Summary: Hereditary thrombotic thrombocytopenic purpura is an ultra-rare disorder caused by biallelic mutations in the ADAMTS13 gene. Because it can be difficult to diagnose, plasma ADAMTS13 activity assessment should be considered in patients with thrombocytopenia, anemia, and schistocytes on peripheral blood smear. We present the diagnostic evaluation of a patient with hereditary thrombotic thrombocytopenic purpura. Genetic testing revealed one known pathogenic mutation and one novel mutation of ADAMTS13 classified as likely pathogenic on the basis of parental genetic testing and in silico analyses. We further discuss off-label use of prophylactic plasma-derived Factor VIII (Koate-DVI) and the benefit of rare disease registries.

Key Words: TTP, congenital TTP, hereditary TTP, thrombotic thrombocytopenic purpura

CASE REPORT

A 9-month-old girl presented to the emergency department with fever, cough, rhinorrhea, and poor oral intake. These symptoms were present for 2 weeks but worsened over the previous 2 days. She had a history of thrombocytopenia in the postnatal period, with a platelet count nadir of 41,000 × 10^9/L, which spontaneously resolved by 3 weeks of life. On examination, she had coarse breath sounds, bilateral acute otitis media, pale and mottled skin, and delayed capillary refill. She lacked lymphadenopathy or hepatosplenomegaly. Respiratory syncytial virus testing was positive. Laboratory studies revealed normal chemistries, creatinine, and transaminases. Complete blood count (CBC) revealed normocytic anemia, with hemoglobin of 55901 (e-mail: carndt@mayo.edu).

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TTP Registry (www.ttpregistry.net) revealed a registered patient diagnosed with hTTP at 5 months of age who had a T>C (p.Leu183Pro) change of the same nucleotide (c.548) that was altered T>A in our patient. The registry patient similarly suffered from thrombocytopenia, hemolysis, and anemia in the immediate postnatal period.

**DISCUSSION**

hTTP is a chronic, lifelong disease with no cure. Acute episodes of anemia and thrombocytopenia are treated with infusions of fresh frozen plasma (FFP), which contains ADAMTS13, to replete the deficient protein. It is common practice to prophylactically treat patients with routine (ie, every 2 to 3 wk) FFP to prevent acute episodes of thrombotic microangiopathy. The observation that one plasma-derived Factor VIII product (Koate-DVI; Kendrion Biopharma) incidentally contains a relatively high concentration of ADAMTS13 has led to off-label use in patients with hTTP. Furthermore, recombinant ADAMTS13 is the subject of an ongoing phase III randomized cross-over clinical trial (ClinicalTrials.gov NCT03393975) comparing prophylactic versus on-demand dosing with a continuation arm. The preceding phase I study reported ADAMTS13 pharmacokinetic parameters similar to what was observed with FFP infusion.

To gather more information about this rare disease, an international Hereditary TTP Registry (www.ttpregistry.net) exists to combine patient data and yield insights into the pathogenesis and management of hTTP. The patient was enrolled in the registry, which provided supplemental information to the treating team to confirm the likely pathogenicity of one of the patient’s genetic VUS and also connected the treatment team with other providers who care for patients with hTTP.

The patient was initially treated with on-demand FFP. However, she required infusions approximately every 4 weeks due to acute exacerbations. For prevention of acute TTP exacerbations, her parents elected to initiate prophylactic management with Koate-DVI to allow for the convenience of rapid, small-volume, in-home infusion and also to potentially reduce the risk of transfusion-associated viral diseases using a solvent/detergent treated product. She was

![FIGURE 1](image_url). Peripheral blood smears (A) on initial presentation to the referral intensive care unit and (B) while the patient was well demonstrate schistocytes and helmet cells (arrows).

![FIGURE 2](image_url). Platelet count over time. Arrows note the time of treatment administration. Acute thrombotic thrombocytopenic purpura episodes are noted with asterisks. Shaded area denotes reference range for platelet count.
initially started at a dose of 25 U/kg intravenously every 2 weeks; however, she experienced breakthrough acute TTP episodes, and her dose was modified several times before arriving at the present dose of 25 U/kg on Mondays and 40 U/kg on Thursdays. Thus far, the patient has been treated for 4 acute episodes with Koate-DVI and demonstrated improvement of anemia and thrombocytopenia within 2 days of receiving “rescue” doses (Fig. 2).

In summary, hTTP is an ultra-rare condition for which diagnosis may be delayed. ADAMTS13 assay should be considered for patients with anemia, thrombocytopenia, and schistocytes on peripheral blood smear. In this patient, persistence of schistocytes while she was clinically well was the clue which led to the diagnosis of hTTP. Patients may be treated with FFP or Koate-DVI. Patients with severe disease may require frequent dosing to prevent recurrent episodes. An ongoing trial of recombinant ADAMTS13 may lead to the availability of a new treatment for this disease in the near future. Through collaboration with a genetic counselor, we were able to establish a novel mutation as likely pathogenic, and we experienced that disease registries can be invaluable to clinicians when caring for patients with rare diseases.

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