmune disease, or it may be congenital. Most patients with TTP harbour ADAMTS 13 inhibitors, while 11.5-17% of patients have non-neutralizing antibodies.Non neutralizing antibodies can only be detected by enzyme linked immunosorbent assay.[1] We are reporting a case of pregnancy associated TTP with non-neutralizing antibodies that was successfully treated with plasma exchange in addition to pulse corticosteroid therapy and Rituximab.

Case report:

A 29-year-old female, gravid 3, para 2, at 32 weeks of gestation had 2 episodes of generalized tonic clonic seizure at home and 1 episode at Emergency room of a tertiary care hospital in Dhaka city. She was immediately transferred to operation theater and her baby was delivered by lower uterine cesarean section (LUCS). She had 1 episode of convulsion during surgery, so she was transferred to ICU for further management.

At presentation she had another episode of convulsion at ICU and she was intubated and put on mechanical ventilation. Her investigations revealed thrombocytopenia and normocytic normochromic anemia. Initial PBF was not consistent with micro-angiopathic hemolytic anemia. Her renal and liver functions were altered and progressively deteriorating. Her serial blood investigations showed worsening of anaemia with reticulocytosis and thrombocytopenia. Lactate dehydrogenase (LDH) was high and coagulation screening tests (PT, APTT and fibrinogen) were normal. D-dimer was elevated. Autoimmune profile (ANA, Anti dsDNA, C3, C4, P-ANCA, C-ANCA) were normal (reports were available later).

To evaluate convulsion, MRI with MRV of brain was done which revealed as PRES (Posterior Reversible Encephalopathy Syndrome) (Fig 1).

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Table I: Blood test results at the time of diagnosis and post-treatment:

Tests	Initial results	Interim period results	Post plasma exchange results	Reference value and unit
Hb	10.3 gm/dl	6.8gm/dl	7.5gm/dl	M:15+2,F:13.5+1.5 gm/dl
Platelet	43,000/cmm	1,12,000/cmm	1,99,000/cmm	1,50,000 -4,00,000/cmm
Reticulocyte	3.65 %			Upto 2%
Creatinine	2.7 mg/dl	4.76 mg/dl	1.25 mg/dl	0.6-1.3 mg/dl
Urea	71 mg/dl	105 mg/dl	43 mg/dl	15-40 mg/dl
Bilirubin	3.8 mg/dl	2.9 mg/dl	0.4 mg/dl	0.0-1.10 mg/dl
SGPT	447 U/L	134 U/L	32 U/L	M<42, F<31 U/L
SGOT	903 U/L	139 U/L	23 U/L	M<37, F<31 U/L
Alk Phosphatase	148 U/L			38-128 U/L
LDH	3876 U/L	816 U/L	497 U/L	120-246 U/L
PT with INR	13/1.14 sec	9.9/0.87sec		10-13 sec
APTT	27 sec	26.6 sec		25-36 sec
D-Dimer	9.07 mg/L			Upto 0.55 mg/L
Fibrinogen	512mg/dl			200-400mg/dl
S. Electrolytes	Normal			
Troponin I	0.09 ng/ml	0.123 ng/ml		0-0.034ng/ml
ANA	Negative			
Anti Ds DNA	Negative			
cANCA, pANCA	Negative			
C3, C4	Normal			
HBsAg, Anti HCV	Negative			
CRP	16 mg/L			<5 mg/L
ADAMTS 13	20%			60-130%
Albumin	3.05 g/dl			3.5-5 g/dl
Ionized Calcium	4.77mg/dl	4.72mg/dl	4.58mg/dl	4.4-5.4mg/dl
Magnesium	4.2 mg/dl	5.6 mg/dl	2.47 mg/dl	1.6-2.30 mg/dl

TTP, Eclampsia and HELLP syndrome were considered as differential diagnoses for this patient. Among these, TTP was considered as more likely diagnosis in view of clinical and relevant abnormal laboratory findings consistent with convulsion, thrombocytopenia and progressive renal dysfunction. To avoid treatment delay, therapeutic plasma exchange was initiated for her. She received 5 sessions of therapeutic plasma exchange within 7 days. Her serial CBC showed rapidly increasing platelet count and normalization of other laboratory results.

She was successfully extubated after 5 sessions of plasma exchange.

PBF was reviewed again which revealed microcytic hypochromic anemia with few ovalocytes, elliptical cells, occasional polychromasia and fragmented cells. Patient's Plasmic score was 6.

Immunosuppression was ensured initially with high dose steroids and then Rituximab.

She received 4 sessions of hemodialysis for acute kidney injury. Ultimately she was transferred to cabin, and later was discharged home in stable condition.

Discussion:

TTP is characterized by occlusive microangiopathy due to intravascular platelet thrombi. The pathophysiology of TTP is due to deficiency of Von Willebrand factor cleaving protein known as ADAMTS13. This deficiency could be congenital or acquired. Dysregulation of the immune system may result in autoantibody formation toward this protein as, for example, in autoimmune diseases. Pregnancy, drugs and infection might work through immune modulation effects, which precipitate TTP development.[3]

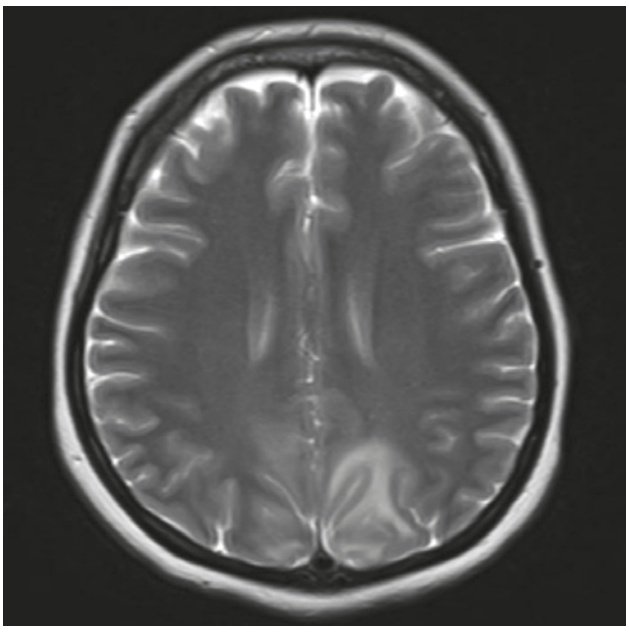
TTP was first described by Moschowitz in 1924. The understanding of the pathogenesis and pathophysiology of this condition has improved dramatically over the last 15 years. Deficiency of ADAMTS13 is the core feature leading to clinical manifestationof this disorder.

Clinical signs of TTP with laboratory evidence of thrombotic microangiopathy remain the mainstay of the diagnosis of

TTP.[3] In our case TTP occurred in the third trimester of pregnancy with the typical features of hemolytic anaemia, thrombocytopenia, renal dysfunction and neurological manifestation.[3]

In the absence of ADAMTS13 test result, the PLASMIC score (Sensitivity 90% and Specificity 92%)[4] can also be helpful to distinguish TTP from a broad range of thrombotic micro-angiopathy subtypes. It is composed of seven elements: platelet count <30 x 10^{09}/L, combined hemolysis variable (reticulocyte count >2.5% or haptoglobin undetectable or indirect bilirubin >2.0 mg/dl); absence of active neoplasia; absence of an organ or stem cell transplant; mean corpuscular value (MCV) <90 fL; international normalized ratio <1.5; and creatinine <2.0 mg/dL.PLASMIC score predicts ADAMTS-13 deficiency in suspected TTP with high discrimination.[4] We performed an independent external validation of the PLASMIC score for clinical prediction of severe ADAMTS-13 deficiency.[4] A plasmic score of 0-4 denotes low risk , a score of 5 denotes intermediate risk and a score of 6 or 7 denotes high risk. High risk recorded in 62-82% of patients with severe ADAMTS13 deficiency. Plasma exchange is recommended for score >6. Plasmic score of our patient was 6.

TTP is a rare hematological disorder in which neurological symptoms are frequently seen in its presentation. Upto 90% patients of TTP have been found to display neurologic symptoms. Neuroimaging in TTP can be performed with either CT or MRI brain imaging. CT is less sensitive in detection of ischemia and micro-hemorrhages compared to MRI. Most common finding in neuroimaging is posterior reversible encephalopathy syndrome (PRES). Typical PRES involves the posterior aspects of the supra tentorial brain parenchyma i.e. the parietal and occipital lobes, with classic appearance of white matter edema on both CT and MR imaging of the brain. In our case, patient's MRI of Brain also revealed PRES which resolved after proper therapy in follow up brain imaging.[5]



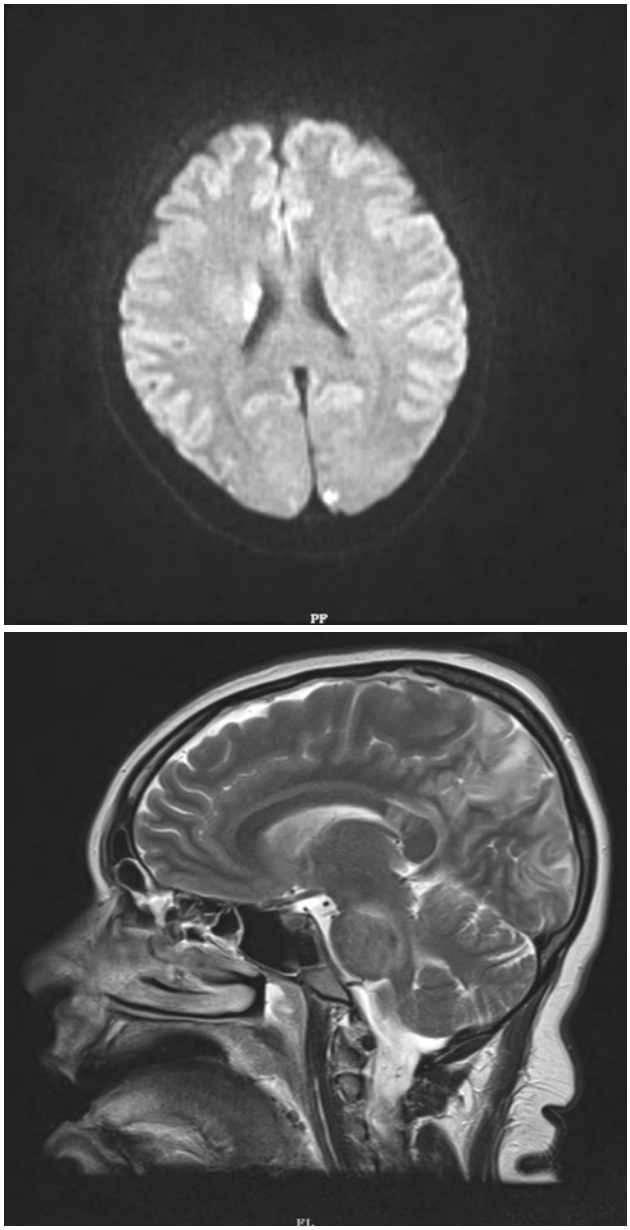


Fig 1: MRI of Brain revealing increased intensity in occipital region- Posterior reversible encephalopathy syndrome

There was lengthy discussion on the diagnosis of TTP. The fact that schistocytes were not initially found in the blood film and patient had eclampsia so diagnosis of HELLP syndrome was considered as differential diagnosis but which was ruled out as the patient presented with repeated convulsion and thrombocytopenia. ADAMTS13 activity was also reduced.

Rapid diagnosis and early treatment are critical to reduce the morbidity and mortality of TTP. Plasma exchange remain the treatment of choice as it replenishes depleted levels of ADAMTS13 and removing anti-ADAMTS13 antibodies. It is recommended that treatment with Plasma exchange should be initiated as soon as possible, within 4 to 8 hours if a patient presents with microangiopathic hemolytic anemia (MAHA) and thrombocytopenia in the absence of another identifiable cause.[3]

The revised criteria of TTP did not give much help, and, therefore, justification of the diagnosis was made based on the clinical ground when no other reason could explain the feature of thrombocytopenia and MAHA in this case.

Corticosteroids are also widely used to treat TTP. Rituximab as treatment in acute TTP and elective therapy to prevent TTP relapse has been the standard of care since 2005.[6] Rituximab has shown efficacy as second line treatment for refractory or relapsing TTP and it has also been proposed in combination with plasma exchange as first line treatment to reduce the risk of relapse.[7] In our case pregnancy was terminated because of eclampsia. TTP has been reported to be predominantly in women, and about 12% to 31% are pregnant or postpartum.[3]

A special issue for young women is the risk for future pregnancies.TTP has an overall relapse rate of 30-60%, pregnancy being a precipitating factor, but the real risk for relapse has not been well documented.

ADAMTS13 assays are not available in most routine medical laboratories worldwide. It is not recommended for the initial diagnosis of TTP. ADAMTS13 antigen and activity assays together with autoantibody detection could assist in the diagnosis and monitoring of patients.

It is important to stress that TTP is a diagnosis made by exclusion of other related conditions supported with clinical and routine laboratory parameters.[3]

Conclusion:

TTP is an uncommon thrombotic microangiopathy seen in the peripartum and postpartum periods. Prompt diagnosis and treatment of TTP is important to ensure complete recovery and a good prognosis. After calculation of the Plasmic score, the therapeutic plasma exchanges became the mainstay of treatment. In addition with TPE, Corticosteroid and Rituximab were effective in managing her platelet and hemoglobin levels to normal. Imaging findings are typically reversible after successful treatment. Surveillance is necessary to avoid its relapse. So, we can come to the conclusion that calculation of Plasmic score in all diagnosed cases of TTP is necessary for better outcome.

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