A previously healthy 13-year-old boy was transferred 2 months ago to our hospital for evaluation of pancytopenia and a sacrococcygeal abscess. His mother reports that 3 months prior to his admission, while visiting his family in Puerto Rico, he developed 2 days of fever, myalgias, bone pain, and swelling of his ankles and elbows. He was seen in an emergency department there and complete blood count (CBC) revealed hemoglobin of 12.9 g/dL, white blood cell count of 3,700/mm$^3$ with 62% neutrophils, 33% lymphocytes, and platelet count of 200,000/mm$^3$. He was discharged and given naproxen and his symptoms resolved.

Two months after his visit to the emergency department in Puerto Rico, he developed a fever of 103°F and pharyngitis. Although Group A streptococcal testing was negative, he was treated with 10 days of oral amoxicillin. His fevers continued throughout this antibiotic course, during which time he started complaining of buttock pain. His mother noted a “hard circle” on his right buttock. He was seen by his primary care physician, a sacrococcygeal abscess was diagnosed, and he was admitted to a local hospital. His mother reported a 15-lb. weight loss in the boy over the previous 3 months. On admission, CBC was notable for pancytopenia hemoglobin of 5.8 g/dL, white blood cell count of 1,200/mm$^3$, and platelet count of 200,000/mm$^3$. He was discharged and given naproxen and his symptoms resolved.

Shortly after transfer, CBC revealed hemoglobin of 9.5 g/dL, white blood cell count of 4,100/mm$^3$ with 69% neutrophils, 25% lymphocytes, no blasts, and platelet count of 223,000/mm$^3$. Blood chemistries were normal except for albumin of 2.7 mg/dL. Neopterin was markedly elevated and serum ferritin was 835 ng/mL (normal is 24-354 ng/mL).

Robert Listernick, MD, moderator: Can leukemia be missed on bone marrow examination?

Elaine Morgan, MD, pediatric oncologist: We can’t make a diagnosis of leukemia if we don’t see blasts in the bone marrow or an extramedullary site. Pancytopenia may be seen in numerous other conditions such as infections, or rheumatologic diseases such as systemic lupus erythematosus.

Dr. Listernick: Have you seen false-positive bone marrow examinations (ie, specimens that look like leukemia that turn out not to be leukemia)?

Dr. Morgan: We have definitely seen children who have had leukemia go into spontaneous remission, usually as a result of a severe infection, only to reemerge later.

Dr. Listernick: Is it important to perform both a bone marrow biopsy as well as an aspirate?

Robert Liem, MD, pediatric hematologist: Particularly in the context of a
child with pancytopenia who may have aplastic anemia, the biopsy is extremely important in assessing cellularity.

**Dr. Listerick:** In the absence of malignancy, the treating physicians considered alternate diagnoses. There was no evidence of rheumatologic disease; in particular, for lupus, antinuclear antibodies, anti-double stranded DNA, and complement levels were normal. The diagnosis of inflammatory bowel disease was entertained because of the sacrococcygeal abscess.

**Barry Wershil, MD, pediatric gastroenterologist:** Pancytopenia is extremely uncommon as a component of the presentation of inflammatory bowel disease (IBD), and is more commonly encountered as a complication of drug therapy, as with azathioprine, or severe infection from immunosuppression. He has a subcutaneous abscess, but I’ve heard no information that it’s a fistula involving the bowel as might be seen in Crohn’s disease.

**Dr. Listerick:** He had computed tomography scans that only showed the subcutaneous abscess. I suppose magnetic resonance enterography would be most sensitive for detecting small fistulae that one might see in Crohn’s disease. I noticed that the treating physicians sent a fecal calprotectin.

**Dr. Wershil:** Calprotectin is a neutrophilic protein found in the stools of individuals who have intestinal inflammation and is most commonly elevated in the setting of infectious gastroenteritis or IBD. It has been used to help differentiate irritable bowel syndrome from IBD, but there are still some false positives. A negative stool calprotectin strongly argues against IBD.

**Dr. Listerick:** I guess we have to comment on the ferritin and neopterin.

**Dr. Liem:** Right off the bat, they apparently were concerned about the possibility of hemophagocytic lymphohistiocytosis (HLH). Not unreasonable in a child with pancytopenia and splenomegaly, HLH is basically a multi-system inflammatory disorder in which the patient has a dysregulated immune system. It can be primary due to mutations in a number of regulatory genes or secondary to any number of infections, malignancies (particularly leukemia), or rheumatologic conditions (particularly systemic-onset juvenile idiopathic arthritis). Despite the elevated ferritin and neopterin, he doesn’t have enough criteria to establish this diagnosis.

**Dr. Listerick:** Moving forward, he was discharged to receive close outpatient follow-up. Within 1 week post-discharge, he felt completely well, back to baseline. Six weeks later, he developed right knee pain, and swelling and erythema over several metacarpal-phalangeal joints and a temperature of 107°F. His doctor prescribed ibuprofen and prednisone over the phone. Although the arthritis resolved the following day, he developed right upper quadrant pain and fever to 101°F.

On admission, he looked ill. His pulse was 120 beats per minute, and his blood pressure was 137/96 mm Hg. He had scleral icterus. His heart examination was normal. His spleen was palpable 3 cm below the left costal margin. The remainder of the examination was unremarkable.

Pertinent laboratory tests included albumin of 2.8 mg/dL, total bilirubin of 6.1 mg/dL, direct bilirubin of 4.9 mg/dL, alkaline phosphatase of 357 IU/L, alanine aminotransferase of 408 IU/L, aspartate aminotransferase of 565 IU/L, gamma-glutamyl transferase of 202 IU/L, ferritin of 28,000 ng/mL, and elevated soluble interleukin-2 receptor. Hemoglobin was 10.2 g/dL, white blood cell count was 700/mm³ with 97% lymphocytes, and platelet count was 30,000/mm³. Bone marrow examination and lumbar puncture revealed central nervous system positive B-cell lymphocytic leukemia.

He was started on prednisone but before further therapy could be instituted, he developed increasing amounts of blood-streaked diarrhea. Polymerase chain reaction (PCR) testing of the stool was positive for the presence of the gene for *Clostridium difficile* toxin B. He was treated with oral metronidazole. However, he developed progressive abdominal pain, hematochezia, and blood clots in the stool. He had ongoing thrombocytopenia and coagulopathy despite aggressive volume resuscitation and transfusions of whole blood and fresh frozen plasma. Because of progressive abdominal distention and the development of signs of peritonitis, he was taken to the operating room.

Let’s start from the beginning. Why couldn’t we establish the diagnosis of leukemia initially?

**Dr. Morgan:** For whatever reason, he was pre-leukemic 2 months ago. The body works in mysterious ways.

**Dr. Listerick:** Forgetting about the rest of his illness and his liver disease for the moment, what would be his prognosis?

**Dr. Morgan:** To answer that question, I ideally would like to have the genetic studies of the lymphoblasts that we receive several weeks following diagnosis. He is high risk simply based on his age. At worst, his long-term disease-free survival is 75% to 80%.
Dr. Listernick: On admission, he had *C. difficile* colitis?

Caroline Reuter, MD, pediatric infectious disease specialist: Not necessarily. The test we perform here is PCR, which identifies the *C. difficile* toxin-producing gene. This test has close to 99% sensitivity for detecting toxin-producing organisms. Previously, we performed an assay that identified the toxin itself. However, the highly sensitive PCR assay also identifies individuals who are colonized with a toxin-producing organism; the results need to be interpreted in the context of the patient’s symptoms and signs. This is analogous to Group A streptococcal testing, which may represent pharyngeal colonization rather than infection. It was reasonable to start treatment with metronidazole in this immunocompromised child at the beginning of his course.

Dr. Wershil: That’s a very important point. Before ordering this test, you need to make a careful clinical assessment and have an understanding of the population at risk. Diarrhea (with or without blood) is the most common presentation of *C. difficile* colitis, and clinical suspicion should be particularly high in patients with prior antibiotic exposure, on chemotherapy, or repeated hospitalizations, although community-acquired disease accounts for more than 25% of all cases. You do not want to do this type of testing on every patient who presents with what appears to be an acute gastroenteritis or in infants younger than age 1 year with diarrhea because they don’t express the receptor(s) for the *C. difficile* toxins and will not develop disease even with bacterial colonization.

Dr. Listernick: What is reasonable treatment for *C. difficile* colitis?

Dr. Reuter: First-line treatment is oral metronidazole because you get good intraluminal concentration of the antibiotic. If the child remains symptomatic or worsens, we generally recommend oral vancomycin followed by intravenous vancomycin for the sickest children. There are ongoing trials with newer antibiotics such as fidaxomicin and tigecycline.

Dr. Listernick: What about fecal transplants?

Dr. Wershil: It is believed that perturbations in intestinal microbiome allow *C. difficile* to flourish and produce toxins. Fecal microbiota transplantation (FMT) replaces “good” bacteria and re-establishes a balanced microbial environment. FMT is extremely effective for patients with recurrent *C. difficile* colitis with a response rate greater than 90%, but is not used in the acute setting.

Dr. Listernick: Are there any risks to the procedure?

Dr. Wershil: FMT was first reported in 1958, but has been more commonly used as a safe and effective treatment for recurrent *C. difficile* colitis over the past decade. Investigation of the microbiome has exploded over this period of time, and there are numerous lines of evidence suggesting that the microbiome plays a significant role in human health and diseases as diverse as autoimmunity, diabetes, heart disease, and obesity. This emerging concern that FMT may carry unknown risks over the course of a lifetime led the US Food and Drug Administration (FDA) to declare it an investigational new drug (IND) requiring a federal application to perform. However, there was an outcry from the medical community that this was too harsh a restriction. Ultimately, the FDA ruled to allow FMT for recurrent *C. difficile* without an IND, but requiring informed consent.

Dr. Listernick: So, why was he taken to the operating room and what was found?

Sifrance Tran, MD, pediatric surgeon: This was a very challenging situation. Although he initially had bloody diarrhea, this rapidly progressed to large amounts of frank blood. Despite replacement with blood and coagulation factors, he remained quite ill with persistent abdominal pain, bleeding and lactic acidosis. We weren’t sure from where the bleeding was coming. A naso-
gastric tube was inserted and the stomach was irrigated but there was no blood return. Although this didn’t exclude the possibility of duodenal bleeding, we thought the bleeding was most likely lower down, perhaps even in the colon.

Dr. Wershil: I’d like to add that emergent colonoscopy has almost no role in this setting. Isolated colonic bleeding sites are rare in pediatric patients and almost impossible to find in an unprepped colon with active hemorrhaging. In addition, the risk of perforation in this setting is high.

Dr. Listernick: Could any radiographic study be helpful in identifying the site of bleeding?

Ellen Benya, MD, pediatric radiologist: First, the patient would have to be stable enough to come to the medical imaging suite, which I don’t believe this child was. As far as angiography, the bleeding would have to be fairly brisk for us to see it, at least 1 cm²/min if not faster. For slower bleeds, tagged red blood cell imaging might be helpful because we image continuously for 1 hour then get delayed images at 3, 6, and 24 hours. Once again, the child would have to be stable.

Dr. Listernick: So what did you find at surgery?

Dr. Tran: We thought we would find a necrotic colon secondary to severe C. difficile colitis. Instead, we discovered patchy, ischemic ulcers throughout the mesentery and the length of the ileum. The bleeding appeared to be arising from these ulcers. We resected the abnormal ileum segments and performed a subtotal colectomy and ileostomy.

Dr. Listernick: Can we see the pathology please?

Lily Marsden, MD, pediatric pathologist: The inflammatory erosions are very patchy throughout the colon and ileum. These erosions had necrotic debris without any inflammatory cells. This is not consistent with C. difficile colitis in which we would see a diffuse process throughout the colon without “skip lesions.” We also identified a monotonous lymphoid infiltrate in the muscle and submucosa of the bowel as well as the adjacent lymph nodes. Immuno-histochemical staining proved these to be immature lymphoid cells consistent with the child’s diagnosis of acute lymphocytic leukemia.

Dr. Listernick: One aspect we haven’t yet discussed is his liver disease. At this point, he has normal serum transaminases and alkaline phosphatase but his total bilirubin is 31 mg/dL with a direct bilirubin 24 mg/dL. I don’t understand.

Estella Alonso, MD, pediatric hepatologist: We see these types of values in ischemic liver disease in which the pathology is central lobular injury to the liver. Given his severe illness with high fever, lactic acidosis, and disseminated intravascular coagulation, it wouldn’t be surprising if he had ischemic liver injury. As the liver heals, the serum transaminases normalize. However, regenerating hepatocytes are not efficient at excreting conjugated bilirubin and so the child becomes icteric. Admittedly, these values are quite high. Perhaps his kidneys also suffered some degree of ischemia and are not able to excrete conjugated bilirubin. These are the best explanations I have.

Dr. Morgan: Although I did give him some additional chemotherapy before he went to the operating room, I can’t treat his leukemia, save for giving prednisone, until his bilirubin returns to much lower levels. There’s a 30% complete remission rate using steroids alone. It appears that his blood counts are slowly beginning to improve. Hopefully, his bleeding will diminish.

Dr. Listernick: Agreed. Thank you, everyone.