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CASE REPORT

Clopidogrel-induced refractory thrombotic thrombocytopenic purpura successfully treated with rituximab

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Abstract
Thrombotic thrombocytopenic purpura (TTP) is a multisystem disorder characterized by microvascular aggregation of platelets and fibrin strands causing thrombocytopenia, microangiopathic hemolytic anemia, and organ dysfunction. TTP can develop as a result of a deficiency in ADAMTS13 enzyme activity due to either a genetic defect or, more commonly, the development of anti-ADAMTS13 autoantibodies. TTP can also be associated with pregnancy, organ transplant, lupus, infections, and drugs. Here, we present a case of TTP that developed shortly after the start of clopidogrel treatment for acute ischemic stroke and acute myocardial infarction, and describe the clinical presentation, refractory course of the disease, and successful induction of remission through the use of rituximab in a setting of pre-existing autoimmune diseases.

Introduction

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are similar disorders classified under thrombotic microangiopathy (TMA) due to the common mechanisms of platelet and red blood cells (RBC) destruction in the microvasculature, and similar histologic

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abnormalities in tissue biopsy specimens from affected organs. Both TTP and HUS are characterized by the deposition of loose platelets and fibrin strands in small vessels, causing mechanical shearing of RBCs and agglutination of platelets and resulting in microangiopathic hemolytic anemia (MAHA) and thrombocytopenia. Although it is rare, TTP can cause chronic remitting and relapsing illness due to congenital deficiency of von Willebrand factor (vWF)-cleaving protease called ADAMTS13. However, most cases of TTP are acquired (also known as idiopathic TTP) and caused by IgG autoantibodies that inhibit ADAMTS13 enzymatic activity. Normally, ADAMTS13 regulates vWF activity by cleaving high-molecular weight vWF multimers, and prevents platelet accumulation and thrombosis in capillaries and arterioles. Failure to cleave the vWF multimers in TTP by ADAMTS13 leads to accumulation of large vWF multimers facilitating platelet accumulation and microvascular thrombosis, which results in tissue ischemia of the affected organs and leads to variable degrees of neurologic symptoms and renal impairment. The classic pentad of MAHA, thrombocytopenia, neurologic symptoms, renal failure, and fever is present in only 5% of patients, and evidence of TMA (MAHA and thrombocytopenia) without another apparent etiology is enough to make a working diagnosis of TTP/HUS.

Typical laboratory findings for TTP include decreased platelet count, elevated lactate dehydrogenase (LDH), negative direct anti-globulin test (DAT), and fragmentation hemolysis (schistocytes) on the blood smear. Levels of creatinine and blood urea nitrogen depend on the presence and severity of renal involvement. Schistocytes are characteristic for TTP, but can also be present with other causes of fragmentation hemolysis, e.g., disseminated intravascular coagulation (DIC), prosthetic valve hemolysis, malignant hypertension, preeclampsia/HELLP syndrome, and vasculitis [systemic lupus erythematosus (SLE), scleroderma]. In contrast to DIC, typically in TTP, prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimer levels are normal. A severely depressed (<10%) level of ADAMTS13 activity is present in TTP, while ADAMTS13 activity is normal in HUS. This distinction is important clinically, but not required to make a working diagnosis of TTP, and to initiate lifesaving treatment with plasma exchange (PLEX).

Case report

A 43-year-old woman with past medical history of hypertension, hyperlipidemia, Sjogren's syndrome (SS), rheumatoid arthritis (RA), and obesity was admitted from the emergency room for rapid onset right-sided paresthesia from acute left-thalamic ischemic stroke. She developed angina while in the hospital, and was diagnosed with non-ST segment elevation myocardial infarction (NSTEMI). Coronary angiogram showed nonobstructive coronary artery disease, and laboratory studies revealed normal blood counts, bilirubin, and creatinine. The stroke and myocardial infarction were presumed secondary to accelerated hypertension. She was started on aspirin, atorvastatin, clopidogrel, carvedilol, and losartan, and was discharged home after 5 days of hospitalization. The patient presented again 2-weeks later with an approximately 3-day history of worsening fatigue, jaundice, and generalized rash. Physical exam was notable for generalized petechial rash, scleral icterus, dark urine, normal mental status, and stable vital signs. Abnormal laboratory studies included a platelet count of 8000/mm^3, LDH of 797 IU/L, hemoglobin of 10.5 gm/dL, creatinine of 2.3 mg/dL (against a baseline of 1.1 two-weeks prior), bilirubin of 4 mg/dL, and haptoglobin <20 mg/dL (normal range: 37—246 mg/dL). Peripheral blood smear showed three schistocytes per high power field, polychromasia, and severe thrombocytopenia. A DAT (Coomb's test) was negative. The patient was diagnosed with TTP/HUS, clopidogrel was discontinued, and she was started promptly on PLEX and 1 mg/kg prednisone. She initially responded to therapy with an improvement in both platelet counts and LDH levels, but then became refractory to PLEX on day 7, as shown in Figure 1. She also deteriorated clinically on day 7, with new onset anginal chest pain, which was concerning for coronary ischemia, that improved with a nitroglycerine infusion. She also complained of new right-sided paresthesia, and magnetic resonance imaging of the brain confirmed a new acute left lentiform and caudate nuclei infarcts. As a result, we started her on 375 mg/m^2 rituximab IV, escalated glucocorticoid therapy to 1 gram methylprednisolone IV daily, and continued daily PLEX. The concomitant use of PLEX, rituximab, and steroid was complicated by transfusion-associated circulatory overload, which responded to IV diuretics, gradual weaning off of the PLEX and steroids, and supportive care. Over the next several days, she continued to improve clinically and went into complete remission from TTP after receiving a total of 24 PLEX treatments, three weekly dosages of rituximab, and a tapering course of prednisone over 3 weeks.

Discussion

Our patient had a positive ADAMTS13 antibody of >8 (normal: <0.5 inhibitor units), with a decrease in ADAMTS13 activity to <5 (normal: 68—163%). This was consistent with TTP, which is the disorder usually described in adults, unlike HUS, which is more common in children and associated with normal ADAMTS13 activity and absence of the inhibitor antibody. Many studies do not distinguish between TTP and HUS, and combine them under the comprehensive term TTP/HUS syndrome, since their presenting features and initial management in adults are essentially the same. Although the levels of ADAMTS13 activity and inhibitor antibody help differentiate between TTP and HUS, one should not wait for the results of these tests to start therapy. When neurological manifestations are more dominant, with renal abnormalities being minimal or absent, the condition is more likely to be TTP; whereas, when acute renal failure is the dominant clinical manifestation, the condition is more likely to be HUS. HUS often presents in children, following bloody diarrhea due to a shiga-toxin producing strain of *Escherichia coli* (O157:H7), and resolves spontaneously with supportive care (D+ HUS). Some HUS patients can present without diarrheal prodrome, and are classified to have D− HUS or atypical HUS. HUS occurs due to dysregulation of complement regulatory proteins. In TTP, in addition to renal and neurologic abnormalities, patients may rarely present with cardiac involvement secondary to platelet thrombi, leading to arrhythmias, myocardial infarctions, heart failure, or even