Thrombocytopenia

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KEYWORDS

- Thrombocytopenia • Immune thrombocytopenia
- Heparin-induced thrombocytopenia • Thrombotic thrombocytopenia purpura
- Atypical hemolytic uremic syndrome

KEY POINTS

- Major causes of isolated thrombocytopenia include immune thrombocytopenia, drug-induced thrombocytopenia, disseminated intravascular coagulation, heparin-induced thrombocytopenia, gestational thrombocytopenia, and inherited thrombocytopenias.
- Patients with mild, chronic, isolated thrombocytopenia often maintain a platelet count in the range of 100 to 150 $\times$ 10^9/L, whereas some develop immune thrombocytopenia with or without a concomitant autoimmune disease.
- Immune thrombocytopenia is a diagnosis of exclusion and requires evaluation for secondary causes of thrombocytopenia.
- Diagnosis and management of heparin-induced thrombocytopenia rely on an assessment of pretest probability of having this disease.
- Microangiopathic hemolytic anemia and schistocytes are defining features of thrombotic microangiopathies.

INTRODUCTION

Platelets are derived from megakaryocytes whose production and maturation in the bone marrow are regulated by thrombopoietin.[1] Platelets play important roles not only in thrombosis and wound repair but also in inflammation, immunity, and cancer biology.[2] Normal platelet values range from 150 to 450 $\times$ 10^9/L. There is some debate as to whether patients with platelet counts in the range 100 $\times$ 10^9/L to 150 $\times$ 10^9/L should be designated as having true versus borderline thrombocytopenia[3]; data suggest that most of these patients remain asymptomatic and maintain their platelet counts in this range, whereas a smaller percentage develop immune thrombocytopenia (ITP) with or without a concomitant autoimmune disease.[4]

Disclosure: The authors have nothing to disclose.
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Prim Care Clin Office Pract 43 (2016) 543–557
http://dx.doi.org/10.1016/j.pop.2016.07.008
primarycare.theclinics.com

A major clinical consequence of thrombocytopenia is bleeding caused by impaired primary hemostasis and platelet plug formation. Mucocutaneous bleeding usually occurs when platelet counts decrease to less than the range of 20×10^9/L to 30×10^9/L. Severe bleeding, including intracranial hemorrhage, occurs with platelet counts of less than 10×10^9/L to 20×10^9/L.[5–7]

Thrombocytopenia is a common problem, affecting 40% to 50% of patients in medical and surgical intensive care units.[8–10] In the outpatient setting, primary care physicians are generally comfortable managing patients with at least modest thrombocytopenia (eg, platelet count 80×10^9/L) without referral to a hematologist, so an understanding of the major mechanisms of thrombocytopenia is essential for practicing internists.[11] However, the evaluation of thrombocytopenia can be challenging, because hematologists confronted with the same case of thrombocytopenia frequently disagree on the underlying diagnosis.[12]

The major underlying mechanisms of thrombocytopenia include pseudothrombocytopenia, splenic sequestration, marrow underproduction, and peripheral destruction (**Box 1**). Clues from a patient's history (including medication exposures, alcohol intake, diet, travel, recent illnesses, and transfusions), physical examination (eg, petechiae, mucosal bleeding, splenomegaly, lymphadenopathy, and skeletal abnormalities), family history, and other laboratory studies may refine the differential diagnosis. Of central importance is the peripheral blood smear to evaluate both for the presence of platelet clumps, indicating pseudothrombocytopenia (**Fig. 1**), and for other abnormal cell morphologies, such as schistocytes, large or giant platelets, or immature or dysplastic cells.

This article presents 4 clinical cases as examples of our diagnostic approach to patients with thrombocytopenia.

Case 1

A 20-year-old male college student presented to his university urgent care clinic 3 weeks ago with fever, chills, sore throat, and headache. He was diagnosed with an upper respiratory tract infection. He now returns with epistaxis and gum bleeding. He does not take any medications, vitamins, or herbal supplements. He denies alcohol or recreational drug use. He consumes a broad diet. There is no known family history of cytopenias or other blood disorders. Physical examination reveals wet purpura in the oral cavity, mild crusted blood in the nares, and petechiae on both legs, with no lymphadenopathy or hepatosplenomegaly. Laboratory studies show a white blood cell (WBC) count of 4,400/μL, hemoglobin level 14.4 g/dL, platelet count 1×10^9/L, and preserved coagulation studies (prothrombin time [PT], International Normalized Ratio [INR], and partial thromboplastin time [PTT]). The peripheral blood smear is shown in **Fig. 2**. What is the patient's diagnosis, and how should he be treated?

Petechiae and mucocutaneous bleeding can be seen with platelet disorders, mild coagulation factor deficiencies, or connective tissue disorders. This patient's severe thrombocytopenia and normal coagulation parameters suggest a platelet disorder. Given that the WBC count and hemoglobin are preserved, the evaluation should focus on causes of isolated thrombocytopenia, namely ITP, drug-induced ITP (DITP), disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia (HIT), gestational thrombocytopenia, and inherited thrombocytopenias.[13] The finding of large or giant platelets on the blood smear suggests either a component of peripheral destruction leading to megakaryocyte hyperplasia in the bone marrow or a platelet structural defect as may be seen in inherited thrombocytopenias; the negative family history points away from the latter. Lack of medication or drug exposure or herbal use renders DITP and HIT unlikely. The absence of systemic symptoms or schistocytes

Box 1
Major mechanisms of thrombocytopenia

Pseudothrombocytopenia

- EDTA (ethylenediamine tetraacetic acid) dependent

Sequestration

- Splenomegaly (portal hypertension)

Bone marrow underproduction

- Infections (Epstein-Barr virus, cytomegalovirus, hepatitis C, human immunodeficiency virus, parvovirus B19, *H pylori*)
- Medications/drugs (antibiotics, alcohol, chemotherapy, radiation)
- Nutritional deficiencies (folate, vitamin B_{12})
- Liver disease
- Bone marrow failure syndromes (aplastic anemia, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome)
- Hematologic disorders (lymphoma, leukemia, myelodysplastic syndrome)
- Tumor infiltration of bone marrow
- Inherited thrombocytopenias (Bernard-Soulier syndrome, gray platelet syndrome, congenital amegakaryocytic thrombocytopenia, Wiskott-Aldrich syndrome, thrombocytopenia with absent radii, MYH9-related thrombocytopenia)

Increased platelet destruction

- ITP
- Drug-induced ITP (quinine, NSAIDs, glycoprotein IIb/IIIa inhibitors)
- Heparin-induced thrombocytopenia
- TTP/HUS
- Atypical HUS
- Medication-induced TTP (mitomycin C, gemcitabine, oxaliplatin)
- Disseminated intravascular coagulation
- Posttransfusion purpura
- [a]Autoimmune-related thrombocytopenia (SLE, CVID, antiphospholipid antibody syndrome, thyroid disease, Evans syndrome)
- Mechanical destruction (cardiopulmonary bypass, intra-aortic balloon pump)

Abbreviations: CVID, common variable immunodeficiency; HUS, hemolytic uremic syndrome; MYH, myosin heavy chain; NSAIDs, nonsteroidal antiinflammatory drugs; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.
[a] Secondary ITP, multiple mechanisms of thrombocytopenia.

and the normal coagulation studies exclude DIC. The most plausible explanation for this patient's severe, isolated thrombocytopenia is therefore ITP.

ITP is an autoimmune disorder caused by antibodies directed against antigens on the surfaces of platelets and megakaryocytes, leading to platelet destruction.[14] Genetic susceptibility in combination with environmental factors (including viral and bacterial infections) may trigger flares of ITP.[15] Despite exhaustive efforts, no disease-causing autoantibody with reliable diagnostic utility has been identified.[16,17]

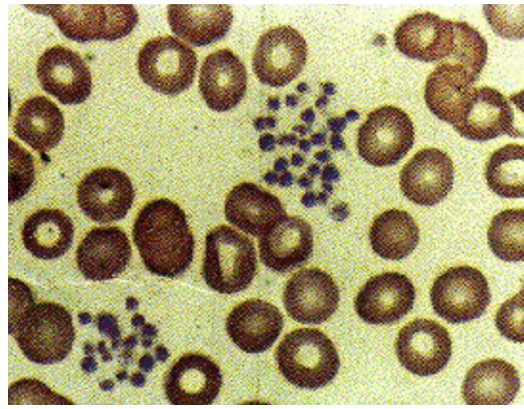

Fig. 1. Pseudothrombocytopenia; this is an in-vitro phenomenon arising from antibodies directed against platelet surface epitopes in the presence of the calcium-chelating agent EDTA (ethylenediamine tetraacetic acid). Measurement of platelet counts using heparin or citrate as the anticoagulant corrects this problem, which is generally of no clinical consequence (hematoxylin-eosin, original magnification ×100). (*From* Shalev O, Lotman A. Images in clinical medicine. Pseudothrombocytopenia. N Engl J Med 1993;329(20):1467; with permission.)

Bone marrow findings in patients with ITP are heterogeneous, rendering the diagnostic utility of this test limited.[18] A diagnosis of ITP therefore remains one of exclusion (see **Box 1**).

ITP may be primary (ie, isolated or idiopathic) or secondary, occurring in the context of other conditions associated with immune dysregulation, such as chronic infections or autoimmune disorders (**Table 1**).[19,20] Clinical manifestations range from mild bruising to severe mucosal bleeding. The risk of bleeding usually correlates with the

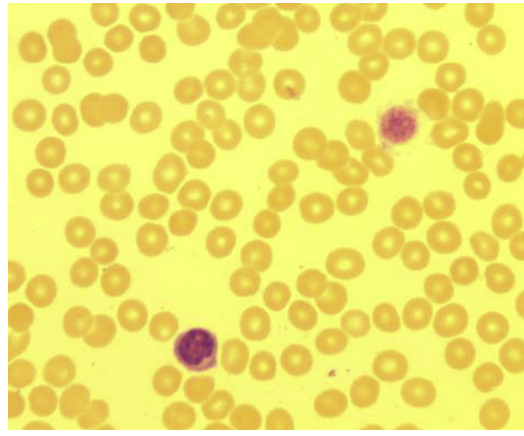

Fig. 2. Peripheral blood smear for case 1. The large cell represents a giant platelet, defined as a platelet of a size similar to a red blood cell. Typically, the smear in ITP shows thrombocytopenia with enlarged or giant platelets, although a smear with strictly giant platelets in the context of a family history of thrombocytopenia should alternatively raise suspicion for an inherited thrombocytopenic disorder (hematoxylin-eosin, original magnification ×100).

Table 1
Causes and evaluation of secondary ITP

Associated Conditions	Recommended Testing
Common variable immunodeficiency	Quantitative immunoglobulins
Evans syndrome	Direct antiglobulin test
Infections	*H pylori*, human immunodeficiency virus, hepatitis C, [a]parvovirus, [a]cytomegalovirus serologies
Antiphospholipid antibody syndrome	[a]Lupus anticoagulant, anticardiolipin antibodies, anti–beta-2 glycoprotein-1 antibodies
Thyroid disease	[a]Thyroid function tests, antithyroid antibodies
[b]Pregnancy	[a]Pregnancy testing
Systemic lupus erythematosus	[a]ANA

Abbreviation: ANA, antinuclear antibody.
[a] Tests of potential benefit per international consensus guidelines.
[b] In women of childbearing age.
Adapted from Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115(2):169.

degree of thrombocytopenia,[21] although increasingly a risk of thrombosis in patients with severe ITP has been recognized.[22]

Once a diagnosis of ITP is considered, clinicians should perform additional testing to exclude causes of secondary ITP. These causes include quantitative immunoglobulins to evaluate for common variable immunodeficiency (CVID), direct antiglobulin test (direct Coombs test) for Evans syndrome (the combination of ITP and autoimmune hemolytic anemia), and serologies for *Helicobacter pylori*, human immunodeficiency virus, and hepatitis C.[23] Identifying such conditions may affect treatment, because antimicrobial therapy may lead to hematologic recovery in cases of ITP caused by chronic infections, whereas lower doses or shorter courses of steroids and other immune suppression may be indicated in patients with ITP with CVID to mitigate infectious risk.[20,24–27]

Treatment is recommended for patients with newly diagnosed ITP whose platelet counts are less than 20×10^9/L to 30×10^9/L, or who are bleeding or have upcoming surgical procedures.[28] First-line treatment is corticosteroids, most commonly prednisone (1 mg/kg daily until platelet recovery, followed by a taper) or dexamethasone (40 mg daily for 4 days), with a recent clinical trial suggesting faster hematologic recovery with the latter.[29] Methylprednisolone (30 mg/kg daily for 7 days) is sometimes administered in more severe cases. Initial response rates for all of these interventions are around 70% to 80%, with a time to response ranging from about 2 days to 2 weeks, and variable response duration.[23,28] In patients with severe thrombocytopenia and bleeding, intravenous immunoglobulin (1 g/kg/d for 1–2 days) or, in Rh(D)+ patients, anti-D immunoglobulin (50–70 μg/kg for 1 dose) may be supplemented with steroids, leading to more rapid count recovery.[23,30] Platelet transfusions are generally not given owing to reduced survival of transfused platelets, but may be used in conjunction with the treatments discussed earlier in situations of life-threatening bleeding or after head trauma[30,31]; this is in contrast with thrombotic thrombocytopenic purpura (TTP), atypical hemolytic uremic syndrome (aHUS), and HIT, in which platelet transfusions are contraindicated because of concerns of disease exacerbation and increased risk of

arterial thrombosis and mortality.[31,32] For patients who fail first-line therapy, second-line treatments include splenectomy, rituximab, or the thrombopoietin receptor agonists eltrombopag or romiplostim.[23,33]

Case 2

Suppose the patient discussed earlier had the same presentation but without an antecedent upper respiratory infection, and instead with a history of recent alcohol intake. What would be an important question to ask to better define the cause of his thrombocytopenia?

Isolated thrombocytopenia without systemic symptoms in the setting of a recent ingestion raises suspicion for DITP. The thrombocytopenia in DITP usually occurs within 5 to 7 days of drug exposure and is often profound, with a platelet count less than 10×10^9/L to 20×10^9/L. A variety of mechanisms underlie the pathogenesis of DITP, the unifying concept being the development of antibodies directed against platelet epitopes that bind strongly only in the presence of a sensitizing agent.[34] Medications commonly associated with DITP include penicillins, cephalosporins, vancomycin, sulfonamide antibiotics, quinine, nonsteroidal antiinflammatory drugs, eptifibatide, abciximab, phenytoin, and valproic acid[35,36]; a more comprehensive list of suspected agents is available from the University of Oklahoma (http://www.ouhsc.edu/platelets).[34] Cessation of the offending agent is the mainstay of treatment of DITP, with platelet counts usually recovering by 1 week later.[35] Drug-dependent antibody testing in suspected cases of DITP is performed by the Blood Center of Wisconsin and can be useful to establish the diagnosis (https://www.bcw.edu/bcw/index.htm).

Historically, quinine was one of the most common causes of DITP.[37] Although no longer widely available, it is still used for relief of muscle cramps and is found in tonic water.[38,39] In the patient presented here, inquiry into the types of alcoholic beverages ingested would be useful, because a predilection for gin and tonic might suggest quinine as the cause of DITP.

Case 3

A 43-year-old woman with metastatic thyroid cancer develops shortness of breath and left lower extremity swelling and is diagnosed with bilateral pulmonary emboli (PE) and deep vein thrombosis (DVT) of the proximal left leg. She is anticoagulated with intravenous unfractionated heparin (UFH), then transitioned to low-molecular-weight heparin (LMWH). She received chemotherapy 3 weeks before her current presentation. Her initial platelet count at the time of diagnosis of PE and DVT is 150×10^9/L; 5 days after starting anticoagulation she develops progressive thrombocytopenia with a nadir of 50×10^9/L. What is the cause of her thrombocytopenia?

A broad differential for this patient's thrombocytopenia includes factors related to her cancer (eg, therapy-induced bone marrow suppression, TTP caused by chemotherapy or by cancer, direct involvement of the bone marrow or spleen by tumor, or DIC[40]), platelet consumption caused by her extensive thrombotic burden, infection, or medications such as UFH or LMWH. The timing and severity of thrombocytopenia in relation to heparin exposure are concerning for HIT.

HIT is an immune-mediated disorder characterized by production of immunoglobulin (Ig) G antibodies with specificity against complexes of platelet factor 4 (PF4, a component of platelet alpha granules) and heparin.[41,42] The large complexes of HIT antibody, PF4, and heparin then bind to and activate platelets, causing release of procoagulant substances and an increased risk of venous and arterial thrombosis.[43,44] The reported incidence of HIT ranges from 0.5% to 5% in adults treated with UFH,

versus 0.2% with LMWH.[45] Treatment of HIT involves cessation of all heparin products and initiation of a nonheparin anticoagulant.[46]

Laboratory testing for HIT consists of screening tests and confirmatory tests. The major screening test is an enzyme-linked immunosorbent assay (EIA) that identifies anti-PF4/heparin IgG, IgM, and IgA antibodies.[47] The EIA has rapid turnaround time and good sensitivity and negative predictive value but poor specificity,[44,47] because false-positive tests can occur in antiphospholipid antibody syndrome, lupus, or following cardiac or orthopedic surgery.[47–49] A positive heparin-PF4 EIA must be followed by a confirmatory functional assay, the most common of which is the serotonin release assay (SRA), which measures platelet activation and degranulation in the presence of heparin.[46] Although highly specific for HIT, the SRA is a technically challenging, time-consuming assay and is performed only at certain reference laboratories.[47]

HIT is a clinicopathologic diagnosis requiring a characteristic clinical picture and identification of PF4/heparin antibodies by both screening and functional assays.[47] It also is a medical emergency, and, in the acute setting, rapid decisions must often be made about anticoagulation before return of laboratory test results.[13] The 4 Ts score (**Table 2**) is a tool designed to help clinicians predict the probability of HIT[50] and carries a high negative predictive value.[51] The HIT expert probability score consists of 8 variables identified by 26 experts on HIT, although studies thus far suggest a similar performance to the 4 Ts score.[52,53] Current treatment algorithms recommend

Table 2
The 4Ts score for pretest probability of HIT

	0 Point	1 Point	2 Points
Thrombocytopenia	Platelet count decrease <30% or platelet nadir $<10 \times 10^9$/L	Platelet count decrease 30%–50% or platelet nadir $10–20 \times 10^9$/L	Platelet count decrease >50% or platelet nadir $\geq 20 \times 10^9$/L
Timing of platelet decrease	Platelet count decrease <4 d without recent heparin exposure	Platelet count decrease days 5–10 (but not clear), or decrease after day 10, or decrease $\leq$1 d and heparin exposure within the past 30–100 d	Clear onset of platelet count decrease between days 5–10 or platelet count decrease $\leq$1 d with heparin exposure within the past 30 d
Thrombosis	None	Progressive or recurrent thrombosis, nonnecrotizing skin lesions, suspected but unproven thrombosis	New thrombosis, skin necrosis at sites of heparin injection, or acute systemic reaction after intravenous heparin bolus
Other causes of thrombocytopenia	Definite	Possible	None apparent

Low pretest probability, 0 to 3; intermediate pretest probability, 4 to 5; high pretest probability, 6 to 8.

Adapted from Cuker A. Clinical and laboratory diagnosis of heparin-induced thrombocytopenia: an integrated approach. Semin Thromb Hemost 2014;40(1):106–14; and Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost 2006;4(4):760.

stopping heparin and pursuing HIT laboratory testing only in patients with intermediate and high 4 Ts scores of greater than or equal to 4.[46]

This patient has a 4 Ts score of 5, consistent with an intermediate probability of HIT. Her anticoagulation is changed to argatroban. EIA and SRA later return positive, confirming a diagnosis of HIT. Her platelet count normalizes over the next several days. Warfarin is added, with continuation of argatroban as bridging therapy. Per institutional protocol, the two anticoagulants are continued simultaneously for 5 days; an INR on the fifth day of bridging is more than 4, at which point argatroban is stopped, and a repeat INR is measured 4 hours later and found to be 2.2. Argatroban is then stopped and warfarin continued.

Options for acute anticoagulation in HIT include a direct thrombin inhibitor (DTI) such as argatroban, bivalirudin, lepirudin, or the factor Xa inhibitor danaparoid; fondaparinux is also used off label, although cases of fondaparinux-induced HIT have been reported.[46,54,55] Direct oral anticoagulants are not recommended, although a recent, small phase II trial of rivaroxaban in HIT reported encouraging outcomes.[56] Parenteral anticoagulation must be continued as monotherapy until the platelet count recovers to the normal range before warfarin is added because of the risk of warfarin-induced protein C deficiency, which may worsen clot burden and cause limb gangrene in acute HIT.[46,57] Once warfarin is started, there should be at least a 5-day overlap with the DTI or factor Xa inhibitor, with attainment of a therapeutic INR before parenteral anticoagulation is stopped.[46,54] Patients with HIT and thrombosis are treated with 3 to 6 months of anticoagulation. The optimal duration of anticoagulation in patients with HIT without thrombosis is unclear; current recommendations suggest 4 weeks or at least until stable platelet recovery.[46,54]

Case 4

A previously healthy 34-year-old woman presents with left facial numbness, headache, and bruising over the past 3 weeks. She denies diarrhea. Her blood pressure is 100/60 mm Hg. Laboratory studies show a WBC count of 8.2 $\times$ 1000/μL, hemoglobin level 9.5 g/dL, platelet count 20 $\times$ 10^9/L, creatinine level 1.5 mg/dL, lactate dehydrogenase level (LDH) 1330 U/L (normal, 118–242 U/L), haptoglobin level less than 10 mg/dL (normal, 30–200 mg/dL), and normal PT, PTT, and INR. Peripheral blood smear is shown in **Fig. 3**. What is this patient's diagnosis, and how should she be managed?

The combination of anemia, schistocytes, thrombocytopenia, and organ injury raises concern for a thrombotic microangiopathy (TMA).[58] The presence of greater than 1% schistocytes on peripheral blood smear with microangiopathic hemolytic anemia (MAHA) defines TMA.[58,59] Conditions associated with TMA include TTP, congenital TTP (Upshaw-Shulman syndrome), classic HUS caused by Shiga toxin–producing *Escherichia coli* hemolytic uremic syndrome (STEC-HUS), aHUS, drug-induced TMA, DIC, catastrophic antiphospholipid antibody syndrome, malignant hypertension, preeclampsia, hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, cocaine use, metastatic cancer, and scleroderma crisis.[60,61] In each of these disorders, microvascular damage leads to platelet activation and aggregation with subsequent thrombosis, thrombocytopenia, and ischemia-induced organ injury; the schistocytes arise from red blood cells traveling through vessels partially occluded by platelets.

The identification of 2 or more schistocytes per 100-times high-powered field on peripheral blood smear in the context of MAHA can satisfy a picture of TMA. However, in the 3 major TMA disorders of TTP, STEC-HUS, and aHUS, many more schistocytes are typically seen. In the past, TTP was associated with neurologic symptoms, aHUS with renal injury, and STEC-HUS in children with bloody diarrhea,[62] but there

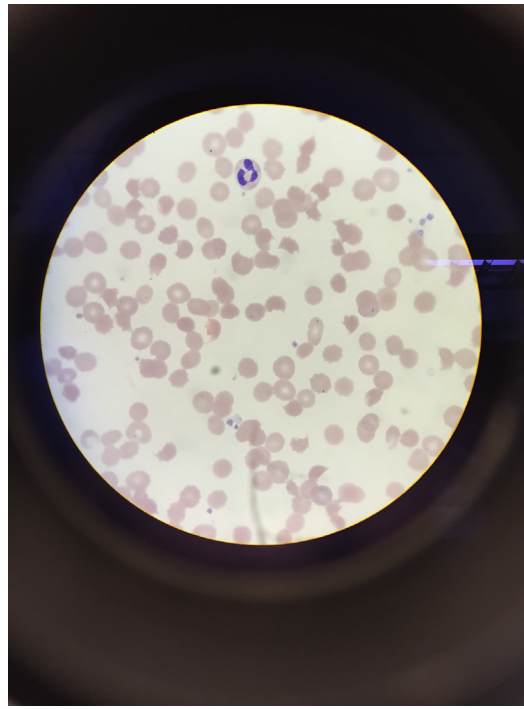

Fig. 3. Peripheral blood smear for case 3. Thrombocytopenia and multiple schistocytes are seen, suggestive of thrombotic microangiopathy (hematoxylin-eosin, original magnification ×100).

is considerable overlap in clinical presentation of these 3 conditions. Patients presenting with unexplained TMA are often initially assumed to have TTP and are treated as such until additional diagnostic results return.

TTP is caused by either congenital or acquired (via production of autoimmune inhibitors) deficiency of the von Willebrand factor (vWF) cleaving protease, ADAMTS13 (**Fig. 4**).[63,64] The normal function of ADAMTS13 is to cleave large multimers of vWF; when ADAMTS13 is deficient or absent, platelets adhere to the resultant ultralarge vWF multimers anchored to endothelial cells, forming platelet thrombi throughout the microvasculature.[58] Thrombocytopenia, MAHA, renal failure, neurologic deficits, and fever comprise the classic pentad of TTP, but only about 5% of patients show all of these symptoms. Other common presenting complaints include nausea, vomiting, abdominal pain, diarrhea, confusion, headache, general weakness, and bleeding.[65,66]

A low ADAMTS13 level of less than 10% supports a picture of TTP rather than the other TMA disorders. Historically this test has not offered sufficient sensitivity, specificity, or turnaround time to guide acute treatment decisions, although many institutions now have in-house ADAMTS13 assays with rapid turnaround time.[67–69] At present, the initial diagnosis of TTP remains largely clinical.

TTP is a hematologic emergency with a mortality of 90% if left untreated.[68] Frontline treatment is plasma exchange (PEX), which replaces the deficient ADAMTS13 and removes anti-ADAMTS13 antibodies. Corticosteroids (eg, prednisone 1 mg/kg daily) are usually added to suppress ADAMTS13 inhibitor production[70]; rituximab may also have an adjunctive role in preventing disease relapse. Current recommendations

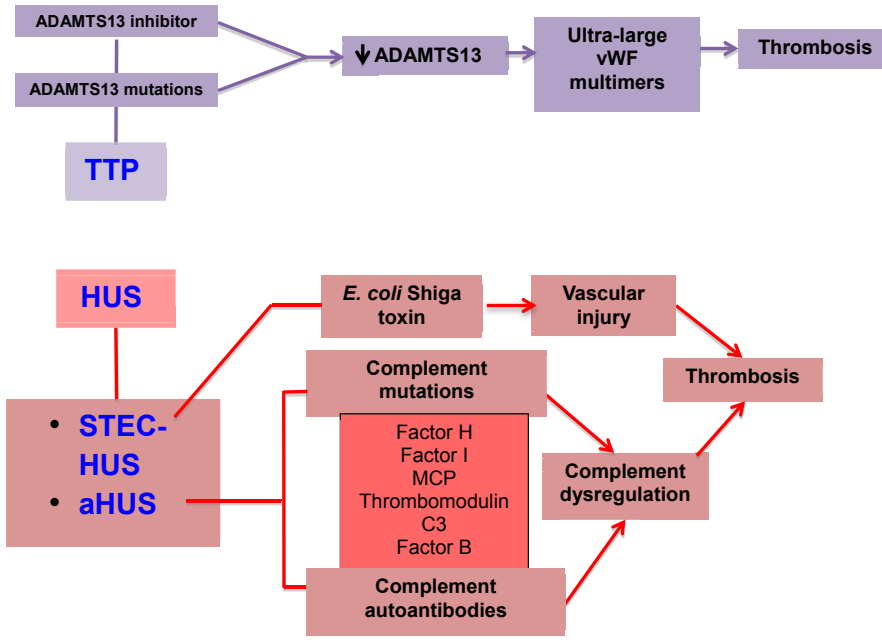

Fig. 4. Pathogenesis of TTP, STEC-HUS, and aHUS.

support initiating PEX in patients with TMA and MAHA for presumed TTP if an alternative cause has not been established.[65,70] While on PEX, complete blood counts, LDH, and blood smears are followed routinely; PEX should be continued until attainment of normal platelet counts for 2 days. Steroids can be tapered off if the platelet count remains normal for 1 to 2 weeks, at which point the plasma exchange catheter can be removed.[65]

The patient is started on prednisone 1 mg/kg. A central venous catheter is placed for initiation of daily PEX. Over the next 4 days, her platelet count increases to 70×10^9/L, but her renal function deteriorates, with an increase in creatinine level to 5 mg/dL. Pretreatment ADAMTS13 activity returns normal at 80%. Blood cultures are negative.

Poor response to PEX and a pretreatment ADAMTS13 activity of greater than 10% raise suspicion for an alternative diagnosis to TTP, such as aHUS, sepsis, malignancy, or an autoimmune disorder.[64,65,70] Although neurologic symptoms, gastrointestinal complains, and renal injury may be seen in both TTP and aHUS, severe renal involvement and progression to dialysis occur more often in aHUS.[64,71] Most cases of aHUS are caused by abnormal activation of the alternative complement pathway because of inherited or acquired mutations in genes involved in complement regulation (eg, factor H, factor I, MCP, or thrombomodulin) or in complement activation (eg, C3 or factor B) (see **Fig. 4**).[70–72] Mutation screening and identification of factor H autoantibodies can confirm a diagnosis of aHUS, but these tests are limited by lengthy turnaround time. Measurement of complement levels (eg, C3; C4; or factors H, I, or B) is done routinely but has limited utility because only about half of patients with aHUS show a reduction in C3 levels, as would be expected from alternative complement activation.[72,73]

PEX is partially effective in aHUS because it replaces missing complement factors and removes mutated components and autoantibodies.[73] Eculizumab is a monoclonal antibody against the terminal complement component C5, blocking formation of the

C5-C9 membrane attack complex and stopping further complement-mediated organ injury.[64] Eculizumab induces significant and lasting improvements in renal function, and should be started as soon as possible in patients with suspected aHUS to improve chances for renal recovery.[71,74] Because of infectious risks, patients must be vaccinated against *Neisseria meningitidis* before initiation.[75] Dosing is 900 mg intravenously (IV) weekly for 4 weeks, followed by maintenance therapy with 1200 mg IV every other week.[71,74] Patients who respond are generally kept on this agent indefinitely because of a high risk of relapse when the medication is stopped.

PEX is discontinued and eculizumab started. Over the next 14 days, her platelet count increases steadily to the range of 200 $\times$ 10^9/L, concomitant with a decrease in LDH level and improvement in creatinine level to 3.0 mg/dL. She is discharged to home with a plan for ongoing eculizumab and close outpatient follow-up. Genetic testing identifies a mutation in the complement factor H gene, the most common gene affected in aHUS.

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