The Journal of the Association of Physicians of Tamil Nadu,
Vol. 2, Issue 2, English Quarterly, April – June 2023

Uncommon Case of Thrombocytopenia

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Thrombotic Thrombocytopenic Purpura (TTP) is a rare blood disorder characterized by clotting in small vessels (thrombosis) resulting in low platelet count. In its classic form, the disease consists of the following pentad

1. Thrombocytopenic purpura
2. Microangiopathic hemolytic anaemia (MAHA)
3. Neurological abnormalities – seizure/ stroke
4. Fever
5. Kidney failure (1)

Background:

First described by Dr Eli. Moskowitz MD in a girl in 1924 who had abrupt onset of petechiae, pallor followed by paralysis – coma and death. On pathological examination found to have thrombi in small arterioles and veins consisting mostly of platelets. Subsequently known as TTP closely related to HUS(Hemolytic Uremic Syndrome) but is more common in children and renal abnormalities are more severe.

Pathophysiology:

Patients with TTP have unusually large multimers of Von Willebrand factor (vWF) in the plasma. The majority of the TTP is due to the formation of an inhibitory autoantibody to ADAMTS 13 which is responsible for the breakdown of these ultra-large vWF multimers synthesised by endothelial cells. Inhibitory antibody to ADAMTS 13 leads to a severe decrease in its activity, leading to the accumulation of ultra-large molecules of vWF and the platelet leading to occlusion of small arterioles and capillaries resulting in digital gangrene, skin necrosis and microangiopathic haemolytic anaemia (MAHA).(2) (3) (4)

Secondary TTP has been reported with the use of certain drugs, namely chemotherapy drugs and antiplatelets like ticlopidine and clopidogrel. Few cases of congenital or hereditary TTP due to a mutation in ADAMTS 13 resulting in a deficiency of ADAMTS 13.(5) (6) (7)

ADAMTS 13 level activity assay is available and activity <10% commonly leads to TTP. Also, ADAMTS 13 antibody assay is also available.(8) Primarily it remains a clinical diagnosis based on Pentad.(9)

Epidemiology:

A rare disease in USA exact figure is not available. France's national registry shows an incidence of 13 per million population.

Mortality:

Untreated cases have 90% mortality rate. Early diagnosis and treatment with Plasmapheresis will reduce the mortality to <10-20%. (10)

Differential Diagnosis:

1. HUS(11)
2. ITP and DIC
3. Drug-induced TMA thrombotic microangiopathy)
4. Cancer-associated TMA
5. Hematopoietic transplant-associated TMA

Treatment:

TTP is a medical emergency. Plasma exchange with FFP and corticosteroids plays a major role intreatment. Also, anti-CD 20 monoclonal antibodies (rituximab), bortezomib,

and vincristine are also being used. A new drug Caplacizumab is developed for the treatment of TTP. The patient may need dialysis till the renal function recovers.(12) (13)

This is a45-year-old female with no comorbidities except being on treatment for schizophrenia on risperidone presented with complaints of generalised weakness, easy fatigability and dyspnoea on exertion for a week time. She also gives a history of numbness on the right side of the body which was transient. No history of tonic-clonic jerks, petechiae rash or bleeding.

Clinical evaluation – pallor+, no icterus no petechial rash. Vitals stable. Systemic examination was normal.

Investigations revealed Hb of 6.9g/dl, TC of 6900 and platelets of 20,000, serum bilirubin was 1.4mg, liver enzymes, renal function and electrolytes were normal. Treated symptomatically with supportive medications. The next day patient developed numbness involving the right half of the body with the inability to speak, CT brain was normal. Repeat laboratory parameters revealed Hb of 7g/dl and platelets were down to 6,000. Peripheral smear showed spherocytes and schistocytes (fragmented RBC). LDH was 2305. With this clinical picture diagnosis of TTP was considered. A haematologist opinion was obtained who also considered the same diagnosis and advised plasmapheresis with FFP replacement. Risperidone was stopped as a possible association with TTP. Also, pulse steroid therapy started.

Plasmapheresis was initiated under nephrology care. The patient remained clinically stable, and mild improvement in platelet count was noted. During her ward stay on day 4 she developed an episode of GTCS, was treated with antiepileptic and shifted to ICU. Continued to have low GCS and hence was electively intubated and ventilated. The repeat CT brain was normal. CBC and LDH serial monitoring were done. Platelets remained low but there was no further drop. Had a bout of significant hematuria with no other bleeding manifestations. Hematologist reviewed and advised a dose of rituximab and vincristine which was also given. Continued with plasma exchange with FFP and steroids.

The patient had persistent low GCS and her creatinine showed a worsening trend (creatinine was >5, urea >200) hence initiated hemodialysis. Developed high-grade fever spikes cultures were sent and antibiotics escalated. The patient has marginal improvement in sensorium following HD but is ventilator dependent hence tracheostomy was done. The patient showed progressive improvement in her clinical status and fever also subsided, sensorium improved. Laboratory parameters also showed improvement – CBC, RFT, and LFT. ANA's profile was negative. Patients had received a total of 9 sessions of plasmapheresis with FFP, 3 doses of rituximab and one dose of vincristine. The patient was gradually weaned from ventilator support to a tracheostomy mask and shifted to the ward. RFT improved rapidly and platelets normalised. Steroids tapered. On day 20 she developed left hemiparesis – CT Brain showed a right frontoparietal lobe infarct. As platelet were normal single antiplatelet and heparin was added along with neuroprotective and physiotherapy. Progressively good clinical improvement. Alert with left hemiparesis power 3/5. Found to have high blood sugar values managed with insulin. Mobilised with support, the tracheostomy was closed. Repeat CBC, RFT was normal. The patient was discharged home after 40 days of hospital stay with a Ryles tube and Foley catheter in a wheelchair.

During follow-up after 15 days started on oral feeds she tolerated without difficulty, spastic left limbs. At 3 months of follow up was ambulant with support, with mild weakness on the left side. Sugars controlled with OHA continued on antiepileptics and dual antiplatelet. The last follow-up was after one year – no complaints except for residual mild weakness of left limbs.

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