CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 36-2017: A 30-Year-Old Man with Fatigue, Rash, Anemia, and Thrombocytopenia

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PRESENTATION OF CASE

Dr. Amy E. Yuan (Medicine): A 30-year-old man was admitted to this hospital during the summer because of fatigue, rash, fevers, anemia, and thrombocytopenia.

Three years before this admission, the patient was involved in a motor vehicle accident that resulted in a large hematoma across the chest and umbilicus. He was evaluated at another hospital. Computed tomography (CT) of the head, cervical spine, abdomen, and pelvis, performed with the intravenous administration of contrast material, revealed stranding of the anterior abdominal wall, the subcutaneous tissues of the left flank, and the fat of the left retroperitoneum (Fig. 1); this finding was reported to be consistent with soft-tissue contusion or hemorrhage. Laboratory test results are shown in Table 1. The patient was discharged home.

Two days later, gross hematuria developed, and the patient was evaluated at the other hospital; laboratory test results are shown in Table 1. He was transferred to this hospital for evaluation of thrombocytopenia and hematuria.

Dr. Amirkasra Mojtahed: CT of the abdomen and pelvis, performed with and without the intravenous administration of contrast material (in accordance with a hematuria protocol), revealed no renal or ureteral stones, solid renal masses, or ureteral or bladder filling defects. The stranding of the anterior abdominal wall, left flank, and left retroperitoneum appeared to have been stable since the previous study had been obtained, 3 days earlier.

Dr. Yuan: The hematuria resolved without intervention. Examination of a peripheral-blood smear revealed anisocytosis and polychromasia of the red cells, with occasional schistocytes, as well as a reduced number of platelets and normal-appearing white cells. Giemsa staining of thick and thin blood smears revealed no intracellular organisms. Tests for IgG and IgM antibodies to *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*, and *Borrelia burgdorferi* were negative. The thrombocytopenia and anemia were attributed to large soft-tissue hematomas and hematuria,

and the patient was discharged home. On follow-up evaluation 1 week after discharge, the platelet count was 242,000 per cubic millimeter (normal range, 150,000 to 400,000); 1 month after discharge, the hematocrit was 44% (normal range, 41 to 53).

The patient had been in his usual state of health until 2 weeks before the current admission to this hospital, when fatigue, generalized weakness, and dyspnea on exertion developed. Four episodes of palpitations, chest tightness, and diaphoresis occurred during the 2-week period leading up to admission; they lasted less than 1 minute each, and the patient attributed them to panic attacks. Five days before this admission, fevers and night sweats developed, and the highest measured temperature was 38.3°C. Three days before this admission, the patient noted an area of erythema in the posterior aspect of the right knee and bruising on both arms. One day before this admission, an episode of weakness and tunnel vision occurred while the patient was standing; he lowered himself to the ground but did not lose consciousness. Severe fatigue persisted after the episode, and he was evaluated in the emergency department of the other hospital. Laboratory test results are shown in Table 1. Giemsa staining of thick and thin blood smears revealed no intracellular organisms. A screening test for antibodies to *B. burgdorferi* was positive. Doxycycline, clindamycin, and quinine were administered, and the patient was transferred to the emergency department of this hospital.

On evaluation in the emergency department, the patient reported a mild headache, which diminished after the administration of ibuprofen; there was no neck pain or photophobia. He had a history of alcohol-use disorder, peptic ulcer disease, Barrett's esophagus, and anxiety. He had no history of easy bruising or bleeding, despite previous trauma, including a fall from a roof 3 years before admission. Recent medications included diazepam and citalopram. He drank alcohol occasionally in a binge pattern but had not had any during the past 2 weeks. He did not smoke cigarettes, use illicit drugs, or take herbal medications. He resided on an island in New England and worked as a restaurant cook. He noted ticks on his body several times per month and had removed a tick 2 weeks before this presentation. His mother had diabetes, and his father had hypertension. There was no family history of hematologic cancer.

On examination, the temperature was 36.6°C, the blood pressure 112/57 mm Hg, the pulse 88 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 99% while the patient was breathing ambient air. He was alert and oriented and did not appear ill. The first and second heart sounds were normal, and the lungs were clear. The abdomen was not

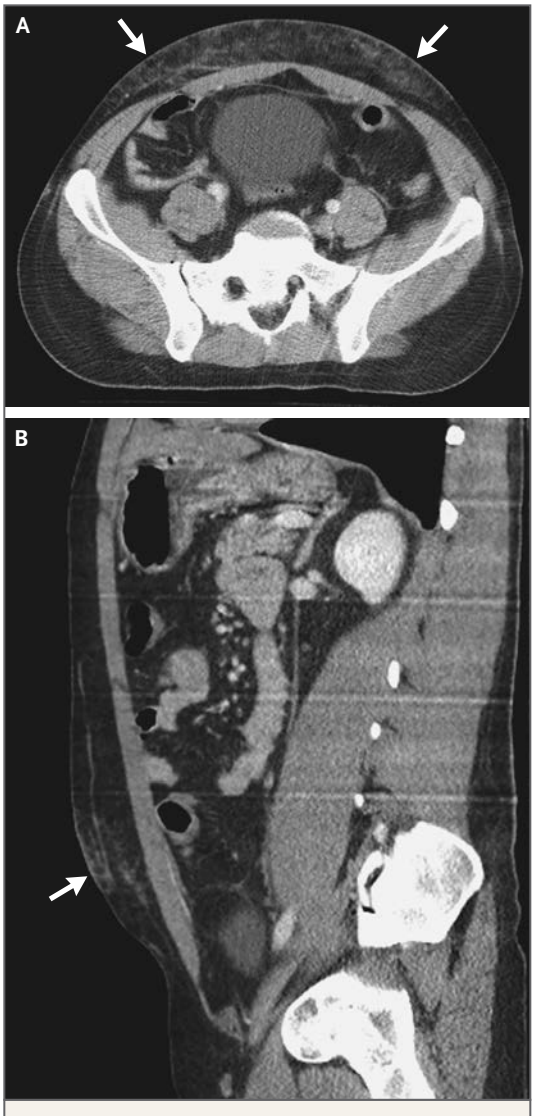

Figure 1. CT Scans of the Abdomen and Pelvis Obtained 3 Years before Admission.

CT scans of the abdomen and pelvis, obtained after the administration of contrast material, show subcutaneous stranding in the ventral abdominal wall (Panels A and B, arrows).

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	Day of Motor Vehicle Accident, 3 Yr before Admission	2 Days after Motor Vehicle Accident, 3 Yr before Admission	Day of Admission, Other Hospital	On Admission, This Hospital	Hospital Day 3
Hematocrit (%)	41–53	50	36	18	17.6	21.7
Hemoglobin (g/dl)	13.5–17.5	17	13	6	5.8	7.3
White-cell count (per mm^3)	4500–11,000	9.8	8.4	9.2	9.0	7.0
Differential count (%)						
Neutrophils	40–70	72	68	61	63	53
Lymphocytes	22–44	20	22	28	23	32
Monocytes	4–11	7	7.9	1	1	6
Eosinophils	0–8	1	1.3	0	1	0
Basophils	0–3	1	0.2	0	0	1
Bands	0–10	0	0	5	5	4
Metamyelocytes	0	0	0	2	5	2
Myelocytes	0	0	0	3	0	2
Platelet count (per mm^3)	150,000–400,000	193,000	22,000	13,000	15,000	17,000
Red-cell count (per mm^3)	4,500,000–5,900,000	5,190,000	3,870,000	1,890,000	1,870,000	2,300,000
Mean corpuscular volume (fl)	80–100	97	93	96	94	94
Mean corpuscular hemoglobin (pg)	26–34	33	33	32	31	32
Mean corpuscular hemoglobin concentration (g/dl)	31–37	34	35	33	33	34
Red-cell distribution width (%)	11.5–14.5	14.1	14.9	19	20	20.7
Reticulocyte count (%)	0.5–2.5	NA	6	NA	16.2	NA
Prothrombin time (sec)	11–14	12.7	13.4	NA	13.4	13.3
Prothrombin-time international normalized ratio	0.9–1.1	1.0	1.0	NA	1.1	1.1
Activated partial-thromboplastin time (sec)	22–35	24.7	24.3	NA	28.9	27.7
Fibrinogen (mg/dl)	150–400	NA	470	NA	441	433
D-dimer (ng/ml)	<500	NA	2489	NA	3043	NA
Haptoglobin (mg/dl)	16–199	NA	NA	NA	<6	NA
Lactate dehydrogenase (U/liter)	110–210	NA	711	NA	1122	1150
Ferritin (μg/liter)	20–300	NA	NA	NA	1161	NA
Triglycerides (mg/dl)	40–150	NA	NA	NA	207	NA
Alkaline phosphatase (U/liter)	45–115	98	96	76	69	68
Alanine aminotransferase (U/liter)	10–55	42	38	47	43	39
Aspartate aminotransferase (U/liter)	10–40	41	44	48	45	41
Total bilirubin (mg/dl)	0–1.0	0.5	1.8	1.2	1.4	1.8

Direct bilirubin (mg/dl)	0–0.4	NA	0.3	NA	0.2	0.3
Sodium (mmol/liter)	135–145	139	138	141	141	142
Potassium (mmol/liter)	3.4–4.8	3.6	3.7	3.8	3.5	3.7
Chloride (mmol/liter)	100–108	99	102	103	105	104
Carbon dioxide (mmol/liter)	23.0–31.9	23	26	26	22	24
Urea nitrogen (mg/dl)	8–25	7	9	21	17	13
Creatinine (mg/dl)	0.60–1.50	0.68	0.67	1.18	1.01	1.03
Estimated glomerular filtration rate (ml/min/1.73 m^2)‡	≥60	>60	>60	>60	>60	>60
Glucose (mg/dl)	70–110	96	100	108	101	128

* To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. NA denotes not available.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

‡ If patient is black, multiply the result by 1.21.

distended; bowel sounds were present, with no tenderness on palpation or hepatosplenomegaly. There was no swelling in the legs. An area of blanching erythema (6 cm in diameter) was present on the right popliteal fossa (Fig. 2A); a similar lesion (5 cm in diameter) was present near the left patella. Areas of petechiae were noted in the erythematous lesions and on the left flank.

Examination of a peripheral-blood smear (Fig. 2B) revealed mostly normocytic erythrocytes, with less than 1 schistocyte per high-power field (i.e., occasional schistocytes were seen, but not in every high-power field), increased reticulocytes, no spherocytes, minor basophilic stippling, and no inclusion bodies in erythrocytes. Platelets were decreased in number but increased in size and had normal granularity. White cells appeared normal and had a normal granulation pattern. Giemsa staining of thick and thin blood smears revealed no intracellular organisms. Tests for human immunodeficiency virus (HIV) p24 antigen and HIV type 1 and type 2 antibodies were negative. Urinalysis showed 2+ blood and 2+ protein, with no glucose, ketones, bilirubin, urobilinogen, or nitrates; the specific gravity and pH were normal, and examination of the sediment revealed 20 to 50 red cells per high-power field (normal range, 0 to 2). Other laboratory test results are shown in Table 1. Two units of packed red cells were transfused; the hematocrit increased from 17.6% on admission to 22.5% (normal range, 41 to 53), and the patient was admitted to the hospital. Azithromycin and atovaquone were administered, and doxycycline was continued.

On the third hospital day, the patient had the sudden onset of expressive aphasia, pronator drift of the right arm, and inability to follow complex commands. The remainder of the neurologic examination was normal. Laboratory test results are shown in Table 1.

Dr. Mojtahed: CT angiography of the head and neck revealed normal intracranial and neck vessels. There was no evidence of intracranial hemorrhage, acute infarction, or intracranial lesions.

Dr. Yuan: A diagnostic test was performed, and management decisions were made.

DIFFERENTIAL DIAGNOSIS

Dr. Gurpreet Dhaliwal: This 30-year-old man had two episodes of anemia, kidney injury, and severe

thrombocytopenia that were separated by 3 years of good health. The second episode is distinguished from the first by the development of severe anemia and an acute neurologic event that is compatible with a transient ischemic attack or stroke. The challenge in establishing the diagnosis in this case is to identify a disease that can be minimally symptomatic and self-limited during the first episode, remain quiescent for 3 years, and then recur in a more severe form.

FIRST EPISODE

Two days after a motor vehicle accident, severe thrombocytopenia, moderate anemia, and hematuria developed in the patient. Thrombocytopenia arises from decreased production or increased consumption of platelets. Decreased production is ruled out by the normal leukocyte count, brisk reticulocytosis, and rapid platelet-count recovery, findings that collectively indicate an intact bone marrow. The disappearance of platelets nearly overnight suggests antibody-mediated clearance, but the patient had not received a drug or had an infection or autoimmune syndrome that would trigger the production of antiplatelet antibodies. Because the patient had occasional schistocytes, it is possible that the platelets were consumed in the microvasculature. However, the normal coagulation measurements and normal fibrinogen level rule out disseminated intravascular coagulation; other microangiopathic conditions, such as thrombotic thrombocytopenic purpura (TTP), are rarely self-limited without supportive care.

Hematuria may have arisen from delayed traumatic bleeding (e.g., contusion of the bladder caused by the seat belt) in the context of thrombocytopenia or from unspecified glomerular or renal parenchymal injury. The indirect hyperbilirubinemia, elevated lactate dehydrogenase level, and reticulocytosis are suggestive of hemolysis; however, resorption of hematomas in the abdominal wall results in the exact same profile and could explain the self-limited anemia.

The reason that the severe thrombocytopenia appeared and resolved so quickly is the biggest mystery in this case. Whatever the cause, it did not trouble the patient for 3 years.

SECOND EPISODE

One week before the current admission, the patient had fever, sweats, and large erythematous macules in flexural regions that were typical of erythema migrans. These findings are sufficient to establish a diagnosis of *B. burgdorferi* infection (Lyme disease) in a patient who has frequent tick bites and lives in a region in which the disease is endemic. Lyme disease, however, does not cause severe anemia and thrombocytopenia, features that were seen in this patient when he presented to the other hospital.

The reticulocytosis and giant platelets once again indicate an intact bone marrow, and the laboratory test results point to hemolysis. The cause of hemolysis can be inherited or acquired. Inherited causes include enzymopathies (e.g., glucose-6-phosphate dehydrogenase deficiency), membranopathies (e.g., hereditary spherocytosis), and hemoglobinopathies (e.g., sickle cell disease

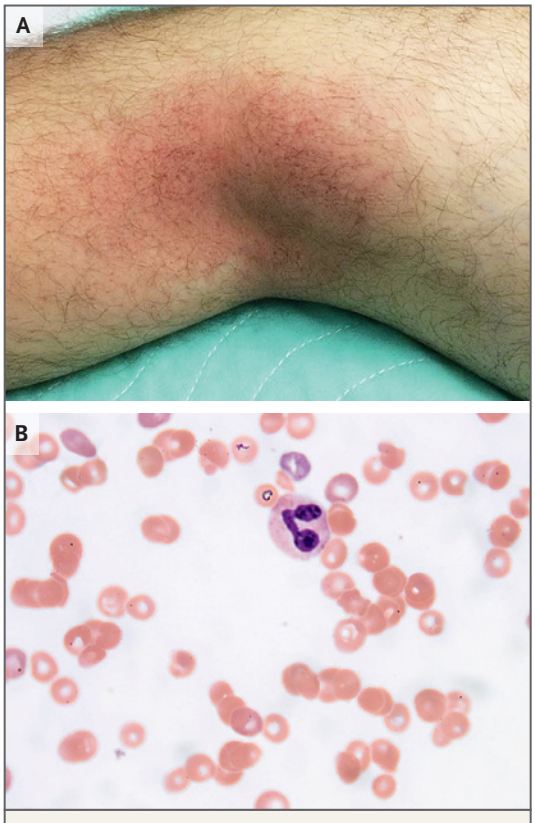

Figure 2. Clinical Photograph and Peripheral-Blood Specimen Obtained on Admission.

Panel A shows a 6-cm lesion with blanching erythema on the right popliteal fossa. Panel B shows a representative field from the initial peripheral-blood smear with evidence of normocytic red cells and thrombocytopenia and with no schistocytes; what appears to be a ring-shaped inclusion in the red cells near the neutrophil is an artifact of the slide preparation.

or thalassemia). Inherited hemolytic anemias do not cause thrombocytopenia, and many are associated with characteristic findings on examination of a peripheral-blood smear that were not present in this patient. Acquired causes of hemolysis involve an attack on the erythrocyte and are often associated with thrombocytopenia. The most common causes of acquired hemolysis — infection, autoimmunity, and microangiopathy — provide a framework for determining the underlying condition in this patient.

INFECTION

A small number of infections directly injure or invade the erythrocyte. The global prototype is malaria, but the local analogue to consider in this case is babesiosis. *Babesia microti* is an intraerythrocytic parasite that causes hemolytic anemia and often thrombocytopenia. It is prevalent in New England and can be transmitted simultaneously with *B. burgdorferi* by the *Ixodes scapularis* tick. Examination of a peripheral-blood smear did not reveal intraerythrocytic ring forms, although these can be absent early in the disease course, when the degree of parasitemia is low.[1] The patient did not have risk factors for severe babesiosis, including asplenia, immunocompromise, or a recent transfusion; however, these are only risk factors and not prerequisites. The pattern of organ injury is incongruous with babesiosis; neurologic injury, particularly focal deficits, is rare in babesiosis (even in the presence of high-grade parasitemia[2]), and renal injury is rare in nonsevere babesiosis. Babesiosis is not a relapsing condition in an immunocompetent host.[3,4] Although it would be reasonable to initiate empirical treatment for babesiosis during the acute phase of this patient's illness, babesiosis does not explain all the features of the current syndrome or the self-limited episode that occurred 3 years earlier.

AUTOIMMUNITY

The Evans syndrome is characterized by simultaneous autoimmune hemolytic anemia and immune thrombocytopenia, but it would not account for the organ damage seen in this patient. Coexisting autoimmune conditions, such as nephritis and cerebritis associated with systemic lupus erythematosus or thrombosis mediated by the antiphospholipid syndrome, would need to be invoked to explain the coexisting kidney and brain injury. A direct antiglobulin test and tests for antinuclear antibodies and antiphospholipid antibodies were not performed to investigate these diagnoses. Spherocytes, which are present in only half the cases of the Evans syndrome,[5] were absent in this case. Autoimmune conditions can relapse and remit spontaneously,[6] but the synchronous appearance of antiplatelet, antierythrocyte, and antiphospholipid antibodies on two occasions that were separated by a period of 3 years would be extremely coincidental.

MICROANGIOPATHY

Microangiopathic hemolytic anemia warrants consideration when schistocytes are seen in a patient with hemolysis. Severe hypertension, disseminated intravascular coagulation, sepsis, and cancer can cause microangiopathic hemolytic anemia and thrombocytopenia, but there was no evidence of these conditions in this case.

Thrombotic microangiopathies are a group of hereditary and acquired syndromes with diverse mechanisms that lead to shared clinicopathological features: microangiopathic hemolytic anemia, thrombocytopenia, and organ injury.[7] The hemolytic–uremic syndrome is a thrombotic microangiopathy that arises when shiga toxin–secreting strains of *Escherichia coli* or, on occasion, *Shigella dysenteriae* induce endothelial damage that leads to bloody colitis and, subsequently, to acute kidney injury; these features were not present in this patient. Two other thrombotic microangiopathies warrant close attention in this case.

QUININE-INDUCED THROMBOTIC MICROANGIOPATHY

Quinine causes a drug-dependent, antibody-mediated thrombotic microangiopathy. The occurrence of arrhythmias, thrombocytopenia, and thrombotic microangiopathy in association with quinine intake prompted the Food and Drug Administration to prohibit its off-label use to treat leg cramps. However, quinine is readily available on the Internet, is a component of tonic water (which is used in the cocktail gin and tonic), and is prescribed for severe babesiosis. Given this patient's history of binge drinking, I wondered whether the self-limited episode that had occurred 3 years earlier arose from quinine exposure after the consumption of gin and tonic.[8] After such sensitization, a more robust immune-mediated reaction could have ensued after the patient had received intravenous quinine at the

other hospital. However, quinine-induced thrombotic microangiopathy is unlikely, because it is associated with an abrupt onset of disease with severe kidney injury, whereas this patient had a more gradual onset of disease with a mildly elevated creatinine level that normalized after 1 day. Furthermore, he had received intravenous quinine after his cytopenias had developed.

THROMBOTIC THROMBOCYTOPENIC PURPURA

The blood protein von Willebrand factor (VWF) has a central role in promoting platelet adhesion and aggregation. The enzyme ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) constitutively cleaves large VWF multimers that are secreted by the endothelium into shorter strands. In acquired TTP, an autoantibody inactivates the ADAMTS13 protease, and thus the VWF multimers remain large and abundant. The multimers bind platelets and form aggregates in the microvasculature that induce thrombus formation. The microthrombi cause tissue ischemia, platelet consumption, and microangiopathic hemolytic anemia. Brain involvement is common and leads to stroke, seizure, confusion, and headache. Renal injury occurs in a minority of patients, and in contrast to the renal injury associated with other thrombotic microangiopathies, it is usually modest. Fever may develop but is often due to a precipitating infection.[9]

During the second episode, this patient had the classic features of TTP: microangiopathic hemolytic anemia, thrombocytopenia, neurologic injury, renal injury, and fever. However, these five features are present in a minority of patients and represent a constellation of organ damage that can be mitigated by the timely initiation of plasma exchange. TTP is challenging to diagnose because it is rare and its initial manifestations frequently mimic common conditions, such as gastroenteritis, influenza, and meningitis.[10,11]

One barrier to the diagnosis of TTP in this case is the paucity of schistocytes, which are usually abundant. Although schistocytes are considered to be an essential feature of thrombotic microangiopathies, there are cases in which schistocytes are persistently absent.[12,13] This patient, however, had occasional schistocytes, a finding that requires contextual interpretation. In the absence of cytopenias, the presence of a single schistocyte is most likely an artifact or an aberration that can be ignored. But in the right context, one schistocyte is one schistocyte too many.

It is precarious to attribute the initial episode of anemia and thrombocytopenia to a disease that is associated with a 90% fatality rate when it goes untreated. However, self-limited cases of TTP (e.g., disease that occurs after a bee sting[14]) have been reported. The Upshaw–Schulman syndrome, which is the rare hereditary form of TTP that is caused by *ADAMTS13* mutations, exemplifies the spectrum of TTP phenotypes that can arise from the interaction between genetics and environmental events.[15] Most patients with TTP that is associated with an *ADAMTS13* mutation present when they are neonates, but others initially present during childhood with bouts of isolated thrombocytopenia[16] or during adulthood in the context of pregnancy or infection.[17] It is also plausible that acquired TTP, similar to other autoimmune diseases, may flare in association with stress and remit once the stressor is mitigated.

DIAGNOSIS AND MANAGEMENT

I suspect that an ADAMTS13 deficiency (inherited TTP) or the inducibility of anti-ADAMTS13 antibodies (acquired TTP) in this patient places him at a fragile equilibrium, such that any physiological stressor may trigger a thrombotic microangiopathic cascade.[18] After the motor vehicle accident, he crossed his threshold for the onset of microvascular thrombosis, but he was able to quickly regain homeostasis as the inflammation of trauma resolved.[19] Three years later, the sustained inflammation associated with *B. burgdorferi* infection[20] triggered a full manifestation of thrombotic microangiopathy, with renal and cerebral injury.

I would examine a second peripheral-blood smear for schistocytes. Regardless of the findings, there are sufficient grounds to initiate plasma exchange. If the level of ADAMTS13 activity were found to be low, a diagnosis of TTP would be confirmed, but further testing would be necessary to determine whether anti-ADAMTS13 antibodies, a primary ADAMTS13 deficiency, or both are responsible for the illness.

Dr. Meridale V. Baggett (Medicine): Dr. Mack, what was your impression when you evaluated this patient?

Dr. Johnathan P. Mack: The low number of schis-

tocytes on examination of the peripheral-blood smear led to the initial clinical impression that an underlying infectious process, most likely a tickborne disease, was causing the anemia and thrombocytopenia. The patient's weakness and dizziness initially improved with the administration of antibiotic agents and fluids. However, when neurologic deficits developed, another blood smear was obtained, and examination revealed an increase in schistocytes to 2 to 3 per high-power field. With this evidence of microangiopathic hemolytic anemia, TTP became the leading diagnosis.

The PLASMIC score[21] is a clinical prediction tool that can be used to guide treatment decisions before the results of diagnostic laboratory tests are available for patients who present with thrombocytopenia and microangiopathic hemolytic anemia. The score is based on seven features of the history and laboratory test results. Patients with a low PLASMIC score (0–4 out of 7) are unlikely to have an ADAMTS13 activity level that is consistent with TTP. This patient had a PLASMIC score of 6 out of 7, which is associated with a high probability of an ADAMTS13 activity level of less than 10% (normal level, ≥70% of the level in plasma pooled from healthy persons), a finding suggestive of TTP (Table 2).

CLINICAL DIAGNOSIS

Thrombotic thrombocytopenic purpura.

DR. GURPREET DHALIWAL'S DIAGNOSIS

Thrombotic thrombocytopenic purpura.

PATHOLOGICAL DISCUSSION

Dr. Stephan Kadauke: Three tests are commonly performed to confirm the diagnosis of TTP: assays for ADAMTS13 activity, ADAMTS13 inhibition, and anti-ADAMTS13 antibodies (Table 3). An ADAMTS13 activity level of less than 10% is highly suggestive of a diagnosis of TTP. Examination of the initial plasma sample obtained from this patient before he underwent plasma exchange revealed an ADAMTS13 activity level of less than 5%.

The assays for ADAMTS13 inhibition and anti-ADAMTS13 antibodies are performed to distinguish between inherited and acquired forms of TTP. The inhibition assay is a mixing study that measures the degree to which the patient's plasma can inhibit the ADAMTS13 activity of normal pooled plasma. The antibody assay is an enzyme-linked immunosorbent assay that detects IgG antibodies to the ADAMTS13 protein. The results of these assays in this patient were inconsistent: the inhibition assay was negative (<0.4 inhibitor units; normal level, ≤0.4), but the antibody assay was positive (56 arbitrary units; normal level, ≤18). Two scenarios could explain the inconsistent results of the two studies. First, the patient may have acquired TTP that is due to an antibody that increases the clearance of ADAMTS13 but has no inhibitory activity. Second, the patient may have inherited TTP, and the detected antibody is nonpathogenic.

To address the inconsistent results of the two studies, gene sequencing was performed at the *ADAMTS13* locus. Two heterozygous pathogenic sequence variants (c.98delT [exon 1] and c.3178C→T [exon 24]) were present, a finding indicative of

Table 2. PLASMIC Score.

Criterion	Present in This Patient	Score
Platelet count <30,000 per mm^3	Yes (platelet count, 17,000 per mm^3)	1
Hemolysis (reticulocyte count >2.5%; undetectable haptoglobin level; or indirect bilirubin level >2.0 mg/dl)	Yes (reticulocyte count, 16.2%; undetectable haptoglobin level)	1
Absence of active cancer	Yes	1
Absence of a history of solid-organ or stem-cell transplantation	Yes	1
Mean corpuscular volume <90 fl	No (mean corpuscular volume, 94 fl)	0
International normalized ratio <1.5	Yes (international normalized ratio, 1.1)	1
Creatinine <2.0 mg/dl	Yes (creatinine, 1.03 mg/dl)	1
Total		6

Table 3. Laboratory Data for ADAMTS13.

Test	Reference Range	This Patient
ADAMTS13 activity (%)*	≥70	<5
ADAMTS13 inhibition (inhibitor units)†	≤0.4	<0.4
Anti-ADAMTS13 antibodies (arbitrary units)‡	≤18	56

* Performed on presentation to this hospital, before the initiation of plasma exchange.
† Performed at the Mayo Clinic Department of Laboratory Medicine and Pathology, Rochester, MN.
‡ Performed at the Blood Center of Wisconsin, Milwaukee.

autosomal recessive inherited TTP. Taken together, the test results are most consistent with a diagnosis of combined inherited and acquired TTP, in which the low level of ADAMTS13 activity at baseline was suppressed by the development of an autoantibody, most likely in the context of an acute infection.

DISCUSSION OF MANAGEMENT

Dr. Mack: Once the diagnosis of TTP was suspected, plasma exchange was initiated urgently. Plasma exchange is the standard of care for the initial management of acquired TTP; in a randomized, controlled clinical trial, plasma exchange was superior to plasma transfusion (without exchange) with respect to the rate of platelet recovery and overall survival.[22] Plasma exchange is continued daily until resolution of organ dysfunction and stable normalization of the platelet count are obtained. Adjunctive therapy with glucocorticoids was also initiated. Patients with acquired TTP receive immunosuppressive doses of glucocorticoids to decrease the production of inhibitory anti-ADAMTS13 antibodies, although to our knowledge, prospective, controlled studies have not been performed to compare outcomes among patients who receive glucocorticoids and those who do not.

The patient had marked improvement in his neurologic deficits after the first treatment with plasma exchange. His headache resolved after the second treatment, and his platelet count normalized after the third treatment. After 6 days, plasma exchange was stopped, and glucocorticoid therapy was rapidly tapered. The ADAMTS13 activity level was 62%.

Approximately 14 days after plasma exchange was stopped, the platelet count had decreased to 120,000 per cubic millimeter and the ADAMTS13 activity level had again fallen to less than 5%. Since the patient did not have a detectable inhibitory antibody and results of genetic testing suggested an inherited ADAMTS13 deficiency, plasma tranfusions were administered. Although the patient received plasma transfusions for 3 days, the platelet count did not increase, which suggested the presence of a concomitant inhibitory antibody. A single session of plasma exchange was performed, and the platelet count increased to 200,000 per cubic millimeter.

Dr. Annemarie E. Fogerty: Because the patient had had an early relapse, potent and enduring inhibition of the anti-ADAMTS13 antibody was indicated. Thus, rituximab therapy was administered weekly for 4 weeks. Outcomes associated with the use of rituximab (both during the initial episode and during relapse) and with the use of standard therapy (plasma exchange and glucocorticoids) in patients with acquired TTP have been compared.[23,24] Data from prospective, randomized trials are limited, because the rarity of TTP and the potential for late relapse make enrollment of patients in such trials difficult. Therefore, a standard time for the initiation of rituximab therapy in patients with TTP has not been established. Although data support the efficacy and safety of rituximab in shortening the time to remission and decreasing the rate of relapse, these benefits appear to be restricted to the first year of treatment. In this case, the patient received rituximab without incident. He had immediate normalization of the platelet count and lactate dehydrogenase level that endured for more than 1 year. When remission is not achieved with rituximab, bortezomib and other immunosuppressant agents have been used. To our knowledge, there are no large case series that compare the effectiveness of such immunosuppressant agents.

Despite achieving complete clinical remission (a normal platelet count, hematocrit, and lactate dehydrogenase level) with immunosuppression

of the anti-ADAMTS13 antibody (acquired TTP), this patient continues to have an undetectable level of ADAMTS13 activity 2 years after remission. Results of genetic testing confirmed a concurrent diagnosis of inherited TTP (the Upshaw–Schulman syndrome), which makes the patient vulnerable to a recurrence of clinical TTP, particularly at times of physiological stress or endothelial injury. Inherited TTP is managed with regular infusions of ADAMTS13, although a specific schedule and target activity level have not been established in the literature. This patient has been receiving an infusion of fresh-frozen plasma (without exchange) every 8 to 10 weeks, with close laboratory monitoring. He has had no further clinical relapses.

FINAL DIAGNOSIS

Combined inherited and acquired thrombotic thrombocytopenic purpura.

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