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AN INTERESTING CASE OF THROMBOTIC THROMBOCYTOPENIC PURPURA

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ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is an acute syndrome with abnormalities in multiple organ systems, characterised by fever, thrombocytopenia, microangiopathic hemolytic anemia (MAHA) and often with neurologic and renal dysfunction. However, this classical pentad is only rarely seen, and management requires early identification and initiation of plasma exchange. Currently only the dyad of unexplained thrombocytopenia and microangiopathic haemolytic anaemia is required to diagnose thrombotic microangiopathy. With increasing use of therapeutic plasma exchange, TTP is now a potentially curable illness.

CASE REPORT

An apparently healthy 33year old married woman, presented with complaints of bleeding per vaginum and fatigue of 11 days. It was intermenstrual bleed, lasting four days with no abdominal pain, or excessive bleeding, and with no history of fever, rash, or arthralgia. There was no recent loss of weight or appetite, or previous history bleeding tendencies. There was no history of chronic renal or liver disease or thyroid disorders.

EXAMINATION

On examination she was conscious, moderately built and nourished. She had severe pallor and icterus. She had no cyanosis, clubbing, lymph node enlargement or edema. Her pulse rate was 88 beats/minute and BP 120/80 mmHg. There were no ecchymotic patches or wet purpura or thyroid swelling. There was no bony tenderness or gum hypertrophy. Head to foot examination was normal. Per abdominal examination revealed soft abdomen, with no tenderness/ guarding/ rigidity or hepatosplenomegaly. Her cardiovascular, respiratory, and nervous system examination was normal. Per vaginal examination was normal.

Differential Diagnoses

From history and examination, we have a 33year old female with intermenstrual bleeding and fatigue of 11 days. Possibilities considered were bleeding disorders due to primary haematological and secondary systemic disorders. Local causes such as an ectopic abortion or threatened abortion were also considered. However, with presence of pallor and icterus on examination, a haemolytic anaemia was also thought of, although presentation with bleeding is unlikely.

Investigations

Her initial laboratory reports were as shown in Table 1

Table 1: Laboratory reports

Haemoglobin	6.9g/dL	Total Bilirubin	5mg/dL
Mean corpuscular volume	78fL	Direct Bilirubin	0.6mg/dL
Mean corpuscular haemoglobin	27pg	Aspartate aminotransferase	38U/L
Mean corpuscular haemoglobin concentration	34g/dL	Alanine aminotransferase	15U/L
Haematocrit	20%	Total Protein	7g/dL
White-cell count	6800/mm^3	Albumin	4.3g/dL
Differential count		Alkaline phosphatase	17 IU/L
Neutrophils	61	Urine routine examination	
Lymphocytes	29	Albumin	Faint Trace
Platelets	17000/mm^3	Sugar	Nil
Erythrocyte sedimentation rate	75mm/hr	Pus cell	2-6/ high power field
Blood Urea	22mg/dL	Prothrombin time -international normalized ratio (PT-INR)	1.21
Serum creatinine	0.8mg/dL	Activated partial thromboplastin time(APTT)	32s
Serum sodium	136mEq/L	Calcium	8.8mg/dL
Serum potassium	3.6mEq/L	Phosphorus	3.9mg/dL
Random blood glucose	72mg/dL	Uric acid	3.8mg/dL

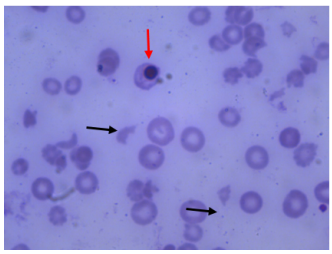

Figure 1: Peripheral smear

Peripheral smear (Figure 1) showed normocytic normochromic and microcytic hypochromic red blood cells with polychromasia and occasional normoblasts (red arrow), occasional schistocytes (black arrows), white-cell count-normal with neutrophilic predominance, and moderate thrombocytopenia.

Her history was reviewed: there was no history of any joint pains/ photosensitivity/ rash or alopecia. No h/o abortions or convulsion.

Sonogram of abdomen showed liver of 16.3cm, no splenomegaly, minimal ascites, oedematous gall bladder. Sonogram of pelvis was normal. Human immunodeficiency virus ELISA, Hepatitis B surface antigen (HBsAg) ELISA and hepatitis C virus ELISA were negative. Direct and indirect Coombs test were negative thrice. Lactate dehydrogenase (LDH) level was 1849U/L. ANA- IF (Anti-nuclear antibody-immunofluorescence) and 24 hour urine copper were awaited. Provisional diagnosis of haemolytic anaemia was considered, and she was started on methylprednisolone pulse.

Course in hospital

Table 2: Laboratory data on subsequent days

	Day 1	Day 2	Day 3	Day 4
Haemoglobin (g/dL)	6.9	6.3	4.8	5.3
White-cell count(per mm^3)	6800	7400	5400	12300
Platelets(per mm^3)	17000	19000	11000	25000
Erythrocyte sedimentation rate(mm/hr)	75			
Blood Urea (mg/dL)	22		61	73
Serum creatinine(mg/dL)	0.8		1	1
Serum sodium (mEq/L)	136			
Serum potassium (mEq/L)	3.6			
Total Bilirubin (mg/dL)	5			
Direct Bilirubin (mg/dL)	0.6			
Aspartate aminotransferase (U/L)	38	6/0.4	8.6/1.5	6.7/3.8
Alanine aminotransferase (U/L)	15			
Total Protein (g/dL)	7g/dL			
Albumin (g/dL)	4.3g/dL			
Alkaline phosphatase (IU/L)	17 IU/L			

Her haemoglobin and platelet counts were followed up on consecutive days (Table 2). On day 3 of hospital admission, she developed an episode of vomiting and abdominal pain which was symptomatically managed with Inj. Pantoprazole and Inj. Ondansetron. Five hours after the episode, the patient was drowsy, blunted responses, E3V4M6, pupils equal and reactive to light, moving all 4 limbs, plantar bilateral flexor. Plain CT brain was taken, which was normal. A repeat smear sent on day 2 again showed evidence of ongoing haemolysis, with anisocytosis seen with polychromasia, normoblasts, micro spherocytes and schistocytes, and neutrophilia with thrombocytopenia.

With the new onset of neurological signs and rising blood urea levels, thrombocytopenia and microangiopathic haemolytic anaemia (MAHA), a diagnosis of thrombotic thrombocytopenic purpura was made, and blood sample for testing for ADAMTS13(A disintegrin and metalloprotease with a Thrombospondin type 1 motif, member 13) levels was sent before initiating on plasma exchange. The patient was urgently initiated on daily plasma exchange with fresh frozen plasma and prednisolone was continued at 1mg/kg/day. A close differential of disseminated intravascular haemolysis was considered, but Prothrombin time -international normalized ratio (PT-INR) was 1.21, 1.38, and 1.16 on first three days on hospital stay. Activated partial thromboplastin time (APTT) was 32s, 30s, and 33s with a control of 30s on the first three days. Her LDH and platelet counts were monitored (Table 3).

D-dimer was 2655ng/mL which is high and repeat value was 2549ng/mL (< 500ng/mL). ANA-IF was 2+, 24hour urinary copper was 49.5µg/24 hrs, Anti ds DNA- 19 (<25), ANA Profile: U1 RNP 1+ positive. Urine pregnancy test was negative. Magnetic resonance imaging of brain with venogram showed minimal postcontrast enhancement in the sulcal spaces of both hemispheres, 2-3 tiny foci of diffusion restriction in right corona radiata and centrum semiovale white matter. Possibilities of meningitis and foci and acute infarcts reported. Cerebrospinal fluid study was done; there were no cells and protein was 21 mg/dL, sugar 86 mg/dL and ADA 9 (<10IU/dL).

During 2rd plasma exchange, she developed hypotension, requiring inotropic support with noradrenaline, which could be weaned off over next 6 hours. During 3rd session, she developed an episode of pulmonary oedema, was intubated and required mechanical ventilatory support. She was started on rituximab. She was weaned off ventilator after 24 hours and continued on plasma exchange with removal of a lower volume of plasma.

Table 3: Monitoring of LDH and platelet counts

Plasma exchange session	1	2		3	4			
LDH (U/L)	1993	1880	1180	1000	810	610	398	310
Platelet (per mm3)	21000	34000	34000	60000	80000	1.08L	1.24L	
Blood Urea (mg/dL) / Serum creatinine (mg/dL)	59/0.8	57/1	43/0.9	40/1	48/1	40/0.7	20/0.8	

Her sensorium gradually improved, urine output and renal parameters were normal. She received a total of four sessions of plasma exchange and 2 doses of rituximab. Her haemoglobin levels also improved, and she was discharged with prednisolone at 1mg/kg/day. Her ADAMTS-13 results showed severe deficiency of ADAMTS-13 activity with no activity detected, and presence of inhibitor (by Technozyme ADAMTS-13 Activity- ELISA).

A final diagnosis of thrombotic thrombocytopenic purpura with severe ADAMTS-13 deficiency, with an underlying evolving connective tissue disorder was considered. The patient continues to remain asymptomatic on follow up at 1month and her platelet count and haemoglobin levels are improving on tapering doses of prednisolone.

DISCUSSION

Thrombotic thrombocytopenic purpura was first described by Moschowitz in 1925 as a disease causing hyaline thrombi formation in multiple organs [(1)]. It is characterised by the classic pentad of thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), neurologic symptoms and signs, renal derangements and fever [(2)]. Microangiopathic haemolytic anaemia is defined as nonimmune haemolysis - presence of fragmented red cells (schistocytes) on the blood smear and a negative direct Coombs' test. Before the routine use of plasma exchange, TTP had a mortality of close to 90% [(3)]. Currently, the dyad of unexplained thrombocytopenia and MAHA is required to establish the diagnosis and start plasma exchange.

Most commonly TTP is idiopathic; other associations being autoimmune disease, infections such as HIV, malignancy, drugs such as quinine, ticlopidine, chemotherapeutic agents, bloody diarrhoea prodrome, pregnancy/postpartum, and hematopoietic cell transplantation[(4)]. Pathogenesis involves von Willebrand factor (vWF) that are assembled in larger multimers compared to normal plasma. These multimers are rapidly degraded to the normal vWF multimers by a specific cleaving metalloproteinase- ADAMTS13 (A disintegrin and metalloprotease with a Thrombospondin type 1 motif, member 13) [(5)]. ADAMTS13 deficiency leads to the accumulation of vWF multimers leading to platelet aggregation, and the platelet thrombi. An inhibitory autoantibody to the ADAMTS13 was found among a high percentage of patients with idiopathic TTP with severe ADAMTS13 deficiency [(6)]. Diagnosis is often made on clinical

grounds and routine blood examination. An ADAMTS- 13 levels helps confirm the diagnosis, although it should not influence the initial treatment decision to initiate plasma exchange. Close differentials include vasculitis and other connective tissue disorders, scleroderma renal crisis, malignant hypertension, disseminated intravascular coagulation, and disseminated malignancy.

Plasma exchange is initiated early, performed daily until the platelet count has normalized and haemolysis largely ceased--a return of the serum lactate dehydrogenase (LDH) concentration to normal or near normal [7][8].

Those with a more severe disease course, prominent neurologic abnormalities who do not respond to plasma exchange, or worsen despite plasma exchange plus steroids, or with disease relapse, may require more intensive immunosuppressive treatment.

Rituximabmay be used during daily plasma exchange and should be given immediately after the apheresis to avoid unnecessary removal of the drug. Although plasma exchange may remove much of the rituximab, plasma exchange on the next day does not to impair its effectiveness [9].

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