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Case Presentations of the Harvard Affiliated Emergency Medicine Residencies

A Case of Bleeding During Infection With COVID-19

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Dr. Patrick Lowe: Our case today is that of a 47-year-old woman who was referred to our emergency department (ED) due to bloody urine, dark tarry stools, red spots on her skin, and bruising throughout her body. Fourteen days prior to presentation, she began exhibiting intermittent fevers, headache, shortness of breath, and a dry cough, and she tested positive for SARS-CoV-2 (the virus that causes COVID-19 pneumonia). Over the 3 days prior to her ED presentation, she experienced a headache that was more intense than the headaches she had been having in the preceding 2 weeks. She reported episodes of both dark urine as well as bright red blood in her urine. In addition, she had multiple dark stools described as tar-like when asked. On the day of her ED presentation, the patient noted a red rash throughout her body. In addition, earlier in the day, she had atraumatic self-limited epistaxis. She denied any falls or head strikes, vision changes, focal weakness or numbness, shortness of breath, chest pain, abdominal pain, or peripheral swelling.

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Keywords—COVID-19; ITP

Dr. Daniel Egan: Does the patient have any personal or family medical history or medications that might be relevant to her presentation?

Dr. Lowe: The patient has anxiety and depression for which she takes escitalopram, propranolol, and trazadone. In addition, she has a history of migraines, for which she takes sumatriptan. She had lung cancer treated with surgical resection 2 decades prior to presentation. In the setting of recent COVID-19 infection and increased headaches, she was taking ibuprofen 800 mg three times most days for the last 2 weeks. She has no personal or family history of known coagulopathies or hematologic disorders. Approximately 1 week prior to being diagnosed with COVID-19, the patient received a SARS-Cov-2 mRNA-based vaccination (BNT162b2; Pfizer-BioNTech) for the first time.

Dr. Kathleen Wittels: Can you describe the physical examination?

Dr. Lowe: On arrival, the patient was normotensive and afebrile with a pulse of 58 beats/min, a respiratory rate of 18 breaths/min, and oxygen saturation of 97% breathing room air. She was well-appearing. Cardiopulmonary examination was significant for a bradycardic rate and regular rhythm without murmur, and breath sounds were clear to auscultation throughout all lung fields. Her abdomen was soft and nontender without organomegaly. Examination of the skin revealed scattered petechiae throughout the trunk, back, and extremities. There were areas of ecchymosis noted on her abdomen, chest, arms, and legs (Figures 1 and 2). Examination of the oropharynx demonstrated petechiae on the hard palate. On neurologic assessment, the patient was alert and oriented with a normal cranial nerve assessment. A complete motor, sensory, and gait assessment were also normal.

Dr. Susan Wilcox: What was on your differential diagnosis?
Dr. Lowe: The patient presented with bleeding from multiple sites, including possible upper and lower gastrointestinal bleeds, bleeding along the urinary tract, and self-resolved epistaxis. Her skin examination demonstrated both petechiae and ecchymoses. These symptoms were in the context of both COVID-19 vaccination and subsequent infection. Our differential diagnosis for the patient’s bleeding symptoms and rash included acquired and congenital coagulopathies and infectious etiologies. We considered thrombocytopenic disorders, including idiopathic, as well as SARS-CoV-2–associated immune thrombocytopenia (ITP) and thrombotic thrombocytopenia purpura. Recent administration of the SARS-CoV-2 vaccine raised suspicion for vaccine-induced immune thrombocytopenia. The patient had not been exposed to heparin or other new medications, making heparin- or drug-induced thrombocytopenia unlikely. Acquired coagulopathies including acute hepatic failure in the setting of viral infection, vitamin deficiency, and disseminated intravascular coagulopathy were all considered. In the absence of diarrheal disease, hemolytic uremic syndrome associated with *Escherichia coli* infection was thought to be unlikely. Other viral infectious etiologies, such as hepatitis viruses and Epstein-Barr virus, were considered. Although endemic in our region, she had no known recent tick bites to suggest zoonotic disease like babesiosis or ehrlichiosis. She had not traveled to any region with risk of Rocky Mountain spotted fever transmission. Congenital coagulation factor deficiencies were deemed unlikely in the absence of familial history or prior bleeding complications in the patient. The patient’s frequent use of nonsteroidal anti-inflammatory ibuprofen may have exacerbated or caused an upper gastrointestinal bleed. Given the clinical context, her hematuria was thought to be secondary to a primary hematologic process. Urinary tract infection and nephrolithiasis were considered less likely in the absence of typical symptoms. The patient had no chest pain or respiratory symptoms and was not tachycardic or hypoxic, lowering concerns for other thrombotic pathology such as acute myocardial infarction or pulmonary embolism.

The change in the patient’s headache raised concern for thrombotic and hemorrhagic pathology, including cerebral venous sinus thrombosis and intracranial hemorrhage, especially intraparenchymal hemorrhage in the setting of signs of bleeding and presumed coagulopathy.

Dr. Egan: Can you describe your initial management and workup of this patient?

Dr. Lowe: On arrival, the patient was hemodynamically stable and displayed no signs of ongoing bleeding that required emergent intervention prior to pursuing laboratory and imaging evaluation. Laboratory studies were notable for normal white blood cell count, a normocytic anemia with hemoglobin of 11.3 g/dL (reference range [RF] 11.6–16.5 g/dL) and mean corpuscle volume 94.3 fL (RF 80–100 fL). Platelet count was 1000/µL (RF 150,000–450,000/µL). Reticulocytes were measured at 1% (RF 0.7–2.5%). Blood smear did not reveal schistocytes. The prothrombin time was 12.2 s (RF 11.5–14.5 s), international normalized ratio was 0.9 (RF 0.9–1.1), and partial thromboplastin was 29.7 s (RF 23.8–36.6 s). The
fibrinogen level was 430 mg/dL (RF 200–450 mg/dL), D-dimer was 1366 ng/mL (RF < 500 ng/mL), lactate dehydrogenase was 276 U/L (RF 135–225 U/L), folic acid was > 20 ng/mL (RF > 4 ng/mL), and vitamin B-12 level was 931 pg/mL (RF 232–1245 pg/mL). Electrocardiography revealed sinus bradycardia without evidence of heart block or ischemia and the high-sensitivity cardiac troponin was not elevated. Urinalysis revealed 3+ blood. A computed tomography (CT) scan of the brain was performed without evidence of bleeding and a CT venogram did not reveal any thrombosis. The patient was consented to receive blood products and the blood type and screen were obtained.

Given the concern for ITP, hematology consultation was obtained. After discussion of the case and their bedside evaluation of the patient, the decision was made to treat for presumed ITP with dexamethasone 40 mg, as well as intravenous immunoglobulin (IVIG) 1 g/kg. Two units of platelets were transfused.

**Dr. Wittels:** What is ITP?

**Dr. Lowe:** ITP is an autoimmune disease caused by destruction of platelets leading to a platelet count < 100,000/µL (1). Although congenital forms of the disease exist, acquired ITP often arises in the setting of some inciting factor. Common triggers include a variety of medications (commonly heparin, antibiotics, and antiepileptics), pregnancy, other autoimmune disorders, malignancy, and infection (2). Viral infection by human immunodeficiency virus, hepatitis C virus, cytomegalovirus, Zika virus, and others have been associated with ITP and the mechanism is thought to be due to cross-reactivity of antiviral antibodies against surface platelet antigens (3). SARS-CoV-2, the virus responsible for causing COVID-19 pneumonia, has similarly been noted to induce thrombocytopenia in infected patients (4,5). Some vaccines for SARS-CoV-2, including Ad26.COVID2.S (Janssen/J&J) and ChAdOx1 nCoV-19 (Oxford-AstraZeneca), have been associated with rare clotting manifestations (such as peripheral venous thrombosis and cerebral venous sinus thrombosis) and thrombocytopenia, a condition termed vaccine-induced thrombotic thrombocytopenia (VITT) (6–9). Although the mechanism of VITT is not yet known, the same vaccine-induced anti–SARS-CoV-2 antibodies that are intended to target viral spike protein may also cross-react with native platelet surface antigens (10). Our patient had recently received the BNT162b2 vaccine (Pfizer-BioNTech), which has been associated with rare non-thrombotic thrombocytopenic events (11).

**Dr. Wilcox:** How do patients with ITP present to the ED?

**Dr. Lowe:** Patients with ITP will often present to the ED manifesting signs and symptoms related to the low platelet count. History may include gingival bleeding with teeth brushing, epistaxis, and easy bruising. Patients may report hematemesis, hematochezia, hematuria, hemoptysis, and menorrhagia, which should prompt the ED clinician to evaluate for evidence of significant or ongoing blood loss. Headache or neurologic deficits may be a sign of intracranial hemorrhage, a risk that increases with age and lower platelet counts at presentation (12). Physical examination findings may include tachycardia and hypotension if blood loss is significant. With or without trauma, evidence of soft-tissue bleeding manifested as ecchymoses or hematomas may be present. Hemarthroses may cause painful joint swelling. Examination of the skin and mucosal surfaces may demonstrate petechiae and purpura, with oral purpura associated with increased risk of additional life-threatening hemorrhage (13). Laboratory analysis will reveal thrombocytopenia and may show anemia if the patient has had any associated hemorrhage initiated. The ED clinician must have a high level of suspicion for injury when these patients experience trauma and have a low threshold to evaluate with imaging.

**Dr. Egan:** How is ITP treated?

**Dr. Lowe:** The treatment of ITP is based on the risk of bleeding (14). Patients without bleeding or only minor bleeding (e.g., mucous membranes or skin) may be discharged without acute treatment or observed with serial examinations and laboratory studies. Those with active bleeding or at risk for severe bleeding are considered for treatment to reduce platelet destruction. Treatment includes systemic steroids (e.g., dexamethasone 40 mg i.v. or prednisone 1 mg/kg daily for 1–2 weeks, followed by a tapered course) and IVIG (1 g/kg). If platelets fail to rise in response to steroids and IVIG, the anti-CD40 agent rituximab or thrombopoietin-stimulating agents may be considered in the inpatient setting (2,15). Platelet replacement therapy with donated platelet transfusion may be considered in the setting of severe life-threatening hemorrhage, including central nervous system hemorrhage, or when other therapies have failed (15). Transfused platelets may be targeted for destruction by already present antiplatelet antibodies and transfusion with initiation of anti-inflammatory treatment, such as steroids or IVIG may occur concurrently (15). Resuscitative interventions with i.v. fluids or packed red blood cells, vasopressors, and more may be indicated if the patient is hemodynamically unstable. Treatment of the precipitating disorder or removal of inciting medication should also be pursued.

**Dr. Wittels:** What was the remainder of the patient’s hospital course?

**Dr. Lowe:** After initiation of steroids, IVIG and 2 apheresis units of platelets in the ED, the platelet count rose from 1000/µL to 6000/µL. The patient was admitted to the hematology service, received dexamethasone 40 mg daily for 3 days, IVIG 1 g/kg daily for 2 days, and a total of 3 units transfused platelets. On the third hospital day, the patient’s platelet count rose to 116,000/µL.
and on follow-up after discharge 1 week after her ED presentation had reached a normal range at 252,000/µL 1 week after presentation. Viral workup did not reveal infection other than the previously documented SARS-CoV-2 infection. Testing for the anti-heparin PF4 antibodies, a proposed causative antibody in SARS-CoV-2 vaccine–induced immune thrombotic thrombocytopenia, was negative (10). During her hospitalization, the patient continued having headache and received i.v. magnesium and metoclopramide. Repeat neuroimaging with both CT and magnetic resonance imaging were negative for acute pathology, including hemorrhage and thrombosis.

Dr. Wilcox: What are the key take-home points of this case?

Dr. Lowe: ITP can have a variety of inciting causes as well as presentations. In the era of the SARS-CoV-2 pandemic, COVID-19 infection has been identified as a possible viral cause of ITP, as was likely in this patient. A patient’s presentation is often prompted by signs and symptoms of bleeding, including minor bleeding of the skin, mouth, or nose, as well as major bleeding along the gastrointestinal, genitourinary, and pulmonary tracts. Rapid evaluation of hemodynamic stability and management of life-threatening bleeding, such as intracranial hemorrhage, is warranted. Treatment includes immunosuppression with systemic steroids and IVIG, as well as transfusion of platelets when indicated. Rapid recovery of platelet count, as in our patient, may occur shortly after initiation of treatment and removal of triggers (e.g., resolution of viral infection or removal of offending drug).

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