Syndromes of Thrombotic Microangiopathy

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KEYWORDS

- Thrombotic thrombocytopenic purpura (TTP) • Hemolytic uremic syndrome (HUS)
- Microangiopathic hemolytic anemia (MAHA)
- Atypical hemolytic uremic syndrome (aHUS)
- Pregnancy induced microangiopathic hemolytic anemia
- Transplant induced microangiopathic hemolytic anemia

KEY POINTS

- The presence of thrombocytopenia and microangiopathic hemolytic anemia should prompt an acute work-up for thrombotic thrombocytopenic purpura (TTP) and consideration of immediate initiation of plasma exchange.
- Congenital TTP or atypical hemolytic uremic syndrome (HUS) should be considered in patients with recurrent episodes of TTP/HUS that do not have appropriate ADAMTS13 (a disintegrinlike and metalloprotease with thrombospondin type 1 Motifs 13) levels or detectable inhibitors.
- Eculizumab has been shown to be effective in improving renal function in atypical HUS.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare hematologic disorder (annual incidence of 11.3 cases per 1 million population), characterized by microangiopathic hemolytic anemia, thrombocytopenia, and varying levels of end-organ damage, including renal insufficiency, neurologic phenomena including stroke, and fever.[1–4] However, only a minority of patients with TTP present with all of the aforementioned features, often making the initial diagnosis challenging. There is no acute test to rule TTP in or out with enough speed and accuracy to safely guide initial therapy. Therefore the diagnosis is mostly a clinical one, based on the presence of thrombocytopenia and the characteristic findings of microangiopathic hemolysis on evaluation of the

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patient's blood smear, including the presence of schistocytosis, increased serum levels of lactate dehydrogenase (LDH), and decreased levels of haptoglobin with no other obvious cause.[5] The LDH level is often extremely increased and is a prognostic factor in TTP.[6] Other features, such as fever and neurologic sequela, are often absent or nonspecific, and cannot be relied on for routine diagnosis.[7] Thrombocytopenia may range from a mild decrease in platelet number to platelets being undetectable. The findings of thrombocytopenia with a normal prothrombin time helps eliminate disseminated intravascular coagulation (DIC) from the differential.[8]

TTP and the hemolytic uremic syndrome (HUS) have a spectrum of presentations and therapies, each unique to its specific pathophysiology. This article outlines the varying types of TTP/HUS by category, describing the current literature on their pathophysiology and therapy.

Classical Thrombotic Thrombocytopenic Purpura

Clinical presentation

Many patients with TTP first have a prodrome of a flulike or diarrheal illness. Patients can present with a variety of conditions ranging from general malaise to sudden death. The disease can strike at any age, although it predominantly occurs between 20 and 50 years of age, with women affected more than men in a 2:1 ratio.[9]

The classic reported pentad of fever, mental status changes, renal insufficiency, thrombocytopenia, and microangiopathic hemolytic anemia is only seen in a minority of patients.[10] As described later, the pentad can range in severity from mild to severe.

Neurologic

Neurologic complaints are present in more than half of patients on presentation and range from mild confusion to a stroke like syndrome.[11] In mild cases these symptoms must only be elicited through direct questioning. Patients often complain of tiredness, confusion, and headaches. Seizures were present in 9% of patients in one series, and may be recurrent.[11] Up to a quarter of patients develop transient focal neurologic defects, which may wax and wane over several hours.[11] MRI can show reversible posterior leukoencephalopathy.[12]

Hematologic

The initial diagnosis of TTP and other thrombotic microangiopathies (TMs) depends on the hematologic picture. By definition of the syndrome, patients are thrombocytopenic, because of the spontaneous aggregation of platelets and their deposition on damaged endothelial surfaces. The platelet count may range from 80,000/μL in mild cases of TTP to less than 1000/μL in severe cases. The median platelet count is generally 10,000 to 30,000/μL.[13] In mild cases of TTP, the thrombocytopenia is mistakenly ascribed to other causes and diagnosis is delayed. The platelet function is impaired because of continual platelet activation. Even though a seemingly adequate number of platelets are circulating, they are unable to support hemostasis, often leading to clinically significant bleeding with platelet counts that are not dramatically decreased.

The hematocrit in TTP is low because of hemolysis. Patients have clinical testing consistent with intravascular hemolysis: high reticulocyte counts, LDH level, and indirect bilirubin with low haptoglobin. Direct antibody (Coombs) test is negative. Review of the peripheral smear is diagnostic for microangiopathic hemolytic anemia. Clinicians should carefully examine the smear for red cell fragments. In very ill patients, rare schistocytes are often present, but in TTP and other TMs there is at least 1 red cell fragment per high-powered field. The presence of microangiopathic hemolytic anemia is the *sine qua non* for diagnosis of any TM. The LDH level is strikingly increased, often more than 2 to 4 times normal. The source of the LDH is not only lysed