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Case Report

A 20-year-old male with no significant past medical history presented to an outside hospital with a two-week history of progressive fatigue, malaise and decreased appetite. Prior to these events, he had been in his usual state of health with normal exercise tolerance and energy level. Upon development of his symptoms, the patient felt as though he had developed an upper respiratory infection (URI). The URI symptoms eventually resolved; however complaints of fatigue and malaise still remained. He then developed progressive dyspnea on exertion and tea-colored urine. The patient reported a singular febrile episode to 38.9˚C associated with nonbilious vomiting two days prior to admission. Upon further questioning, he admitted to a twenty-pound weight loss over the last month. The patient's mother also noticed unprovoked bruising on his forearms bilaterally. He denied night sweats, gingival bleeding, epistaxis, hematuria, or melena.

The patient is of Afro-Jamaican descent; his family originating from Trinidad. He reported no family history of hematologic disorders, and only acknowledged a maternal grandmother with breast cancer. The patient denied chronic medications, including herbal and over-the-counter medications. He denied food or drug allergies, as well as alcohol, tobacco or illicit drug use. He reported being sexual active with one partner in the past 6 months and denied any sexually transmitted infections.

Hospital Course

On admission to the outside hospital, laboratory results revealed a profound anemia (hemoglobin 6.3 g/dL) with an elevated red cell distribution width (RDW) (22.4%), thrombocytopenia (platelet count 44 B/L) and acute kidney injury (serum creatinine 1.9 mg/dL). Subsequent testing reported the presence of 4+ schistocytes on peripheral blood smear concerning for microangiopathic hemolytic anemia (MAHA). Given his triad of anemia, thrombocytopenia and presence of schistocytes, there was a concern for thrombotic thrombocytopenic purpura (TTP). He was transferred to our institution for further management. Prior to transfer, the patient was medically supported with blood products and underwent a bone marrow biopsy that was determined to be non-malignant.

Upon arrival to our institution, further laboratory results revealed a significantly elevated lactate dehydrogenase (LDH) (956 IU/L) with essentially undetectable haptoglobin (<10 mg/dL). Urinalysis was positive for 2+ protein and 1+ blood. Direct Coombs test was negative. Repeat peripheral blood smear was positive for the presence of 3+ schistocytes, confirming concern for TTP. The patient was transferred to the medical intensive care unit and immediately started on intravenous methylprednisolone, folate, and blood products until an apheresis catheter could be placed for plasma exchange therapy. Once the catheter was placed, the patient underwent five sessions of plasma exchange therapy without complications. Human immunodeficiency virus (HIV) antibody, hepatitis B and C serologies were negative. His steroids were tapered, and blood counts and LDH were monitored daily. Upon discharge, hemoglobin had increased to 8.2 mg/dL, RDW 20.3%, platelet count 259 B/L, and LDH 263 IU/L. Haptoglobin had increased to 46 mg/dL and serum creatinine had improved to 0.8 mg/dL. A Disintegrin-like And Metalloprotease with ThromboSpondin type 1 member 13 (ADAMTS13) activity was determined to be severely low at <5%, and ADAMTS13 inhibitor activity was <0.4 units. Following discharge, the patient returned to the Emergency Department two weeks later for fever of 38.4˚C and malaise, however blood counts showed hemoglobin 9.8 g/dL, RDW 15.9%, platelet count 145 B/L, and serum creatinine 1.1 mg/dL, so he was deemed stable for close follow-up as an outpatient.

Introduction

Congenital thrombotic thrombocytopenic purpura (CTTP), also known as Upshaw-Schulman Syndrome (USS), is a very rare, but potentially life-threatening disease. It is characterized by the symptoms also seen in acquired or idiopathic TTP, including thrombocytopenia, MAHA, and subsequent microvascular thrombosis. However this constellation of symptoms is seen in conjunction with significant and persistent deficiency in ADAMTS13 with concurrent absence of an ADAMTS13 inhibitor. ADAMTS13 is a protease responsible for modifying the larger precursor of von Willebrand factor (vWF), a necessary component of the clotting cascade. Continued disruption of this process leads to microvascular embolization and may ultimately cause potential end organ failure, including heart, brain, and kidneys.

Historical Background

Cases concerning for CTTP were first reported in 1953, when Dacie and colleagues described a 6-year-old female who suffered repeated episodes of thrombocytopenia, hemolytic anemia, presence of schistocytes, and significant jaundice since birth. The young patient underwent splenectomy without improvement of symptoms, and eventually died of renal failure at age 7. Upon review of the patient's family history, she had two other siblings, who were jaundiced as newborns and both died of hemorrhage by the age of 4. However the fourth child and both parents were asymptomatic, so Dacie suspected that the patient and her family had some yet to be determined inherited blood disorder.[1] In 1960, Schulman reported an 8-year-old female who suffered

from repeated bleeding episodes secondary to chronic thrombocytopenia and MAHA. Symptoms dramatically improved with fresh frozen plasma (FFP), suggesting that the patient had a congenital deficiency in some "platelet-stimulating factor."[2] Upshaw and colleagues in 1978 would later report a 29-year-old female who had repeated episodes of thrombocytopenia and MAHA since childhood, that was treated with FFP.[3]

The syndrome for CTTP was coined by Rennard and Abe, who recognized the similarities between the Upshaw and Schulman's cases, and they postulated that these patients developed their sequelae as a result of increased fibronectin during the symptomatic phase of their disease.[4] However, multiple subsequent studies would later show there was no association with fibronectin and disease activity.[5,6,7] The assay to assess ADAMTS13 activity was created in 1997, but it was not until 2001 that the link between ADAMTS13 mutation and subsequent deficiency and CTTP or USS was confirmed by Levy and colleagues by means of linkage analysis performed on four pedigrees with CTTP.[8]

Pathophysiology

USS is inherited through an autosomal recessive pattern, though based upon clinical evaluation of USS patients, there is a variable degree penetrance that does not necessarily follow a structured genotype-phenotype correlation.[9] It is caused by mutations in the gene encoding ADAMTS13, and to date, there have been 76 distinct reported mutations.[9] The majority of these mutations are compound heterozygous in patients (64% of reported USS cases), thereby making it difficult to connect specific gene mutations to presentation characteristics of clinical disease. However, it is noted that the majority of mutations occur in the N-terminus portion of the protein, a sequence that is responsible for encoding the domains specific to the metalloprotease activity function of ADAMTS13.[9]

USS, just as idiopathic or acquired TTP (ATTP), occurs as a result of microthrombi formed from inappropriately formed vWF precursor complexes, causing embolic ischemic damage to end organs, typically heart, brain and kidney. Both are usually prompted by stress-inducing triggers, such as infection or pregnancy, but the etiology of microthrombi formation differs as do the prognosis and recurrence risk. In ATTP, microthrombi are formed as a result of auto-antibodies directed towards ADAMTS13, thereby acting as an inhibitor to the enzyme. In USS, an inherent deficiency in ADAMTS13 prevents appropriate modification of the vWF precursor, allowing formation of microthrombi.

VWF is a large glycoprotein produced in endothelial cells lining the vasculature, and secreted in response to endothelial cell activation or injury.[9] It serves as an adhesion protein, recruiting circulating platelets to collect at that activation site and form a platelet plug. Just prior to platelet recruitment, vWF is present in circulation as a larger multimeric precursor protein, ultra-large vWF (UL-vWF), of which ADAMTS13 immediately cleaves into vWF for appropriate function in the clotting cascade. In the absence of ADAMTS13, UL-vWF released from vascular endothelial cells is not cleaved appropriately, which induces platelet hyperagglutination under high shear stress.[9] Uncleaved UL-vWF then binds to circulating platelets forming microthrombi, which both embolize into the microvasculature of end organs and cause fragmentation of adjacent circulating erythrocytes, thereby producing MAHA.

Epidemiology

The incidence and prevalence of USS is extremely rare. It is estimated that there have only been 100 cases worldwide to date, with an incidence rate of no more than 1/1,000,000 person/year.[9,10] USS comprises only 10% of all TTP patients with known ADAMTS13 deficiency,[11] Time of initial presentation varies considerably; in one study of 43 USS patients in Japan, age of onset ranged from early childhood to 79 years.[12,13] With regard to racial predilection, USS cases have been reported in all continents, although there is an increased reported incidence among patients of Japanese, Central European, and Jamaican descent.[9] The most commonly reported mutation in ADAMTS13, c.4143dupA, was found through haplotype analyses to have a common ancestral background stemming from Central Europe.[14] A single nucleotide polymorphism (SNP), specifically a p.P475S mutation, is reported to be relatively common among the Japanese population, with 9.6% of asymptomatic Japanese individuals being heterozygous for that single mutation.[15]

Clinical Course

The classical presentation of USS is an initial episode of severe neonatal jaundice with a negative Coombs test, requiring an exchange blood transfusion, and repeated childhood episodes of thrombocytopenia and MAHA, reversed by FFP, because of the repletion of the deficient ADAMTS13 metalloprotease.[13] However this is a rare occurrence and the majority of USS have a subclinical presentation, with significant variability in age of onset and severity of presentation.[13] Patients may present young after typical childhood infections, during pregnancy, or even late in adulthood despite having prior stress triggers. Although patients who present early in life will likely have recurrent episodes of overt TTP, even adult presenters are subject to relapsing, recurrent disease.[9] Presenting symptoms can range from singular asymptomatic episodes of thrombocytopenia to full-blown multi-organ failure and imminent death without treatment.[3,9]

Given that patients with USS can often have delayed onset of presentation and do not persistently manifest symptoms of overt TTP despite chronic deficiency in ADAMTS13, one questions the pathophysiology of the disease. Studies in ADAMTS13 gene knock-out mice revealed the presence of circulating UL-vWF

in the peripheral blood; however, these animal models did not manifest acute symptoms of overt TTP.[16,17] Therefore, it is assumed that disease activity operates under a "two-hit hypothesis" in which the patient is chronically at increased risk for TTP, compared to patients with normal ADAMTS13 activity, and can be considered as having a prothrombotic predisposition. Overt disease will not usually manifest unless instigated by a trigger or stress-inducing event, thereby representing the "second hit."[13] At the level of the microvasculature, transient endothelial damage may occur, initiating the release of inflammatory cytokines and thrombomodulin, setting off a cascade heralding overt disease activity.[18]

Treatment

USS is initially treated in the same manner as ATTP, since the diagnosis of USS is usually obtained after the patient has already began treatment. Given the life-threatening and rapidly progressive course of untreated TTP, the standard of care, plasma exchange therapy, is immediately initiated upon the constellation of symptoms: thrombocytopenia, MAHA, and presence of schistocytes on peripheral smear. It is not appropriate to wait for determination of ADAMTS13 activity prior to beginning treatment. During plasma exchange, a venous-placed apheresis catheter removes blood from the patient, separates the blood cells from plasma, and returns the cells back while discarding the plasma in exchange for new donor plasma. This serves to remove the implicated autoantibody to ADAMTS13 in ATTP. However if it is determined that the patient has USS, he or she can be treated with FFP transfusions, which contain ADAMTS13, since the etiology of overt TTP in this case is due to a lack of ADAMTS13 as opposed to inhibition of inherent ADAMTS13 activity.[3]

Given the chronic, subclinical nature of USS, patients should receive expedited evaluation if they exhibit signs of infection, trauma, pregnancy, or alterations in their neurologic or renal function. Work-up should include a complete blood cell count with differential, haptoglobin, LDH, and peripheral blood smear to examine for schistocytes. Once determined that the USS patient is having an episode of overt TTP, he or she can receive FFP transfusions as well as erythrocyte and platelet transfusions until platelets reach 140 B/L and LDH has corrected to within normal range.

Additional developments in more curative forms of treatment for USS are currently under investigation. A recombinant human ADAMTS13 enzyme has been developed to correct deficiencies in vWF cleaving activity in vitro, as well as early studies in using monoclonal antibody rituximab for definitive therapy.[19]

Summary (a potential consideration in patients with progressive microangiopathic disease of brain, kidney unknown etiology)

USS, though very rare, is a chronic progressive disease that can easily become life-threatening without proper early recognition and treatment. Once diagnosed with USS, management should focus on preventative measures and early evaluation at the onset of disease triggers.[3] Given the asymptomatic nature of the disease when the patient is in his or her normal state of health, it is safer and more cost-effective to treat with plasma transfusions and exchange therapy as needed only when symptoms arise, rather than scheduled sessions of transfusion treatment. However, this places the onus of responsibility on patients and their families. They must be educated on USS manifestations and motivated to pursue early evaluation as well as routine medical assessments for renal and neurologic abnormalities, which may signal an acutely developing disease.[3]

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