This patient's presentation was marked by a variety of nonspecific symptoms and signs, which makes arriving at a diagnosis difficult. From the clinical history, however, we can distill the presentation down to several core symptoms and signs:

• The patient has normocytic anemia and marked thrombocytopenia, with a normal white blood cell count. Therefore, 2 of the 3 blood cell lines are diminished. The patient shows no signs of blood loss through the gastrointestinal tract.
• The patient has elevated aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) with normal liver function tests, raising the possibility of hemolysis because these enzymes are present in red blood cells.
• Normal coagulation parameters with normal fibrinogen, prothrombin time (PT), and activated partial thromboplastin time (aPTT), indicate the patient does not have disseminated intravascular coagulopathy.
• The patient has acute renal failure.
• The patient shows signs of mental status changes, in the form of lethargy and malaise.

In this setting, it is sometimes easier to approach the differential diagnosis for several of the patient's key symptoms and signs. One possibility is to approach the patient's thrombocytopenia to make a differential diagnosis. Possibilities here include decreased production that could arise from a viral infection, bone marrow infiltration by malignancy or granulomatous inflammation, or bone marrow failure in the setting of myelodysplastic syndrome or acute leukemia. More commonly, thrombocytopenia arises from increased destruction, such as occurs from idiopathic thrombotic thrombocytopenic purpura (ITP) (which may be idiopathic or drug associated), infection (overwhelming sepsis or viral infection), malignancy, or consumption. Platelet consumption occurs by either disseminated intravascular coagulation or a microangiopathic hemolytic anemia. A bone marrow exam to look for increased or decreased megakaryocytes, or a platelet transfusion to indicate shortened platelet survival, is sometimes necessary to determine the etiology of thrombocytopenia. Thus, it is difficult to narrow this patient's differential diagnosis from her thrombocytopenia.

Alternatively, the differential diagnosis could be approached by examining the possible causes of her anemia. Anemia can be divided into hypo and hyperproliferative states. Hypoproliferative anemias are generally characterized by a low reticulocyte count. The differential diagnosis includes deficiencies of the building blocks of red blood cells (Vitamin B12, folate, or iron); parvovirus infection, which specifically targets erythroid precursors; bone marrow failure or infiltration, such as with leukemia or granulomatous disease, respectively; or chronic inflammation, which gives rise to the anemia of chronic disease. Hyperproliferative anemias are characterized by increased reticulocyte counts that cannot compensate for increased destruction or blood loss. The patient shows no evidence of blood loss through the gastrointestinal tract or elsewhere. Hyperproliferative anemias resulting from red blood cell destruction, or hemolysis, can be either extravascular or intravascular. Extravascular destruction occurs in the spleen, as antibodies coat red blood cells, leading to phagocytosis in the reticuloendothelial system. This type of hemolysis is associated with a positive Coombs test and microspherocytes on peripheral smear. The latter results from the pinching off of fragments of cell membrane by the spleen's sinusoidal macrophages. Intravascular causes of hemolysis are associated with increased LDH and AST, which are released from red blood cells, and decreased haptoglobin levels. Intravascular hemolysis is often associated with low platelet counts (consumptive thrombocytopenia) and is characterized by schistocytes on peripheral smear.

Examination of the provided peripheral blood smear helps greatly to characterize this patient's anemia. The first
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finding of note is the markedly decreased platelet count. On a blood smear, each platelet seen in a high-power field correlates with approximately 10,000 platelets in the peripheral circulation. Because the normal platelet count is approximately 140,000/mm³, 14 platelets should be visible in a high-power field; far fewer than that number are visible in the provided peripheral smear images. The few white blood cells seen in the smear appear normal, which correlates with the normal white blood cell count noted in the peripheral smear. The most striking finding in the blood smear, however, relates to the red blood cells. There is indirect evidence of reticulocytosis in the marked polychromasia of the red blood cells. Although a few microspherocytes are present, the dominant finding is that of numerous schistocytes and helmet-shaped cells. The presence of these numerous schistocytes establishes that this patient has a microangiopathic hemolytic anemia.

Microangiopathic hemolytic anemias occur from mechanical shearing of the red blood cells and consumption of platelets, and the differential for this syndrome is limited. One of the more common causes is disseminated intravascular coagulation (DIC). In a patient with a skin rash, as in this patient, meningococcal sepsis leading to DIC is a possibility. However, patients with DIC typically have abnormal coagulation factors (increased PT and aPTT, decreased fibrinogen), which this patient did not have. Patients with sepsis also typically have fever and hypotension. Another possibility is the HELLP [hemolysis, elevated liver enzymes, low platelets] syndrome, which may develop in pregnant patients and is associated with marked liver function abnormalities. Neither of these was true in this patient. Another possibility is the “waring blender syndrome,” in which hemolysis is associated with heart valve abnormalities. The absence of a cardiac murmur or previous valve replacement argues strongly against this possibility. Occasionally, patients with vasculitis, lupus, or antiphospholipid syndrome present with microangiopathic hemolytic anemia; however, this patient did not demonstrate any signs of these disorders. Another possibility is malignant hypertension, which is eliminated by the patient’s normal blood pressure.

The final category of microangiopathic hemolytic anemia includes the distinct but related thrombotic syndromes, thrombotic thrombocytopenic purpura (TTP) and the hemolytic-uremic syndrome (HUS). These syndromes are characterized by thrombocytopenia, hemolytic anemia, fever, renal abnormalities, and neurologic abnormalities. HUS is characterized by greater renal dysfunction, less severe thrombocytopenia, less elevation of LDH, and fewer schistocytes than TTP. TTP is characterized by predominant neurologic abnormalities, but these disorders may have significant clinical overlap. Although most cases are idiopathic, these disorders have several associations. TTP can be familial, associated with human immunodeficiency virus infection, or associated with bone marrow transplants or medications (eg, cyclosporine and ticlopidine). There is an association of HUS with the Shiga
toxin produced by Escherichia coli 0157:H7. The classic pentad associated with TTP comprises microangiopathic hemolytic anemia, thrombocytopenia, fever, mental status changes, and renal dysfunction. This patient lacked significant fever; approximately 50% of patients with TTP will not have all of the 5 signs of the pentad of TTP. Other subtle features of TTP include a typically normal white blood cell count and liver and lung functions. The mental status involvement is not chronic, as patients may rapidly return to normal central nervous system function after being essentially comatose.

Given this patient’s constellation of clinical findings, the most likely diagnosis is TTP. The treatment of TTP involves plasmapheresis, which has been thought to work by removing an abnormal factor that promotes coagulation from the blood and/or restoring an absent factor to the blood. This patient was treated for TTP with plasmapheresis; despite therapy, the patient died. An autopsy was performed.

The autopsy findings confirmed the diagnosis of TTP. Examination of multiple organs revealed small arterioles with organizing platelet thrombi. These were most evident in the heart, where they were associated with small foci of myocyte loss with replacement fibrosis (Figure 1). Higher-power examination of these thrombi revealed evidence of organization with endothelial cell proliferation, consistent with this patient’s onset of symptoms approximately 8 to 9 days before death (Figure 2).
A recent autopsy series from The Johns Hopkins Hospital compared the autopsy findings in a large series of patients with TTP and HUS. The results showed several similar clinical features between these 2 types of patients, including similar age and the presence of purpura, anemia, and thrombocytopenia. However, several key differences (which reached statistical significance) were noted. As in the case presented here, patients with TTP were far more likely to have thrombi affecting the heart. Thrombi in the brain (Figure 3) were more common in TTP, which correlates with the clinical presentation with mental status changes. The pancreas was more likely to be involved with TTP, and thrombi classically affected the small venules within islets of Langerhans (Figures 4 and 5). The adrenal was also more frequently involved in TTP, and the platelet thrombi characteristically affected the peripheral zona glomerulosa of the adrenal cortex (Figure 6). The platelet-rich composition of the thrombi in TTP can be confirmed by special stains. The thrombi are strongly immunoreactive for von Willebrand factor by immunohistochemistry (Figure 7), but do not label well with the phosphotungstic acid hematoxylin (PTAH) stain, which is a good marker for fibrin (Figure 8). In contrast, the thrombi in HUS are more likely to be true fibrin thrombi, which label with the PTAH stain (Figure 9). Clinically, HUS was far more likely to be associated with acute renal failure compared with TTP.

Recently, the pathogenesis of TTP has become more apparent. It had long been known that patients with TTP had unusually large von Willebrand factor multimers in their plasma, which were postulated to promote abnormal platelet aggregation and cause thrombi. Nonfamilial acquired TTP has been found to be associated with an acquired inhibitory antibody against the von Willebrand factor–cleaving metalloprotease, which normally cleaves such multimers. Familial forms of TTP are associated with a constitutional deficiency of this protease. In contrast, the HUS is not associated with these
antibodies; thus, this single laboratory test may help distinguish 2 syndromes that overlap clinically. It is hoped that this new knowledge may lead to more rational therapies for TTP in the future. One possibility is the direct administration of the inhibited protease (also known as ADAMTS13).1

REFERENCES