Case 37-2010: A 16-Year-Old Girl with Confusion, Anemia, and Thrombocytopenia

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the initiation of oral contraceptives for dysmenorrhea and did not resolve after discontinuation of the medication. A renal biopsy revealed immune-complex glomerulonephritis. At that time, the erythrocyte sedimentation rate was 49 mm per hour; the titer of antinuclear antibody (ANA) was positive at 1:1280 dilution (reference range, negative at 1:40 and 1:160 dilutions), with a speckled pattern; tests for antibodies to double-stranded DNA were positive at 1:20 dilution (reference range, negative at 1:10 dilution); tests for antibodies to Ro, La, Sm, and ribonucleoprotein were negative; and tests of renal function and levels of complement were normal. Mycophenolate mofetil and prednisone were administered, with improvement in proteinuria, and the erythrocyte sedimentation rate decreased to 13 mm per hour. At a routine follow-up 2.5 months before admission, the patient's mental status alternated between somnolent and agitated. She opened her eyes in response to voice or touch; she did not make eye contact or respond to questions, she moaned frequently, and she occasionally called for her parents. She showed purposeful and symmetric limb movements in response to stimuli. Neurologic examination was limited by her men- tual status, but no focal abnormalities were detected; the remainder of the physical examination was normal. Serum levels of electrolytes, calcium, phosphorus, magnesium, total protein, albumin, globulin, amylase, lipase, antithrombin-III, IgG and IgM antibodies, fibrinogen, and C-reactive protein were normal, as were tests of renal function; results of tests for ANA and antibodies to double-stranded DNA, Ro, La, Sm, and ribonucleoprotein were unchanged, and testing for lupus anticoagulant and toxicology screening of the blood and urine were negative; other laboratory-test results are shown in Table 1.

The ABO blood type was O, Rh-positive, with negative antibody screening. Urinalysis revealed red cloudy urine (specific gravity, 1.020; pH, 7.0; 3+ blood and protein; 20 to 50 red cells and 10 to 20 white cells per high-power field; 5 to 10 hyaline casts and 0 to 2 granular casts per low-power field; few squamous cells; and mucin). Agitation precluded CT of the head. The patient was admitted to the pediatric intensive care unit (ICU) 5 hours after arrival.

Additional diagnostic testing was performed, and a management decision was made.

**Differential Diagnosis**

*Dr. William D. Binder:* I am aware of the diagnosis. This 16-year-old girl with a history of lupus nephritis presented with a complex array of signs and symptoms, including a change in mental status, anemia, and thrombocytopenia. After the ABCs — airway, breathing, and circulation — have been evaluated for stability, a finding of altered mental status requires a rapid and focused assessment in the emergency department.1

**Assessment of Altered Mental Status**

Causes of impaired consciousness can be categorized as structural, infectious and inflammatory, toxic or metabolic, and paroxysmal.2 The medical history taking and physical examination are important in defining the cause of altered mental status. Important historical data include the time course and circumstances of the onset of symptoms, recent or previous illnesses, and the use of medications, illicit drugs, or alcohol. Constitutional symptoms (e.g., fever, headache, and nausea and vomiting) and behavioral changes are clinically significant and must be elucidated. In this case, the patient's hemodynamic and respiratory functions were stable, and the physical examination showed no focal weakness and in-
termittently comprehensible speech. The neurologic examination was otherwise limited by her altered mental status.

CAUSES OF ALTERED MENTAL STATUS
Although this patient was not known to have suffered trauma, structural abnormalities due to occult trauma must always be considered. However, the CT scan performed at the other hospital did not reveal a subdural or epidural hematoma or subarachnoid hemorrhage. Although subarachnoid hemorrhage can be missed on CT, a bleed large enough to cause confusion would most likely be apparent. Other structural abnormalities such as tumors are unlikely in view of the age and history of this patient and the normal CT.

Infectious and inflammatory causes of altered mental status are possible. The patient was febrile and alternately confused and agitated. Patients with systemic lupus erythematosus (SLE) who are receiving immunosuppressive therapy are at risk for bacterial and viral infections.3 The triad of mental-status changes, fever, and neck stiffness occurs in less than 50% of immunocompetent persons who have bacterial meningitis and in an even smaller percentage of immunocompromised patients.4 Vascular and inflammatory changes in the central nervous system (CNS) occur in up to 90% of children and adolescent

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Table 1. Laboratory Data.

| Variable                          | Reference Range, Adjusted for Age and Sex† | 6 Wk before Admission | Day of Admission, Other Hospital | On Admission, This Hospital |
|----------------------------------|-------------------------------------------|-----------------------|==================================|-----------------------------|
| Hematocrit (%)                   | 36.0–46.0                                 | 39.9                  | 23.2                             | 19.7                        |
| Hemoglobin (g/dl)                | 12.0–16.0                                 | 13.9                  | 7.9                              | 6.8                         |
| Reticulocytes (%)                | 0.5–2.5                                   | 20.8                  |                                  |                             |
| White-cell count (per mm$^3$)    | 4500–13,500                               | 4600                  | 9100                             | 10,500                      |
| Differential count (%)           |                                          |                       |                                  |                             |
| Neutrophils                      | 40–62                                     | 71                    | 73                               | 86                          |
| Band forms                       | 0–10                                      | 0                     | 2                                | 0                           |
| Lymphocytes                      | 27–40                                     | 23                    | 25                               | 10                          |
| Monocytes                        | 4–11                                      | 5                     | 0                                | 4                           |
| Eosinophils                      | 0–8                                       | 1                     | 0                                | 0                           |
| Platelet count (per mm$^3$)      | 150,000–450,000                           | 317,000               | 16,000                           | 16,000                      |
| Mean corpuscular volume ($μm^3$)| 78–102                                    | 88                    | 88                               | 85                          |
| Erythrocyte count (million per mm$^3$) | 4.10–5.10                             | 4.54                  | 2.64 (ref 3.60–5.00)             | 2.31                        |
| Red-cell distribution width (%)  | 11.5–14.5                                 | 12.7                  | 17.7                             | 18.9                        |
| Smear description                |                                          |                       |                                  |                             |
| Anisocytosis                     | None                                      | Slight                | 2+                               |                             |
| Polychromasia                    | Normal                                    | Occasional            | 1+                               |                             |
| Schistocytes                     | None                                      | Occasional            | 1+                               |                             |
| Basophilic stippling             | Negative                                  | Occasional            | Present                          |                             |
| Erythrocyte sedimentation rate (mm/hr)| 1–17                                | 15                    | 45                               |                             |
| Haptoglobin (mg/dl)              | 16–199                                    | 25.9                  | 25.4                             |                             |
| Activated partial-thromboplastin time (sec) | 21.0–33.0                           | 11.4                  | 14.2                             |                             |
| Prothrombin time (sec)           | 10.8–13.4                                 | 11.4                  | 14.2                             |                             |
| D-Dimer (ng/ml)                  | <500                                      | 3508                  |                                  |                             |
| Fibrinogen (mg/dl)               | 150–400                                   | 368                   |                                  |                             |
| Glucose (mg/dl)                  | 70–110                                    | 84                    | 135                              |                             |
| Urea nitrogen (mg/dl)            | 8–25                                      | 10                    | 17                               |                             |
| Creatinine (mg/dl)               | 0.60–1.50                                 | 0.78                  | 1.05                             |                             |
patients with SLE. The spectrum of neuropsychiatric disorders associated with SLE includes cerebrovascular disease, cognitive dysfunction, seizures, and the acute confusional state. CNS lupus was a leading consideration in this case.

There is an enormous list of toxic and metabolic reasons for a change in mental status. In this patient, we can rule out most inborn errors of metabolism, although late-onset disorders can be triggered in some circumstances. Complications of diabetes, such as diabetic ketoacidosis, were ruled out at the other facility. Other endocrine diseases such as hypothyroidism and hyperthyroidism are possible but unlikely. Finally, ingestion of illicit or prescription drugs could create a stuporous state and must be considered in this 16-year-old patient.

Paroxysmal causes of confusion, such as seizure, were not witnessed. However, seizures can be present, with unusual behaviors and depression as their only manifestations. In some studies, seizure disorders have been reported in approximately 50% of pediatric patients with SLE.

**Laboratory-Test Results**

While we were strongly considering a diagnosis of primary CNS lupus, laboratory data provided critical clues to the diagnosis. The patient had thrombocytopenia, which can result from a failure of production, abnormal distribution or sequestration, or destruction of platelets. She did not have splenomegaly, so it is unlikely that there is sequestration or an abnormal distribution of platelets. Failure of production is possible, but thrombocytopenia in patients with SLE is more commonly caused by platelet destruction.

The patient also had a normocytic anemia. Anemia, thrombocytopenia, and leukopenia are present in up to 75% of pediatric patients with SLE. Anemias may be due to a failure of production of red cells, blood loss, or destruction of red cells. Although mycophenolate mofetil may cause gastroenteritis, this patient did not have evidence of gastrointestinal bleeding. Causes of decreased red-cell production include iron deficiency, viral hepatitis, infection with Epstein–Barr virus, and parvovirus infections, but the physical examination and the laboratory studies are not suggestive of any of these diagnoses. Red-cell destruction may be due to either intrinsic abnormalities of the red cells or extrinsic causes. Data from this patient suggest a pattern of extrinsic hemolysis. The blood smear reportedly showed 1+ schistocytes, a finding that is sugges-
tive of a microangiopathic hemolytic anemia. The elevated lactate dehydrogenase (LDH) and indirect bilirubin levels were further evidence of hemolysis.

In this patient with fever and changes in mental status, the laboratory findings of microangiopathic hemolytic anemia and thrombocytopenia were suggestive of a diagnosis of thrombotic thrombocytopenic purpura (TTP). We asked for consultations from the neurology, rheumatology, hematology, and nephrology services, and the patient was admitted to the pediatric ICU.

LUPUS NEPHRITIS

Dr. Avram Z. Traum: This teenage girl had presented 2 years earlier with hematuria, proteinuria, and hypertension, no extrarenal symptoms of SLE, and normal complement levels. We obtained renal-biopsy specimens at that time, which would be informative to review now.

Figure 1. Renal-Biopsy Specimen.

Panel A (periodic acid–Schiff) shows globally thickened glomerular basement membranes. Subepithelial, amorphous, electron-dense deposits are present in the glomerular basement membrane (Panel B, arrows). Immunofluorescence reveals finely granular deposits of IgG along the glomerular basement membrane (Panel C), and electron microscopy reveals tubuloreticular structures in the glomerular endothelial cells (Panel D, arrow). These features are typical of membranous lupus nephritis class V. There was no evidence of thrombotic microangiopathy.

Pathological Discussion

Dr. Robert B. Colvin: The renal-biopsy specimen (Fig. 1) had more than 20 glomeruli, which looked normal on light microscopical examination except for mildly thickened basement membranes; on immunofluorescence, there were numerous granular deposits of IgG, IgM, IgA, C3, and C1q along the glomerular basement membrane in a haphazard, scattered pattern. These were better seen by electron microscopy, pene-
trating the basement membrane and surrounded by spikes of new basement membrane, features that are typical of membranous glomerulonephritis. Another feature, which represented a response to interferon-α, was the presence of tubuloreticular structures in the endothelium. The vessels were normal, with no evidence of thrombotic microangiopathy. This pattern of membranous glomerulonephritis can be seen in many diseases other than lupus, but the presence of the tubuloreticular structures and the penetrating deposits in a so-called full house (the presence of all three immunoglobulin classes [IgG, IgM, and IgA] and complement factors C3 and C1q) led us to conclude that the membranous glomerulonephritis was most likely lupus nephritis class V, according to the International Society of Nephrology and the Renal Pathology Society classification. Membranous lupus nephritis is a unique category of lupus nephritis. Although classes I through IV represent escalating degrees of severity of glomerulonephritis, class V lupus nephritis does not represent a more severe form than class IV but, rather, is a distinct diagnosis.

**Differential Diagnosis**

*Dr. Traum*: After the biopsy findings were reported, I obtained an ANA titer, which was positive at 1:1280, along with an anti–double-stranded DNA titer that was positive at a low titer of 1:20, confirming the diagnosis of class V lupus nephritis. This form of lupus nephritis is unique, with its own manifestations, including normal complement levels and the absence of extrarenal disease. Proteinuria is more prominent than in other types of lupus nephritis, and nephritic features such as red-cell casts may be absent. The risk of thrombosis appears to be higher in membranous nephropathy than in other subtypes of nephrotic syndrome.

Because of her hypertension and proteinuria, this patient was initially treated with mycophenolate mofetil and prednisone, with improvement in her proteinuria and inflammatory markers. I had been tapering her prednisone to a relatively low dose (10 mg on alternate days), with close monitoring of her proteinuria and inflammatory markers. At the time of this acute presentation, she had been on a stable dose for some months.

**CNS Lupus**

A systemic lupus flare with cytopenias and CNS involvement was a serious consideration in this case. SLE-related cytopenias can be autoimmune in nature, and this patient's elevated indirect hyperbilirubinemia and LDH levels were suggestive of hemolysis, supporting this diagnosis; however, the antibody screening was negative. Antiphospholipid antibodies can be present in patients with lupus and can lead to a clinical picture of thrombocytopenia and changes in mental status; in this patient, screening for antiphospholipid antibodies had been negative 2 years earlier. Hypertensive crisis can lead to changes in mental status and can cause a thrombotic microangiopathy with anemia and thrombocytopenia. However, the patient's blood pressure was normal at the time of this presentation.

**Thrombotic Thrombocytopenic Purpura**

Laboratory-test results showed 1+ schistocytes, a finding that is suggestive of a microangiopathic hemolytic anemia. In thrombotic microangiopathy, an insult to the microvasculature leads to microthrombus formation with consumption of platelets, shearing of red cells with hemolysis, and the laboratory findings of schistocytes, thrombocytopenia, and anemia. The subsequent signs and symptoms are due to end-organ ischemia from microthrombi, particularly in the brain and renal glomeruli. Our patient had all these features, and additional laboratory testing revealed undetectable haptoglobin and an elevated reticulocyte count, which are further evidence of hemolysis. The differential diagnosis includes TTP and the hemolytic–uremic syndrome, both of which share features of microangiopathic hemolytic anemia and thrombocytopenia.

TTP is a rare disease but is seen more commonly in women, blacks, obese persons, and patients with autoimmune disease, including lupus; this patient had all these risk factors. TTP is due to a deficiency of ADAMTS 13, a protease that breaks down large, thrombogenic von Willebrand factor multimers into monomers. The presentation of TTP can be identical to that of the hemolytic–uremic syndrome. Usually, however, renal involvement is more prominent in the hemolytic–uremic syndrome. Fever is absent, and neurologic symptoms are variable. In diarrhea-associated hemolytic–uremic syndrome, which is typically seen in younger children, Shiga toxin produced by *Escherichia coli* O157:H7 or other related bacteria leads to endothelial injury. Hemolytic–uremic syndrome associated with the absence of a diarrheal prodrome
can follow other infections or can be due to genetic causes, such as mutations in genes encoding factor H, factor I, or membrane cofactor protein (MCP).

In this patient, the preexisting diagnosis of lupus, the mild nature of the renal disease, the microangiopathic hemolytic anemia, and the thrombocytopenia, in the absence of a diarrheal prodrome, make TTP the more likely diagnosis. The treatment of choice for TTP is plasma exchange, so the Blood Transfusion Service was consulted.

**CLINICAL DIAGNOSIS**

Thrombotic thrombocytopenic purpura.

**PATHOLOGICAL DISCUSSION**

Dr. Robert S. Makar: With Dr. Verena Gobel (Pediatric Hematology), we reviewed the peripheral-blood smear (Fig. 2); this revealed schistocytes and reticulocytes and virtually no platelets, indicating a microangiopathic hemolytic anemia that was consistent with a thrombotic microangiopathy. The differential diagnosis of a thrombotic microangiopathy is broad (Table 2) and includes many conditions that require distinct therapeutic interventions. TTP is caused either by congenital deficiency of the plasma enzyme ADAMTS 13 (Upshaw–Schülman syndrome), or by autoantibody inhibitors of ADAMTS 13 that result in a deficiency of the enzyme. In patients with idiopathic TTP, microvascular hemostasis is disrupted; plasma exchange is a lifesaving procedure for these patients, because it corrects the perturbation by replacing the ADAMTS 13 enzyme and removing, over the course of several procedures, the autoantibody inhibitor that is often detected during the acute illness. Therefore, a clinical diagnosis of TTP and treatment with plasma exchange is appropriate when there is evidence of a thrombotic microangiopathy without clinical or laboratory evidence of an alternative cause. Although this patient had evidence of end-organ injury, in the form of altered mental status and a very mild elevation in her serum creatinine level, neither a neurologic finding nor acute renal failure is required to make the diagnosis of idiopathic TTP and initiate plasma exchange.

In this patient, a diagnosis of idiopathic TTP was made and plasma exchange was begun.

**DISCUSSION OF MANAGEMENT**

Dr. Makar: Patients with idiopathic TTP used to be treated with either plasma infusion or plasma exchange, but a randomized, controlled trial conducted approximately 20 years ago showed the superiority of plasma exchange. Plasma infusion is appropriate only as a temporary measure while arrangements are being made for plasma exchange. Therapeutic plasma exchange requires excellent venous access to support the blood flow required by the instrument, at least a 17-gauge needle for a withdrawal and an 18-gauge intravenous catheter for return. Because most patients require multiple procedures, a central venous catheter for apheresis is often required before plasma exchange can start. Although a recently published case series found no evidence of harm from platelet transfusion in patients with TTP, prophylactic platelet transfusion before insertion of the catheter is not recommended.

Patients with TTP undergo daily plasma exchange, typically accompanied by glucocorticoids, until clinical remission (i.e., a normal platelet count, rising hemoglobin level, and normal or near-normal LDH level) occurs and persists for several days. Plasma exchange is then performed on alternate days or is stopped, and the
administration of glucocorticoids is tapered. The number of postremission exchanges is empirical and reflects institutional practice. No matter which strategy is used to discontinue plasma exchange, vigilant monitoring is required for evidence of disease exacerbation (recurrence within 30 days after diagnosis) or relapse. Our patient’s mental status cleared after the first plasma exchange and her hematologic parameters normalized after six treatments, so we decided to move to an alternate-day regimen. Unfortunately, after one exchange was skipped, the platelet count fell markedly (Fig. 3), the hematocrit fell, and the LDH level rose, so daily plasma exchange was reinstituted.

Although testing for ADAMTS 13 enzyme activity and inhibitor is not necessary for the diagnosis of TTP, such testing may provide useful prognostic information for this patient. A severe deficiency of ADAMTS 13 and the presence of detectable autoantibody inhibitors at diagnosis are associated with an increased risk of relapse. Furthermore, high titer of autoantibody inhibitors may predict a delayed response or refractoriness to plasma exchange. We use a fluorescence resonance energy transfer assay to measure ADAMTS 13 activity. This method involves incubating the patient’s plasma with a fluorogenic von Willebrand factor peptide fragment containing the site where ADAMTS 13 cleaves von Willebrand factor. When the peptide is cleaved, a fluorescent signal is detected that is proportional to the ADAMTS 13 activity in the specimen. Several days after we started treating this patient, results of ADAMTS 13 testing showed less than 5% enzyme activity and a high titer of autoantibody inhibitors (3.6 Bethesda units). These results suggested that the patient might be at increased risk for recurrent disease after the discontinuation of plasma exchange. Indeed, although she remained asymptomatic throughout her treatment course, thrombocytopenia and microangiopathic hemolytic anemia recurred whenever we attempted to withdraw plasma exchange (Fig. 3).

Rituximab has gained favor as an adjunctive agent to treat refractory or relapsing TTP. Clinical trials are required to clarify whether rituximab should be used in conjunction with plasma exchange for all patients with TTP or only for those with refractory or relapsing disease. For this patient, we suggested a course of rituximab, which, together with intermittent plasma exchange, resulted in a durable clinical remission.

Dr. Nancy Lee Harris (Pathology): Dr. Traum, would you tell us how the patient is doing?

Dr. Traum: One year after this episode, the patient is doing well. Her kidney disease is in remission, TTP has not recurred, and her platelet count, hematocrit, and LDH level are normal. Her proteinuria is slightly better than before the

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<th>Table 2. Differential Diagnosis of Thrombotic Microangiopathy.</th>
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<td><strong>Disease</strong></td>
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<td>Evans syndrome</td>
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<td>Antiphospholipid-antibody syndrome</td>
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<td>Severe vasculitis</td>
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<td>Malignant hypertension</td>
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<td>Disseminated cancer</td>
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<td>Pregnancy-related</td>
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<td>Hemolytic–uremic syndrome</td>
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* HELLP denotes hemolytic anemia, elevated liver enzymes, and low platelet count; PT prothrombin time; and PTT partial-thromboplastin time.
A secondary form of the disease is associated with drugs such as the thienopyridines ticlopidine and clopidogrel, both of which appear to elicit the formation of an anti–ADAMTS 13 autoantibody, although clopidogrel may also trigger the disease through a nonimmune mechanism. In patients with severe deficiency and an autoantibody inhibitor, relapse rates range from 30 to 70%.22

A Physician: If you suspect TTP, is it ever right to give platelets?

Dr. Makar: Platelet transfusion may be associated with acute deterioration or even death from TTP. For this reason, platelet transfusion is relatively contraindicated in patients with thrombotic thrombocytopenic purpura and should be limited to the treatment of life-threatening bleeding.

PATHOLOGICAL DIAGNOSIS

Thrombotic thrombocytopenic purpura due to autoantibodies to ADAMTS 13 in a patient with class V lupus nephritis.

This case was discussed at Emergency Medicine Grand Rounds, November 10, 2009. No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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