

CLINICAL VIGNETTE

Congenital Thrombotic Thrombocytopenia Purpura

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Congenital Thrombotic thrombocytopenic purpura (TTP), previously known as Upshaw-Schulman syndrome (USS) is a rare autosomal recessive bleeding disorder characterized by repeated episodes of thrombocytopenia and microangiopathic hemolytic anemia (MAHA).

We present a Transgender Male (born female) diagnosed with congenital TTP at age 20.

He is now a 31-year-old male with history of hemolytic anemia, jaundice and thrombocytopenia since age 2. He was in the NICU for bilirubin of 32 at birth and had recurrent episodes of hemolytic anemia and thrombocytopenia treated with steroids and IVIG without any response. He was diagnosed with hemolytic uremic syndrome at age 5 after the first documentation of hematuria with hemolysis and responded to fresh frozen plasma (FFP) treatment.

He transitioned from female to male at age 20 and underwent bilateral mastectomies. Intraoperatively, he had severe hemolysis and thrombocytopenia and reevaluated by a hematologist who suspected TTP and measured ADAMTS13 levels which were severely depleted. He also did not have any detectable levels of antibodies to ADAMTS13. He was diagnosed with Upshaw-Schulman syndrome and started on prophylactic FFP treatments every 3-4 weeks to prevent episodes of severe TTP and thrombocytopenia. He continued to have periodic episodes of acute TTP that resolved over 1-2 days with FFP administration. These generally were triggered by recurrent urinary tract infections. Eventually, he was treated every 2 weeks with prophylactic FFP.

Thrombotic Thrombocytopenic Purpura (TTP) is a rare pathological condition where blood clots composed of agglutinated platelets and Von Willebrand factor form in small blood vessels inhibiting blood flow, consuming platelets and increasing risk of bleeding.

There are two main forms of TTP:

1) Acquired TTP which is more common, affects females more often with an incidence of 3 per 1 million adults per year, based on data from the Oklahoma TTP-HUS Registry. The Acquired form can be further classified as primary TTP or secondary TTP.¹

2) Congenital (hereditary TTP or USS) is a rare autosomal disorder, affects males and females equally with estimated prevalence of 0.5-2 cases per million.^{1,2}

Normally after an injury, Von Willebrand factor (VWF), made by endothelial cells and megakaryocytes, helps platelets stick together and adhere to the walls of blood vessels at site of vascular injury. The adhesive activity of VWF depends on the size of the multimers. In 1996, ADAMTS13 which is the Von Willebrand Factor cleaving enzyme was identified.³⁻⁵ The function of ADAMTS13 is to cleave large VWF multimers into smaller, less adhesive multimers that are cleared from circulation.⁶ In the absence of ADAMTS13, the large VWF multimers can accumulate and trigger intravascular platelet aggregation and microthrombosis and ensuing signs and symptoms of TTP.

All forms of Acquired TTP, have circulating *autoantibodies* that inhibit ADAMTS13 function or increase ADAMTS13 clearance, decreasing levels of ADAMTS13 leading to possible TTP. However, in congenital or hereditary TTP there are no antibodies formed to ADAMTS13 enzyme. Instead a biallelic mutation causes severe deficiency of ADAMTS13.

Severely decreased levels of ADAMTS13, is characteristic of TTP and was initially thought to be diagnostic of TTP. However, measurements of ADAMTS13 levels are not sufficiently sensitive or specific to reliably distinguish TTP from other severe systemic disorders.⁷

ADAMTS13 activity below 10 percent has also been reported in patients with other causes of Microangiopathic hemolytic anemia and thrombocytopenia including sepsis and systemic cancer.⁸

Discussion

Our patient had levels of ADAMTS13 as well as antibodies to ADAMTS13 measured on separate occasions when he had normal platelet counts without any evidence of anemia. He had no evidence of ADAMTS13 antibodies and his ADAMTS13 activity level was less than 5% on two separate occasions. ADAMTS13 activity level <5% is consistent with severe deficiency and is a specific finding in patients with a clinical diagnosis of TTP. Persistence of severe ADAMTS13 deficiency during clinical remission is associated with increased risk for recurrence clinical episodes of TTP.

Interestingly, patients with hereditary TTP and severe ADAMTS13 deficiency can remain asymptomatic without hemolytic anemia, thrombocytopenia or microvascular thrombosis. However, situations that increase concentrations of VWF such as infection, inflammation, pregnancy, trauma, excessive alcohol use and even desmopressin which releases VWF, may trigger acute episodes of TTP.⁹

This patient did not have family members with bleeding disorders and his younger brother tested negative for the genetic disorder. He continues to receive prophylactic FFP transfusions with provide ADAMTS13 enzyme and prevent clinical episodes of TTP.

Two periods of life that are consistently reported to be associated with extreme risk in patients diagnosed with hereditary TTP: pregnancy and the first few days of life.^{1,9} Therefore, neonates who have thrombocytopenia accompanied by severe hyperbilirubinemia should be tested for hereditary TTP and treated with plasma infusion. Pregnant females with early onset preeclampsia in first trimester, should have hereditary TTP considered as part of their differential diagnosis and potentially be administered plasma.¹

Synthetic ADAMTS13 has been developed and is currently being evaluated in clinical trials for potential home administration.

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