Presentation of Case

Dr. Emer McGrath (Neurology): A 32-year-old woman was admitted to this hospital in the fall because of severe headache and loss of peripheral vision.

The patient had been in her usual state of health until 4 weeks before admission to this hospital, when she underwent elective termination of pregnancy with methotrexate. The pregnancy had occurred despite the presence of an intrauterine device, and the device was removed a few days after the termination. Oral contraception was initiated.

Three weeks later and 1 week before admission to this hospital, pain in the left upper quadrant, vaginal bleeding, and headache developed. The patient was admitted to another hospital. The blood level of human chorionic gonadotropin was 24 IU per liter (normal range, <6 IU per liter); the level had been 21,000 IU per liter 3 weeks earlier, when she was pregnant. Blood levels of electrolytes, glucose, amylase, lipase, total protein, and albumin were normal, as were results of renal-function tests, the prothrombin time, the international normalized ratio, and the partial-thromboplastin time. An examination of a peripheral-blood smear for babesia and a direct antiglobulin test were negative; other laboratory test results are shown in Table 1. Imaging studies were obtained.

Dr. R. Gilberto Gonzalez: Computed tomography (CT) of the abdomen and pelvis (Fig. 1), performed after the administration of intravenous contrast material, revealed splenomegaly (spleen length, 15.6 cm in the craniocaudal dimension; normal range, ≤12 cm), as well as a central filling defect in the splenic vein that was compatible with acute splenic-vein thrombosis. CT of the chest, performed after the administration of intravenous contrast material, revealed low lung volumes, scattered ground-glass opacities, and no evidence of pulmonary embolism.

Dr. McGrath: Oral contraception was stopped. On the third hospital day, the patient's abdominal pain diminished, and she was discharged home.
Four days later, severe bifrontal headache and loss of vision in the left visual field developed. The patient was evaluated by her primary care physician. On examination, she had decreased peripheral vision superiorly and inferiorly in the left visual field. Magnetic resonance imaging (MRI) of the head was scheduled, but the severity of her headaches increased, and she was evaluated at the other hospital. Additional imaging studies were obtained.

Dr. Gonzalez: CT of the head and neck (Fig. 2) revealed a confluent area of hypodensity and sulcal effacement involving the superior right parietal lobe that extended inferiorly into the right occipital lobe and the right aspect of the splenium of the corpus callosum (a finding suggest-
tive of a recent infarct) and small, focal areas of hyperdensity (findings consistent with hemorrhagic conversion). Although a focal occlusive thrombus was not identified, the distal branches of the right posterior cerebral veins were not visible. The patient was transferred to the emergency department of this hospital.

Dr. McGrath: On evaluation in the emergency department, the patient reported persistent headache, vision changes in the left visual field, photophobia, phonophobia, and pain with extraocular movements. She had a history of chronic back pain that was related to a vertebral disk herniation, for which she had undergone spinal-fusion surgery 4 years before admission to this hospital. During the 3 years before admission, she had had two episodes of self-limited thrombocytopenia that were thought to be associated with methotrexate treatment for an unknown skin disorder. She had no history of bleeding or clotting disorders and had had no spontaneous miscarriages. She had a 2-year history of waxing-and-waning dull epigastric pain that was associated with nausea and occasional episodes of bilious emesis; the pain partially improved with omeprazole.

The patient’s medications included diclofenac, baclofen, controlled-release morphine sulfate, hydrocodone–acetaminophen, and omeprazole. She had taken oral contraception in the past for extended periods of time. She lived in coastal New England and worked in communications. She drank alcohol occasionally and smoked less than 1 pack of cigarettes per week; she had not smoked during the past few months. She did not use illicit drugs, over-the-counter medications, or herbal medications. There was no family history of bleeding or clotting disorders, spontaneous miscarriage, or hematologic cancer.

On examination, the temperature was 38.3°C, the blood pressure 126/72 mm Hg, the pulse 54 beats per minute, the respiratory rate 20 breaths per minute, and the oxygen saturation 96% while the patient was breathing ambient air. She was in mild distress because of her headache, but she was alert and oriented to time and place. Examination of the neck, heart, lungs, abdomen, skin, and oral mucosa was normal. Left homonymous hemianopia was present; other cranial-nerve functions were normal, although function of the first cranial nerve was not tested. Strength, sensation to light touch, and deep-tendon reflexes of the arms and legs were normal. Finger–nose–finger testing showed no dysmetria. Examination of a peripheral-blood smear showed 0 to 2 schistocytes per high-power field, teardrop and pencil cells, occasional large platelets, and normal-appearing white cells. Urinalysis showed 1+ ketones, 2+ blood, 1+ protein, 1+ urobilinogen, a specific gravity greater than 1.040 (normal range, 1.001 to 1.035), and a pH of 5 (normal range, 5 to 9) by dipstick; microscopic examination of the sediment revealed no red cells and 3 to 5 white cells per high-power field (normal range, 0 to 2). Other laboratory test results are shown in Table 1. The patient was admitted to the intensive care unit of this hospital, and additional imaging studies were obtained.

Dr. Gonzalez: MRI of the head confirmed the infarcts and hemorrhagic conversion that had been seen on CT angiography and venography (Fig. 2). A cortical vein was not visible over the lesion, which suggested either cortical-vein thrombosis or secondary compression due to mass effect of the parenchymal lesion. On the second hospital day, transfemoral cerebral angiography...
The new england journal of medicine

(Fig. 2) showed multiple cerebral venous thromboses involving the right frontal and parietal cortical veins, with no involvement of the major dural sinuses.

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

Differential Diagnosis

Dr. David B. Sykes: In this 32-year-old healthy woman, abdominal pain, vaginal bleeding, and headache developed 3 weeks after elective termination of pregnancy, and an evaluation revealed splenic-vein thrombosis and cerebral venous thromboses. Laboratory testing revealed thrombocytopenia and hemolytic anemia. This constellation of findings is worrisome for disseminated intravascular coagulation and microangiopathic hemolytic anemia, entities that require urgent diagnosis and treatment.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation is not a diagnosis but rather an uncontrolled consumptive process that results from an underlying condition, such as sepsis or advanced cancer. Scoring
systems have been established to help evaluate the likelihood of disseminated intravascular coagulation in patients with abnormal laboratory values. In this patient, the prothrombin time was slightly prolonged, the fibrinogen level was normal, and the thrombocytopenia was mild. This pattern argues against disseminated intravascular coagulation, despite the markedly elevated d-dimer level. The elevated d-dimer level can be explained by the known thromboses and most likely reflects the normal process of fibrinolysis, in which fibrin degradation products such as d-dimers are released into the bloodstream. Overall, disseminated intravascular coagulation is unlikely in this patient.

**Microangiopathic Hemolytic Anemia**

Microangiopathic hemolytic anemia, which is a disorder characterized by mechanical damage of red cells, can occur with thrombotic thrombocytopenic purpura and the hemolytic–uremic syndrome. Microangiopathic hemolytic anemia can also occur with malignant hypertension, eclampsia, vasculitis, and valvular heart disease, but these diagnoses do not seem to be likely in this patient. When microangiopathic hemolytic anemia is considered, examination of a peripheral-blood smear is critical to rule out the presence of schistocytes. Typically, the presence of more than 1% schistocytes per high-power field raises concerns about a microangiopathic process. This patient had 0 to 2 schistocytes per high-power field (with >200 erythrocytes per field); although microangiopathic hemolytic anemia is possible, it is unlikely in this case.

**History**

On the basis of the laboratory test results and the findings on a peripheral-blood smear, the immediately life-threatening processes of disseminated intravascular coagulation and microangiopathic hemolytic anemia seem unlikely in this case, and we can now focus on the salient features of the history (Fig. 3). The patient had no history of clinically significant anemia and is therefore unlikely to have an inherited red-cell disorder, such as an enzyme deficiency, a membrane defect, or hemoglobinopathy.

The patient described a 2-year history of episodic abdominal pain, which raises concerns about acute porphyria, a diagnosis that is often sought but rarely found. On the basis of the imaging findings, the abdominal pain appears to be due to splenic-vein thrombosis; the patient also had cerebral venous thromboses. Because she had multiple thromboses in unusual locations and thrombosis is not a common finding in patients with porphyria, this is an unlikely diagnosis in this case.

One feature of this patient’s presentation that should be considered is the relationship between the timing of her illness and the elective termination of pregnancy and initiation of oral contraception. The high-estrogen state of pregnancy and the estrogen-containing contraceptive agent are both prothrombotic, as is tobacco use (although she reportedly had not smoked cigarettes recently). Although this constellation of events may help to explain the development of thromboses, it does not account for the other features of this case, such as anemia.
LAbORATORY TEST RESULTS
A closer evaluation of the laboratory test results may help us to determine the most likely diagnosis. The combination of anemia, an elevated lactate dehydrogenase level, and an undetectable haptoglobin level suggests a hemolytic process. However, examination of the peripheral-blood smear did not show spherocytes, which are seen in autoimmune hemolytic anemia, or red-cell clumping, which is seen in cold agglutinin disease. Furthermore, a Coombs’ test (direct antiglobulin test) was negative, which argues against such common processes as warm and cold autoimmune hemolytic anemia.

The complete blood count showed anemia and thrombocytopenia, and the mean corpuscular volume suggested an underlying macrocytosis. The reticulocyte count was disproportionately low relative to the degree of anemia, a finding that indicates underproduction of red cells. The macrocytosis is unlikely to be explained by the presence of reticulocytes alone, because the average size of a reticulocyte is only 111 fl and the presence of approximately 4% reticulocytes would not be expected to increase the mean corpuscular volume to a level higher than 100 fl (which was seen in this patient). If the patient were to have an underlying concomitant iron deficiency, I would expect the red-cell distribution width to be larger, and if she were to have a process that causes spherocytosis, such as warm autoimmune hemolytic anemia, I would expect the mean corpuscular hemoglobin concentration to be elevated.

On urinalysis, there was a discrepancy between the dipstick analysis, which showed 2+ blood, and the microscopic analysis, which did not show any red cells. In the context of a suspected hemolytic process, this combination of findings would be most consistent with hemoglobinuria without hematuria. This pattern is suggestive of intravascular hemolysis, in which free hemoglobin is released into the plasma (as opposed to extravascular hemolysis, in which red cells are removed by the phagocytic monocytes of the reticuloendothelial system). Taken together, the hemoglobinuria, macrocytosis, thrombocytopenia, and unusual thrombotic events raise concerns about a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH).

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA
Several aspects of this patient’s presentation are consistent with a diagnosis of PNH. Approximately one third of female patients with PNH receive the diagnosis at the time of pregnancy; the elevated estrogen levels presumably contribute to the increased thrombotic risk. Despite the name of the condition, the majority of affected patients do not report nocturnal hemoglobinuria. In PNH, intravascular hemolysis occurs, releasing free hemoglobin into the plasma. It is believed that the release of free hemoglobin leads to scavenging of nitric oxide, which triggers smooth-muscle dystonia and can cause episodic abdominal pain (which was reported in this patient). Unusual thromboses and bone marrow dysfunction (macrocystsis and thrombocytopenia) are both prominent features of PNH, but the mechanisms behind these processes are poorly understood. On the basis of the findings in this case, I suspect that the most likely diagnosis is PNH. To confirm this diagnosis, I would obtain a blood specimen for flow cytometry to look for altered expression of glycosylphosphatidylinositol (GPI)–anchored proteins, such as CD55 and CD59, on erythrocytes and leukocytes.

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

Dr. Aneesh B. Singhal: The neurology team was initially concerned about the patient’s headache in the context of new focal neurologic deficits. Several features of her presentation suggested a secondary cause for headache; these included the escalating head pain, abdominal pain, splenic-vein thrombosis, abnormal hematologic laboratory test results, and new homonymous hemianopia, which indicated the presence of a right temporopontal brain lesion. Aneurysmal subarachnoid hemorrhage and pituitary apoplexy were unlikely, since these conditions are usually associated with the sudden onset of a severe thunderclap headache. The absence of fever and neck stiffness made infectious causes unlikely. Given the sudden onset of a new focal deficit and the presence of several risk factors for stroke (i.e., the history of smoking, recent pregnancy, and use of oral contraceptive pills), our leading diagnosis was either embolic or venous stroke in the right temporopontal region. The
worsening headache over a span of 1 week, the recent pregnancy and initiation of oral contraception, and the elevated v-dimer level made cerebral venous thrombosis the most likely neurologic diagnosis.

Dr. Baggett: Dr. Colling, what was the impression of the hematology team during consultation?

Dr. Meghan E. Colling (Medicine): In this patient, the recent termination of pregnancy with a complication of vaginal bleeding, the exposure to methotrexate, and the initiation of oral contraception could explain the anemia, thrombocytopenia, and thromboses but not the ongoing hemolysis. We focused our differential diagnosis on processes that cause concomitant thrombosis and hemolysis. The paucity of schistocytes on the peripheral-blood smear, the stable platelet count, and the presence of macrothrombi (not microthrombi) made thrombotic thrombocytopenic purpura unlikely. Although the v-dimer level was elevated, the fibrinogen level was normal and the prothrombin time was only slightly prolonged, and thus disseminated intravascular coagulation was low on the differential diagnosis. In the context of a recent pregnancy, we considered the HELLP syndrome (characterized by hemolysis, elevated liver-enzyme levels, and low platelet counts), but we thought the timing of her presentation was outside the typical time frame for this diagnosis. Methotrexate exposure and glucose-6-phosphate dehydrogenase deficiency could cause hemolysis, but neither condition would explain the thromboses. Given her history of abdominal pain, we favored PNH as the most likely cause of Coombs’-negative hemolysis and thrombosis.

**Clinical Diagnosis**

Cerebral venous thrombosis in the context of paroxysmal nocturnal hemoglobinuria.

**Dr. David B. Sykes’s Diagnosis**

Paroxysmal nocturnal hemoglobinuria.

**Pathological Discussion**

Dr. Andrea P. Moy: PNH is an acquired, life-threatening, clonal hematopoietic stem-cell disorder that is caused by an acquired mutation in the gene encoding phosphatidylinositol glycan class A (PIG-A). The mutation reduces or inhibits the expression of GPI-anchored proteins on the surface of hematopoietic cells. The cell-surface markers CD55 and CD59 are the most widely expressed GPI-anchored proteins, and they function in complement regulation. The GPI-anchored proteins CD24 and CD14 are normally expressed on neutrophils and monocytes, respectively.

Peripheral-blood flow cytometry is a sensitive and specific way to detect decreased expression of GPI-anchored proteins, and it allows for the measurement of the PNH clone. Monoclonal antibodies against specific GPI-anchored proteins (e.g., CD59, CD24, and CD14) and fluorescein-labeled proaerolysin (FLAER) staining are typically used in the analysis.

In this case, flow cytometry revealed abnormal loss of GPI-anchored proteins and abnormal FLAER staining (Fig. 4). Approximately 1% of glycoprotein A+ erythrocytes showed a partial deficiency of surface CD59, and approximately 5% of glycoprotein A+ erythrocytes showed a complete deficiency of CD59. In addition, approximately 57% of CD15+ neutrophils showed loss of CD24 expression and no FLAER staining, and approximately 60% of CD64+ monocytes showed loss of CD14 expression and no FLAER staining. Overall, these findings are diagnostic of PNH.

**Discussion of Management**

Dr. Rachel P. Rosovsky: This patient had hemolysis, thrombosis, and evidence of PNH in the absence of other causes of bone marrow dysfunction; these features are consistent with classic PNH. There is often a delay in the diagnosis of PNH (as was seen in this case), because the condition is rare and is associated with unusual clinical features. Since PNH was first recognized, its treatment has become more advanced, because there has been an increase in the understanding of the disease pathophysiology and in the development of biologic therapies that target the underlying abnormality.

Thrombotic events occur in up to 40% of patients with PNH and are the leading cause of death associated with this condition. This patient was treated with unfractionated heparin, which was transitioned to warfarin before discharge. Treatment with folic acid, iron supple-
The new England journal of medicine

mentation, and medroxyprogesterone was also initiated.

The patient had several indications for the treatment of PNH, including thromboses, pain, and severe fatigue. The two options for the treatment of classic PNH are eculizumab and allogeneic bone marrow transplantation. Eculizumab is a humanized monoclonal antibody that blocks conversion of C5 and formation of the membrane attack complex (C5–9) and protects PNH-associated erythrocytes from complement-mediated intravascular hemolysis. Eculizumab is relatively safe and has been associated with reduced hemolysis, fatigue, and need for transfusions, as well as improved quality of life in patients with PNH.10-14 Treatment with eculizumab not only decreases the risk of thrombosis but also improves survival.12,14-16 Before eculizumab became available, median survival among patients with PNH was only 10 years.9 In a recent retrospective study, the 6-year overall survival rate was 92% among patients with PNH who were treated with eculizumab, as compared with a rate of 68% among a historical control cohort.15

In this patient, eculizumab was initiated at the standard adult dose; the patient was monitored for evidence of hemolysis weekly for the first 4 weeks and has been monitored monthly since then. She has not had any breakthrough hemolysis, but if this occurs, we can either shorten the interval between doses of eculizumab or increase the dose.

Several side effects are associated with eculizumab, and this patient has had many of the most common ones, including headache, nasopharyngitis, nausea, back pain, dizziness, and fatigue. Most of her symptoms had dissipated by week 26 of therapy, which is consistent with

Figure 4. Results of Peripheral-Blood Flow Cytometry.

Panel A shows the level of CD59 expression in glycoporphin A+ erythrocytes; approximately 1% of the glycoporphin A+ erythrocytes show a partial CD59 deficiency (these are known as type II cells), and approximately 5% show a complete CD59 deficiency (type III cells). Panel B shows the level of CD24 expression and fluorescein-labeled proaerolysin (FLAER) staining in CD15+ neutrophils, which have a high level of side scatter of light (SSC, a marker of cytoplasmic complexity and granulation) (top graph); approximately 57% of the CD15+ neutrophils show loss of CD24 expression and no FLAER staining, a finding consistent with a paroxysmal nocturnal hemoglobinuria (PNH) clone (bottom graph). Panel C shows the level of CD14 expression and FLAER staining in CD64+ monocytes, which have a low level of SSC (top graph); approximately 60% of the CD64+ monocytes show loss of CD14 expression and no FLAER staining, a finding consistent with a PNH clone (bottom graph).
biopsy specimen was normocellular for the patient here today to share her experience with us.

Dr. Baggett: We are fortunate to have the patient here today to share her experience with us.

The Patient: When you make a new diagnosis, especially if it is a complex one, it is very helpful for you to take the time to explain it to the patient, repeat the explanation, and then give the patient time to process, read over information, understand the implications of the diagnosis and how it affects them, and understand the language of the diagnosis. Then, it is helpful for you to take the time to go back over the diagnosis with them. Let them ask the questions. The time my doctors have taken with me to answer questions and explain what to expect along the way has made all the difference. Even the occasional answer of “I’m not sure” or “I’ll have to look into that” is more reassuring than I can explain. It helps to humanize the complexities that come along with difficult and rare diagnoses. As time goes on and new research is done, more questions and answers will come. If you’re there for your patients, it will make all the difference to them.

**Final Diagnosis**

Paroxysmal nocturnal hemoglobinuria.

This case was presented at the Internal Medicine Comprehensive Review and Update 2017, directed by Rocio Hurtado, M.D., and Katrina Armstrong, M.D.

We thank Olga Kharchenko, Ph.D., for preparation of an earlier version of Figure 3.

---

**References**