Presentation of Case

Dr. Jeffrey L. Greenwald: A 73-year-old man with multiple chronic medical illnesses was admitted to this hospital because of confusion and irritability.

Two days before this admission, increasing weakness, lethargy, chills, and diarrhea developed. The patient became less responsive to his family and increasingly irritable and confused. He stopped taking his medications. On the day of admission, his oral intake was 500 ml of liquid. His family reported that he was in an “almost catatonic” state; he was unable to arise from bed, had recurrent epistaxis, and reported pain in his chest and left arm. He was brought to the emergency department of this hospital.

The patient had been in poor health, with a recent diagnosis of atypical pneumonia, which was treated with levofloxacin. He had a history of diabetes mellitus, atrial fibrillation, coronary artery disease, diastolic heart failure, and pulmonary hypertension. Cardiac evaluations that had been performed over the previous decade had revealed an exudative pericardial effusion that had spontaneously resolved, as well as heart failure predominantly on the right side (left ventricular ejection fraction, 69%; pulmonary arterial systolic pressure, 61 mm Hg). A biopsy of the right side of the heart did not reveal a cause of the heart failure. The patient had had recurrent epistaxis since childhood, and it had recently worsened. Additional medical history included hyperlipidemia, pancytopenia, obstructive sleep apnea, gastroesophageal reflux disease, and headaches; there was also a possible history of an arteriovenous malformation of the brain, which had been noted on an imaging study obtained 20 years earlier but had not been confirmed on magnetic resonance imaging (MRI) performed at this hospital 7 years before this admission. He had undergone excision of a basal-cell carcinoma and an appendectomy.

One month before this admission, the patient had been admitted to this hospital because of acute confusion and worsening edema. During that admission, ultrasonography of the right upper quadrant was performed.

Dr. Shaunagh McDermott: An image of the right lower lobe of the liver showed a communication between the right portal vein and the right hepatic vein, a finding...
Case Records of the Massachusetts General Hospital

consistent with a hepatic venovenous malformation with portosystemic shunting (Fig. 1).

Dr. Greenwald: A diagnosis of hepatic encephalopathy was made. The confusion improved after the initiation of treatment with lactulose and rifaximin.

On the current admission, medications included warfarin, metoprolol, simvastatin, furosemide, spironolactone, potassium chloride, lactulose, rifaximin, ferrous sulfate, glipizide, metformin, omeprazole, and, owing to enrollment in a clinical trial investigating therapies for pulmonary hypertension, either sildenafil or placebo. The patient had had adverse reactions to azithromycin, lansoprazole, and metolazone. He lived with his wife and was retired from a position in higher education. He did not smoke tobacco, drink alcohol, or use illicit drugs. His parents had died when they were in their 70s; his father had had heart disease, and his mother had had a stroke. His mother and his daughter had a history of recurrent epistaxis and of easy bleeding.

On examination, the patient was somnolent but easily roused by vocal stimulation. He was oriented and cooperative, with waxing and waning attention, and he was uncertain about why he was in the hospital. The temperature was 37.4°C, the blood pressure 141/61 mm Hg, the pulse 103 beats per minute, the respiratory rate 28 breaths per minute, and the oxygen saturation 99% while he was breathing ambient air. The mucous membranes were dry, and dried blood was noted around the nares. There were multiple telangiectasias on the face, lips, and torso, and there were nonblanching cherry angiomas on the chest. The heart sounds were irregularly irregular; the first and second sounds were otherwise normal. The lungs were clear bilaterally. There was mild tenderness in the right upper quadrant, with no rebound or guarding. Bowel sounds were present. There was no abdominal distention, and the edge of the liver was palpable 2 cm below the right costal margin. Testing for Murphy’s sign was negative. No rectal masses were detected on palpation; the stool was brown, with trace blood. There was no asterixis. The legs were dark and discolored, a finding consistent with chronic venous insufficiency. The remainder of the general and neurologic examinations was normal.

Blood levels of total and direct bilirubin, total protein, albumin, globulin, phosphorus, magnesium, calcium, aspartate aminotransferase, alanine aminotransferase, amylase, lipase, and lactic acid were normal, as were levels of vitamin B₁₂ and folate, which had been obtained 1 week earlier; other laboratory test results are shown in Table 1. Urinalysis revealed clear yellow fluid, with a specific gravity of 1.020, a pH of 5.5, and
trace blood; the urine sediment showed 0 to 2 white cells and 0 to 2 red cells per high-power field, 20 to 100 hyaline casts and 0 to 2 granular casts per low-power field, and mucin. Screening of the urine for toxins was negative. An electrocardiogram revealed atrial fibrillation, frequent premature ventricular contractions, ST-segment depression of at least 1 mm in leads II, III, and aVF, and downsloping ST-segment depression of 2 mm in lead V6.

**Dr. McDermott:** A radiograph of the chest showed evidence of persistent interstitial edema and focal opacities in both lower lobes; these findings could represent alveolar edema, superimposed pneumonia, or aspiration. Computed tomography (CT) of the abdomen, performed...

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**Table 1. Laboratory Data.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Adults†</th>
<th>On Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>41.0–53.0 (men)</td>
<td>31.7</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.5–17.5 (men)</td>
<td>10.6</td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>4500–11,000</td>
<td>6600</td>
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<tr>
<td>Differential count (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>40–70</td>
<td>85</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>22–44</td>
<td>9</td>
</tr>
<tr>
<td>Monocytes</td>
<td>4–11</td>
<td>3</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0–8</td>
<td>3</td>
</tr>
<tr>
<td>Platelet count (per mm³)</td>
<td>150,000–400,000</td>
<td>274,000</td>
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<tr>
<td>Red-cell distribution width (%)</td>
<td>11.5–14.5</td>
<td>15.2</td>
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<tr>
<td>Mean corpuscular volume (μm³)</td>
<td>80–100</td>
<td>97</td>
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<tr>
<td>Erythrocyte count (per mm³)</td>
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<td>3,270,000</td>
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<td>Peripheral blood smear description</td>
<td>1+ Hypochromia</td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin time (sec)</td>
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<td>34.0</td>
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<tr>
<td>Prothrombin time (sec)</td>
<td>11.0–13.7</td>
<td>34.4</td>
</tr>
<tr>
<td>Prothrombin-time international normalized ratio</td>
<td>3.4</td>
<td></td>
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<tr>
<td>Sodium (mmol/liter)</td>
<td>135–145</td>
<td>142</td>
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<tr>
<td>Potassium (mmol/liter)</td>
<td>3.4–4.8</td>
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<tr>
<td>Chloride (mmol/liter)</td>
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<tr>
<td>Carbon dioxide (mmol/liter)</td>
<td>23.0–31.9</td>
<td>23.7</td>
</tr>
<tr>
<td>Urea nitrogen (mg/dl)</td>
<td>8–25</td>
<td>41</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.60–1.50</td>
<td>1.74</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (ml/min/1.73 m²)‡</td>
<td>≥60</td>
<td>41</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>70–110</td>
<td>137</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/liter)</td>
<td>45–115</td>
<td>149</td>
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<tr>
<td>Creatine kinase MB isoenzymes</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Troponin I</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Troponin T (ng/ml)</td>
<td>&lt;0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Ammonia (μmol/liter)</td>
<td>12–48</td>
<td>55</td>
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</table>

* 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. To convert the values for ammonia to micrograms per deciliter, divide by 0.5872.

† 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 the patient is black, multiply the result by 1.21.
The administration of oral contrast material, revealed nonspecific pneumatosis of the ascending colon to the level of the hepatic flexure, without associated portal venous gas or other inflammatory changes. Cholelithiasis, atherosclerotic disease of the aorta and mesenteric vessels, and cardiomegaly were also present (Fig. 2).

Dr. Greenwald: Intravenous normal saline, vancomycin, cefepime, and oral potassium chloride were administered, and the patient was admitted to this hospital. On his arrival in the inpatient unit, the dose of rifaximin was increased, warfarin and furosemide were discontinued, and lactulose and other outpatient medications were resumed. On evaluation the next morning, approximately 12 hours after his presentation, the patient was less confused.

Diagnostic tests were performed.

**Differential Diagnosis**

Dr. Robert L. Fogerty: This 73-year-old man with a long and complex medical history presented to this hospital with confusion. Because there are many causes of confusion, one approach to narrowing the differential diagnosis in this case is to first consider common causes of confusion and then look for findings in the patient’s history, physical examination, and initial laboratory testing that are consistent with these causes. In addition to considering common causes of confusion such as medications and infections, we should consider the following three potential clues in this patient’s presentation that may help us to narrow our differential diagnosis: a history of hepatic encephalopathy that is presumably due to a vascular malformation, a history of recurrent epistaxis since childhood with a family history of nosebleeds, and the presence of telangiectasias on physical examination.

**Common Causes of Confusion in an Elderly Patient**

Medication-related changes in mental status are a common cause of confusion. This patient was recently treated with levofloxacin, a fluoroquinolone antibiotic agent that can cause confusion and mental-status changes, especially in older patients. However, this is an unlikely diagnosis in this case, since the patient’s confusion did not begin until after he had already completed his course of therapy.

Infection causing generalized encephalopathy should also be considered in this case. This patient has pneumatosis of the colon on CT and diarrhea, and he is at risk for *Clostridium difficile* colitis because of his recent fluoroquinolone exposure. However, he has a normal white-cell count and no fever, features that argue against a diagnosis of infectious colitis. Although the pneumatosis of the colon needs to be further evaluated, it is a nonspecific finding. I would pursue further testing to investigate the possibility of *C. difficile* colitis, but hepatic encephalopathy remains a more likely cause of this patient’s confusion.

**Hepatic Encephalopathy**

Is this patient’s confusion caused by hepatic encephalopathy? Although he does not have asterixis, the absence of this finding does not rule out a diagnosis of hepatic encephalopathy. He has a history of hepatic encephalopathy, with improvement of associated symptoms after treatment with lactulose and rifaximin and during his current presentation; he also has evidence of a recent nosebleed. Epistaxis often leads to the swallowing of blood, which could explain the presence of trace blood in this patient’s stool. In patients who have a predisposition to hepatic encephalopathy, the swallowing of blood can trigger an episode of acute encephalopathy owing to increased protein ingestion.

One of the unusual features of this patient’s history is the hepatic encephalopathy, which is attributed to portosystemic shunting associated...
with a hepatic venovenous malformation. If we focus on the confirmed abdominal vascular malformation, suspected cerebral arteriovenous malformation, recurrent epistaxis, and telangiectasias, we begin to see a pattern of widely diffuse vascular abnormalities in this patient. Each abnormality could be considered to be a random finding, but the presence of multiple abnormalities in distinct locations suggests the diagnosis of hereditary hemorrhagic telangiectasia (HHT).

**HEREDITARY HEMORRHAGIC TELANGIECTASIA**

Does this patient have HHT? The diagnostic criteria for HHT, which are known as the Curaçao criteria, include recurrent epistaxis, visceral arteriovenous malformations, multiple telangiectasias, and a first-degree relative with HHT.\(^3^,\(^4\)\) Even without a confirmed family history, this patient meets three of the four criteria and would be classified as having a definite diagnosis. An underlying diagnosis of HHT could explain both his confusion and several aspects of his medical history. Recurrent hepatic encephalopathy can occur in patients with HHT despite the presence of normal hepatocellular function, depending on the magnitude of the shunt.\(^5\) Furthermore, pulmonary hypertension, heart failure, and anemia have all been associated with HHT.\(^6^,\(^8\)\)

I would draw special attention to the patient’s personal and family history of epistaxis. This subtle signal can be easily overlooked, but it may be a key clue in the diagnosis of HHT in this case. I wonder whether the family history was obtained orally or through a retrospective chart review. The difference between the two approaches can be profound. Chart review can yield a single word that was buried in a lengthy discharge summary or was automatically populated into a field in the patient's electronic health record. Oral history-taking can offer a detailed account of nosebleeds that have occurred over multiple generations and in multiple family members. With both approaches, the information obtained (e.g., a family history of epistaxis) is the same, but the signal is likely to be much stronger when the information is conveyed orally.

My final diagnosis is hepatic encephalopathy in a patient with HHT. I would confirm this diagnosis with genetic testing.

_Dr. Eric S. Rosenberg_ (Pathology): Dr. Greenwald, what was your clinical impression when you evaluated this patient?

_Dr. Greenwald:_ The patient arrived at the inpatient unit at night and was still quite confused, which limited the history that the admitting house officer was able to obtain. Our initial working diagnosis for the patient’s confusion was acute hepatic encephalopathy precipitated by the swallowing of blood during recurrent epistaxis events, which were associated with a known portosystemic shunt. This patient’s condition was probably exacerbated by several missed doses of rifaximin and lactulose, as supported by the overnight improvement in the patient’s confusion after the reinitiation of these medications.

In addition, the finding of pneumatosis of the colon was very worrisome, and the team immediately discussed the patient’s condition with our colleagues in surgery and radiology. In this multidisciplinary discussion, we agreed that there was an overall low likelihood of an acute intestinal process in this patient, given the nonspecific nature of the findings on abdominal CT, the reassuring results of the abdominal examination, and the absence of fever and leukocytosis. In addition, stool studies were negative for _C. difficile_ toxin.

The next morning, additional information was available. The patient was alert and coherent after receiving lactulose. His wife and daughter were also present and recounted the extensive history of epistaxis in the patient’s daughter and mother. In the light of day, it was obvious that the patient had multiple telangiectasias, which were visible on his torso, face, and lips. We discussed the role of the portosystemic shunt in causing the hepatic encephalopathy. We thought that the patient’s overall presentation might be syndromic, and the house officers raised the possibility of HHT, which we investigated with genetic testing. While awaiting the results of diagnostic testing, we requested that the study drug the patient was taking for the pulmonary hypertension trial be discontinued, since sildenafl could increase the risk of bleeding and worsen shunting.

**CLINICAL DIAGNOSIS**

Hereditary hemorrhagic telangiectasia.

**DR. ROBERT L. FOGERTY’S DIAGNOSIS**

Hepatic encephalopathy in a patient with hereditary hemorrhagic telangiectasia.
The New England Journal of Medicine

DIAGNOSTIC TESTING

Dr. Angela E. Lin: I was asked to assist in the diagnostic evaluation of this patient. When his mental status improved, the diagnostic features of HHT were reviewed with him. The patient was a good historian, and he reliably expanded the family history of nosebleeds beyond his mother and daughter to include his sister and maternal grandmother, great-grandmother, and great-great-grandmother. All except one of these family members had had clinically significant epistaxis and numerous telangiectasias. His mother had died at 71 years of age from a "stroke." He and his sister had pancytopenia that resembled myelodysplasia, which is not a diagnostic feature of HHT but is a finding we have seen in other patients with this syndrome. The patient’s epistaxis, which began during childhood, was recurrent and similar to the epistaxis seen in his daughter, which often resulted in copious bleeding. The telangiectasias ranged from punctate to 2 mm in size and were located on the fingertips, lower eyelids.9 Although a few lesions on his cheek had visible venules, none of them resembled the large spider angiomas that are typically associated with liver failure.10

No single clinical feature of HHT is diagnostic, and several features can masquerade as various other systemic diseases, but the combination of features associated with HHT is distinctive. With this patient’s strong personal and family history (including two first-degree relatives) of epistaxis and with the presence of classic telangiectasias, the diagnosis of HHT was considered to be definite on the basis of the Curaçao criteria.9,11

The patient was offered clinical molecular genetic testing with a multigene panel, which, at that time, tested for mutations in the following three genes involved in the transforming growth factor β–bone morphogenic protein signaling pathway: ENG (also known as HHT1), which encodes the cell-surface coreceptor endoglin; ACVRL1 (previously known as ALK1 and also known as HHT2), another gene encoding a cell-surface receptor; and SMAD4, an intracellular gene that encodes a signaling molecule. Molecular genetic testing now includes tests for mutations in two additional genes (BMP9–GDF2 and RASA1) that are associated with HHT-like phenotypes. SMAD4 mutations are associated with HHT–juvenile polyposis; this is a distinctive genotype–phenotype correlation. In contrast, the other major HHT genes (ENG and ACVRL1) lack unique phenotypic characteristics that would allow for conclusive clinical differentiation. However, several other useful correlations are recognized. For example, as compared with ACVRL1 mutations, ENG mutations are associated with an increased occurrence of arteriovenous malformations involving the lungs or brain. As compared with ENG mutations, ACVRL1 mutations are associated with an increased occurrence of nosebleeds and of arteriovenous malformations involving the liver, as well as with pulmonary hypertension without shunting, late onset of symptoms, and arteriovenous malformations involving the spine. Telangiectasias frequently occur in patients with any of these mutations, and they occur in 100% of such patients who are 40 years of age or older. New mutations are uncommon in both ENG and ACVRL1.11

As we predicted, this patient was heterozygous for a single base substitution in ACVRL1: c.314(−1)G→A at the −1 position. Although this mutation has not been previously reported in the HHT mutation database as a disease-causing allele, other mutations around this splice site are noted to be disease-associated alleles. Since the phenotype seen in this patient and his family was entirely consistent with HHT, the mutation was considered to be causative. The proband (the patient) and his diagnosis established the familial mutation for at-risk relatives, which could be of potential use for prenatal and preimplantation diagnosis. This family-centered approach can be more cost-effective than repeated clinical screening.12 Genetic counseling that focused on the autosomal dominant inheritance of HHT and the 50% risk of recurrence in affected persons was provided.

HHT is characterized by arteriovenous malformation and telangiectasias (which are much smaller cutaneous arteriovenous malformations) that have been attributed to disordered angiogenesis. These pathophysiological features have led to the use of intravenous bevacizumab in trials involving patients with severe hepatic vascular malformations and high cardiac output.13 Epistaxis can be managed through nasal hygiene, procedures to ablate nasal telangiectasias, and treatment with several oral and topical drugs; none of these approaches can provide a complete cure.11 In addition to intravenous bevacizumab,
both bevacizumab nasal spray\textsuperscript{44} and an intranasal injection of bevacizumab\textsuperscript{45} for the treatment of epistaxis have been studied.

**MANAGEMENT AND FOLLOW-UP**

*Dr. Greenwald:* In addition to genetic testing, echocardiography was performed after the injection of agitated saline. The echocardiogram showed late-appearing bubbles on the left side of the heart, a finding consistent with an intrapulmonary shunt. Because the patient had recurrent epistaxis, warfarin was discontinued after discussions of the risks and benefits with the patient and his family.

Over the next 2 years, the patient was monitored at this hospital and at an HHT center at another hospital, where a Young’s procedure to surgically close the nostrils was recommended. He underwent this procedure without difficulty, and his epistaxis improved considerably. The HHT center also recommended that the patient undergo CT angiography of the portahepatic shunt to determine whether closure would be beneficial. Angiography showed that the dominant fistula was surrounded by numerous smaller fistulae that had not been noted on previous imaging studies. It was thought that closure of the dominant fistula might offer a short-term benefit but that the benefit would be quickly lost as the smaller fistulae became dilated. Thus, fistula closure was not pursued.

Over the next several years, the patient was readmitted to the hospital numerous times with upper gastrointestinal bleeding from esophageal and gastric arteriovenous malformations. He had several complications, including ventilator-associated pneumonia, bacteremia, and *C. difficile* infection. For his frequent episodes of upper gastrointestinal bleeding, several therapies, including bevacizumab and thalidomide, were considered. Bevacizumab therapy was not pursued because of the procoagulant effect in the presence of atrial fibrillation no longer treated with warfarin. Thalidomide was not administered because of the family’s concerns about the potential side effects.

Through several of his hospitalizations, the patient worked with our palliative care service to discuss goals of care, especially in terms of his declining quality of life due to frequent admissions to the hospital. During his final hospitalization, he chose to be transferred to a hospice facility, where he died 1 week after discharge from the hospital. An autopsy was performed.

**PATHOLOGICAL DISCUSSION**

*Dr. James R. Stone:* At autopsy, gross examination of the liver showed a nodular pattern on the cut surface (Fig. 3A). Histologic examination revealed diffuse nodular regenerative hyperplasia and multiple vascular malformations that were characterized by enlarged ectatic vascular spaces and an increased number of small vessels, as well as perivascular, sinusoidal, and periductal fibrosis (Fig. 3B, 3C, and 3D).\textsuperscript{16} Three-dimensional reconstruction of liver tissue obtained during autopsy of another patient with HHT has shown direct communications between ectatic sinusoids and arterioles that are consistent with arteriovenous shunts, as well as large and frequent communications between ectatic sinusoids and portal veins that are consistent with portovenous shunts.\textsuperscript{17} In this patient, focal vascular malformations were also identified in the stomach, esophagus, and lungs (Fig. 3E, 3F, and 3G). The stomach contained 970 ml of partially clotted blood, and the small and large bowels were both filled with blood; these findings are indicative of a fatal gastrointestinal bleed. Sudden death due to HHT often results from hemorrhage into the brain, lungs, or gastrointestinal tract.\textsuperscript{18}

The heart was enlarged (weight, 900 g; normal range in a man of this patient’s height, 256 to 510)\textsuperscript{19,20} and showed biventricular hypertrophy and dilatation, bialtrial dilatation, and a thrombus in the left atrial appendage (Fig. 3H). The cardiac changes are consistent with high-output heart failure due to shunting through arteriovenous
malformations. At autopsy, the hearts of patients with heart failure due to HHT are typically enlarged and have ventricular hypertrophy and dilatation.

ANATOMICAL DIAGNOSIS

Vascular malformations in the liver, stomach, esophagus, and lungs that are consistent with hereditary hemorrhagic telangiectasia, complicated by massive gastrointestinal hemorrhage.

This case was presented at Medical Grand Rounds.

Dr. Stone reports receiving consulting fees from GlaxoSmithKline, lecture fees from Alnylam Pharmaceuticals, and fees from USP Labs for expert testimony in a case regarding dimethylamylamine toxicity. No other 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.

We thank Dr. David Kuter for assistance with this case.

REFERENCES


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