An 8-year-old boy with no significant past medical history presented to his pediatrician with 5 days of fever, diffuse abdominal pain, and pallor. The pediatrician referred the patient to the emergency department (ED), out of concern for possible malignancy. Initial vital signs indicated fever, tachypnea, and tachycardia. Physical examination was significant for marked abdominal distension, hepatosplenomegaly, and abdominal tenderness in the right upper and lower quadrants. Initial laboratory studies were notable for pancytopenia as well as an elevated erythrocyte sedimentation rate and C-reactive protein. Computed tomography (CT) of the abdomen and pelvis showed massive splenomegaly. The only significant history of travel was immigration from Albania 10 months before admission. The patient was admitted to a tertiary care children’s hospital and was evaluated by hematology–oncology, infectious disease, genetics, and rheumatology subspecialty teams. Our multidisciplinary panel of experts will discuss the evaluation of pancytopenia with apparent multiorgan involvement and the diagnosis and appropriate management of a rare disease.
immunodeficiency, autoimmune diseases, cancers, or metabolic disorders.

Initial laboratory studies revealed pancytopenia (white blood cell count $1.4 \times 10^3$ per µL, absolute neutrophil count 900), hemoglobin 7.2 g/dL, platelet count $64 \times 10^3$ per µL, mean corpuscular volume 78.9 fL) (Table 1) as well as elevated inflammatory markers (erythrocyte sedimentation rate: 74 mm per hour, C-reactive protein: 6.84 mg/dL). Point-of-care finger-stick hemoglobin done by our patient’s pediatrician 2 months before presentation was normal, suggesting acute onset of anemia. Reticulocyte count was 89.9, with a slightly elevated percentage of 3.6%. The metabolic profile, bilirubin, lactate dehydrogenase, and uric acid levels were normal.

A CT scan of his abdomen and pelvis revealed a liver size within normal limits and marked splenomegaly ($24 \times 16 \times 5$ cm). Although the CT showed displacement of the bowel by the enlarged spleen, the bowel and appendix were normal, with no signs of neutropenic colitis or appendicitis and no lymphadenopathy. Chest CT revealed mild to moderate pleural effusions and 3-mm calcified granuloma within the left upper lobe of the lung (Fig 1) without any lymphadenopathy.

In the setting of fever and neutropenia, a blood culture was drawn, and cefepime was initiated to provide empirical coverage for potential bacteremia. Hematology–oncology was consulted because of the patient’s pancytopenia and massive splenomegaly. Dr Rahmani, given the physical examination and laboratory findings, are you concerned about a primary hematologic or oncologic process at this point?

**DR RAHMANI (PEDIATRIC HEMATOLOGIST–ONCOLOGIST)**

Given our patient’s fever, splenomegaly, and pancytopenia, I am concerned about acute lymphoblastic leukemia (ALL), the most common hematologic malignancy in children and adolescents. Fever can be caused by ALL itself or in the setting of an opportunistic infection, both of which can result in elevated inflammatory markers. Leukemic infiltration of the liver and spleen results in hepatosplenomegaly, and replacement of bone marrow with leukemic lymphoblasts results in pancytopenia. In our patient, the absence of lymphadenopathy, as noted in half of patients with ALL, does not narrow the differential.

Given the high suspicion for leukemia,

<table>
<thead>
<tr>
<th>TABLE 1 Initial Laboratory Evaluation: Admission, 24 Hours After Beginning Treatment and After Completion of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBC count (4.5–13.5), k/µL</strong></td>
</tr>
<tr>
<td><strong>Hemoglobin (12.0–14.4), g/dL</strong></td>
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<tr>
<td><strong>Hematocrit (35–40), %</strong></td>
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<tr>
<td><strong>Platelet count (150–400), k/µL</strong></td>
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<tr>
<td><strong>Mean corpuscular volume (77–95), fl</strong></td>
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<tr>
<td><strong>Red cell distribution width (11.5–13.4), %</strong></td>
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<tr>
<td><strong>Mean corpuscular hemoglobin concentration (31–37), g/dL</strong></td>
</tr>
<tr>
<td><strong>RBC count (4.00–5.20), MIL/µL</strong></td>
</tr>
<tr>
<td><strong>Neutrophil count (1.5–8.0), k/µL</strong></td>
</tr>
<tr>
<td><strong>Lymphocyte count (1.5–6.0), k/µL</strong></td>
</tr>
<tr>
<td><strong>Monocyte count (0.3–0.5), k/µL</strong></td>
</tr>
<tr>
<td><strong>Eosinophil count (0.1–0.3), k/µL</strong></td>
</tr>
<tr>
<td><strong>Spleen size</strong></td>
</tr>
</tbody>
</table>

LLQ, left lower quadrant; MIL, millions.

**FIGURE 1**

A and B, CT scan of the abdomen without contrast. There is marked splenomegaly ($24 \times 16 \times 5$ cm). Spleen is heterogeneous in appearance with ill-defined areas of low density scattered throughout the spleen. This is a non-specific finding. The liver is not enlarged. There is no peritoneal or pelvic fluid. The gallbladder is not enlarged. The bowel is displaced medially and inferiorly by the spleen, but the intestines and mesentery are normal. The appendix is normal. There is no abdominal or pelvic lymphadenopathy. There are small to moderate pleural effusions with subsegmental atelectasis at the lung bases and posteriorly in the lungs.
a bone marrow aspirate and biopsy should be obtained because they are the most sensitive and definitive tests to diagnose leukemia and allow for histologic review. One may also consider other diagnoses that occur in this age group, such as Langerhans cell histiocytosis or lymphomas and, although rare, primary hepatic malignancies, including hepatoblastoma and hepatocellular carcinoma.4

Pancytopenia can also be caused by inherited or acquired bone marrow failure syndromes, although these are not typically associated with splenomegaly. Inherited or congenital causes typically present in the first few years of life, and our patient has been previously healthy. Our patient lacks classic features of bone marrow failure syndromes, including dyskeratosis congenita (skin pigmentation, nail dystrophy, and mucosal leukoplakia),3 Fanconi anemia (musculoskeletal malformations),2 and Shwachman-Diamond syndrome (neutropenia and exocrine pancreatic dysfunction).2

Acquired bone marrow failure in children is most commonly caused by medications, chemicals, or infections. The most frequently implicated medications include chemotherapeutics and antiepileptic drugs, although antibiotics and nonsteroidal anti-inflammatory drugs can also trigger marrow suppression and secondary pancytopenia. Infectious causes include hepatitis, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and HIV, which may be associated with hepatosplenomegaly. Drug exposure was not reported with our patient and was not a concern, although an infectious etiology explaining pancytopenia is quite possible.

Finally, pancytopenia can also be caused by peripheral destruction or splenic sequestration of blood cells; these may occur in the setting of malignancy, infection, hepatic disease, autoimmune disorders, and certain genetic disorders, such as lysosomal storage diseases (LSDs).2 The latter 3 diagnoses are not likely given the negative family history of autoimmune and genetic disorders.

DR OFFENBACHER
Because the patient’s presentation was highly concerning for acute leukemia, we initiated precautions for tumor lysis syndrome, including hyperhydration (1.5 cc per hour maintenance fluids) and allopurinol. However, the patient’s bone marrow evaluation did not reveal a malignant infiltrative process and, in fact, demonstrated normal trilineage hematopoiesis. Consistently, flow cytometry and peripheral smear were unable to identify any leukemic lymphoblasts. Thus, a leukemic process was ruled out, and allopurinol and hyperhydration were discontinued.

Given the absence of leukemic infiltration in the bone marrow and the presence of normal trilineage hematopoiesis, our differential shifted to focus on other etiologies of pancytopenia. We considered infectious etiologies, hepatic sources, rheumatologic causes, and metabolic disorders. Dr Joseph, what infectious etiologies would you consider in a patient who is persistently febrile with pancytopenia and splenomegaly?

DR JOSEPH (PEDIATRIC INFECTION DISEASE)
When concerned for an infection in the setting of neutropenia, we should determine if underlying neutropenia is the risk factor for infection or if the infection is causing the neutropenia. Because we have already determined that a malignancy or primary immunodeficiency is unlikely in this patient, we can focus on infectious causes of neutropenia. The neutropenia could be caused by viral suppression of the bone marrow (like EBV, CMV, or parvovirus), or by bone marrow or spleen infiltration.

Although the most recent travel history was 10 months ago, we should also consider typical pathogens that cause fever in a recent immigrant or returned traveler and of course be aware of those exposures specific to Albania. Of the infections endemic to this region, those that cause fever, splenomegaly, and pancytopenia include tuberculosis, malaria, visceral leishmaniasis (VL), and brucellosis.

Disseminated tuberculosis can cause infiltration of the bone marrow, liver, and spleen. Although only 0.5% to 3% of children develop symptomatic lymphohematogenous spread of tuberculosis,5 given our international patient’s significant presentation, it must be worked up. This progression can present months after the initial infection, but it can also remain occult and present even later during acute stress. Tuberculous bacilli can infiltrate the liver, spleen, and bone marrow, as well as skin, lungs, kidneys, heart, and brain. Despite the severity and the widespread dissemination of the infection, timely treatment is usually successful in an immunocompetent host.5

Malaria can present with nonspecific symptoms in children and should be considered in any child with a febrile illness in the context of appropriate exposure.5 For our patient in particular, I would be concerned for hyperreactive malarial splenomegaly, a chronic stimulation of the immune system thought to be related to chronic malaria exposure.6 The syndrome results in massive hepatosplenomegaly, anemia, and often thrombocytopenia and neutropenia; therefore the risk of secondary bacterial infections can be significant.6 Although malaria is uncommon in Albania, there have been several cases reported of Plasmodium falciparum, ovale, and vivax; the latter 2 can remain asymptomatic in the liver for months,
making his travel 10 months before presentation pertinent.

Leishmaniasis is a protozoal, vector-transmitted infection that is currently endemic to India, Africa, the Middle East, South America, and the Mediterranean, therefore making the diagnosis of VL a possibility in our patient. Patients typically present with fever, notable hepatosplenomegaly, and bone marrow suppression due to proliferation of parasites and infected macrophages throughout the spleen, liver, and bone marrow. 

parasites may be visible on bone marrow examination, but the sensitivity is 60% to 85% and it cannot morphologically distinguish between species. Therefore, when there is high suspicion for VL, testing should be performed by the Centers for Disease Control and Prevention by using serology and molecular testing on serum and bone marrow. 

The incubation period of Leishmania parasites can be as long as several years, so although our patient immigrated from Albania 10 months ago, he is still at risk.

In the setting of any patient with prolonged fevers, occult brucellosis should be considered in the absence of an alternative source. Brucellosis is a bacterial zoonotic infection and is particularly endemic to the Mediterranean basin, including Albania. 

Foodborne sources (eg, unpasteurized milk and cheese) and direct contact with infected animals are the primary modes of transmission; our patient did not endorse these specific exposures. The most common presentation of localized brucellosis is osteoarticular involvement, but it can present with splenomegaly and cytopenias. Significant complications can include neurobrucellosis and endocarditis.

Finally, HIV can alter your immune system and cause myelosuppression, and testing would be useful as many organisms could manifest as opportunistic infections in HIV patients, with a fulminant course.

**DR OFFENBACHER**

Appropriate testing for malaria, brucellosis, leishmaniasis, HIV, and tuberculosis was sent. Microscopic examination of the bone marrow did not reveal fungi or Leishmania parasites. In addition, the result from a peripheral smear was negative for malaria parasites and plasmodium antigens. HIV testing for HIV p24 antigen and antibodies to HIV type 1 and/or type 2 were nonreactive. Blood cultures did not show growth of Brucella. The screening and diagnosis of tuberculosis were evaluated by using an interferon-γ release assay as well as an acid-fast bacterial (AFB) blood culture. The interferon-γ release assay results were indeterminate because of failure of the positive control, and the AFB blood culture showed no organisms on initial smear and was incubated for 6 weeks with no growth. EBV and CMV serum polymerase chain reactions (PCRs) returned and were nonreactive. To further evaluate his prolonged fever of unknown origin, an echocardiogram was performed, which showed no intracardiac vegetation suggestive of endocarditis.

Dr Rahmani, how else can you explain pancytopenia in a patient with normal trilineage hemapoiesis in the marrow?

**DR RAHMANI**

With a normal bone marrow evaluation and no obvious infection, the etiology of pancytopenia is likely secondary to splenomegaly, or splenic sequestration of peripheral blood cells. Congestive splenomegaly can result from splenic vein thrombosis or any entity that increases hepatic venous pressure, such as liver disease, portal hypertension, and congestive heart failure. Therefore, an evaluation of blood flow through the portal vein should be examined via Doppler ultrasound.

When considering splenomegaly in the setting of a febrile patient with pancytopenia, it is important to consider hemophagocytic lymphohistiocytosis (HLH), an uncommon but life-threatening disorder of severe uncontrolled activation of the immune system. Patients are generally considered to have HLH if they fulfill 5 of the following 8 criteria: (1) fever ≥38.5°C, (2) splenomegaly, (3) cytopenias affecting 2 lineages in the peripheral blood (hemoglobin <9 g/dL, platelets <100 g/dL, neutrophils <1 × 10^9/mL), (4) hypertriglyceridemia (fasting, >265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL), (5) hemophagocytosis in the bone marrow, (6) low or absent NK cell activity; (7) hyperferritinemia >500 ng/mL, and (8) high levels of sCD25 (soluble interleukin-2 receptor).

**DR OFFENBACHER**

Ultrasound with Doppler noted normal flow through the portal vein, effectively ruling out portal vein dysfunction. Markers for HLH, including ferritin, fibrinogen, NK cell activity, and sCD25 levels, were all within normal limits. Triglyceride levels were mildly elevated, but not to levels consistent with HLH. In addition, the previous bone marrow aspirate demonstrated no hemophagocytosis. Although several markers and genetic testing for HLH were not immediately available, a normal ferritin level is reassuring. The patient only met 3 out of the 8 criteria and therefore was not thought to have HLH.

There are also several causes of splenomegaly that have a genetic origin. Although the patient’s presentation was acute, this does not necessarily rule out a genetic condition. Dr Levy, would you
consider a genetic cause for our patient’s symptoms?

DR LEVY (PEDIATRIC GENETICIST)

Glycogen storage disease type IV often presents with hypoglycemia and hepatomegaly. Splenomegaly usually arises secondary to cirrhosis and portal hypertension. However, as previously described, there was no evidence of cirrhosis or portal hypertension on imaging, so a glycogen storage disease is unlikely.

Splenomegaly is a consistent finding in many LSDs, such as Gaucher disease, mucopolysaccharidoses, and Niemann Pick type A, B, or C. Gaucher disease, in which lipid-laden macrophages accumulate in the liver, spleen, bone marrow, and other affected organs, can present at variable ages with hepatosplenomegaly.16

Mucopolysaccharidoses are LSDs that result from deficiency of various enzymes required to break down glycosaminoglycans.17 These accumulate in lysosomes resulting in diverse diseases that may include hepatosplenomegaly.17 Although some of the mucopolysaccharidoses present at birth, other more-attenuated forms can present in late childhood or early adulthood with musculoskeletal or joint complaints.17 Niemann Pick types B and C can both present at any age with hepatic, splenic, and respiratory disease.18,19

Gaucher disease, mucopolysaccharidoses, and Niemann Pick types B and C are quite rare (1:25 000–1:250 000 live births)19–22 and are associated with symptoms absent in our patient. Although it is rarer to have these diseases present at 8 years old without other significant signs and symptoms, it is important to screen for them because early intervention can reduce morbidity and mortality. I would send an LSD panel, which tests for the enzymatic deficiencies that are present in the most common LSDs. I would obtain a formal ophthalmologic examination to assess for cherry red spots, which can occur in Niemann Pick disease.

DR OFFENBACHER

A quantitative immunoglobulin panel was significant for elevated immunoglobulin G of 2750 mg/dL (normal 700–1600 mg/dL), which can be seen in infectious or rheumatologic conditions. Dr Rubinstein, would you consider a rheumatologic origin for our patient’s presentation, particularly given the prolonged fevers and cytopenias?

DR RUBINSTEIN (PEDIATRIC RHEUMATOLOGIST)

In the setting of unexplained fevers and pancytopenia, an important rheumatologic etiology to rule out is systemic lupus erythematosus, which is possible but rare in young boys. The patient’s antinuclear antibody testing was negative, making this highly unlikely. Other rheumatologic etiologies can be complicated by and can present with macrophage activation syndrome, an entity highly similar to HLH, but as discussed previously, his ferritin, bone marrow findings, and other testing were not consistent. The additional finding of a small 3-mm calcified granuloma in the left upper lobe seen on chest CT could be evidence of a granulomatous disease such as sarcoidosis.

Sarcoidosis is a systemic inflammatory disease that typically affects the eyes, lungs, and liver but can affect any organ.23 Rarely, sarcoidosis can include splenic involvement that presents with pancytopenia secondary to hypersplenism.24 This patient also developed respiratory distress with pleural effusions, which may be compatible with pulmonary manifestations of sarcoidosis.23 It is reasonable to proceed with formal ophthalmology examination to evaluate for uveitis, which is a common finding in sarcoidosis.23 An angiotensin converting enzyme level, which is often elevated in sarcoidosis,23 should be checked as well.

DR OFFENBACHER

A formal ophthalmologic examination was performed. There were no findings suggestive of LSDs, such as fatty deposits in the sclera or a cherry red macular spot. To be conclusive, an LSD panel was sent, with the understanding that results would take several weeks. There was also no evidence of uveitis, which would have been suggestive of rheumatologic etiology. Although his angiotensin converting enzyme level was mildly elevated to 72 U/L (normal 8–52 U/L), this is a nonspecific finding, and there is some evidence that the value may be normal for a male child.24

While we continued our workup, our patient continued to have persistent fevers with pancytopenia. Ten days after admission, we were notified by the Centers for Disease Control and Prevention of positive antibody serology and serum PCR testing for *Leishmania donovani* complex, confirming a diagnosis of VL. The LSD panel and AFB blood culture later resulted as negative.

FINAL DIAGNOSIS AND SUMMARY: VISCERAL LEISHMANIASIS

Drs Offenbacher and Joseph

Our patient’s presentation with fever, splenomegaly, and pancytopenia made us especially concerned for leukemia. When evaluation for a malignancy did not reveal the source, an infectious workup ensued, with VL high on our differential given his massive splenomegaly and previous travel history from an area known to have high rates of leishmaniasis.
Leishmaniasis is rarely seen in New York City and the United States, although the global health burden is significant. There are concentrated regions in Somalia, Brazil, Ethiopia, Kenya, India, South Sudan, and Sudan, which encompass over 90% of the worldwide cases of VL.25 VL is also endemic in Albania; between 1998 and 2016, ~1631 zoonotic VL cases were reported, with domestic and wild canines serving as a reservoir and the bite of the *Phlebotomus* and *Lutzomyia* species of sandfly as vectors.26,27

VL generally presents as a subacute illness with insidious onset of fever, malaise, splenomegaly, and pancytopenia. Patients generally complain of abdominal pain secondary to massive splenomegaly. Progression of the disease is typical in the months after infection from a sandfly bite but can range from weeks to years. Our patient’s travel history was significant for migration from Albania, although it was 10 months before what appeared to be an acute illness. This long incubation period combined with the rarity of US cases of VL originally made it seem unlikely to be the patient’s diagnosis. Although the sensitivity of a bone marrow evaluation for *Leishmania* parasites is 60% to 85%, reaching a diagnosis was prolonged by its negative result.

Diagnosis can be made by PCR or by serological testing for the antibody to the K39 antigen of the *L donovani* complex; however this does not distinguish between the species *L. infantum*, or *L. chagasi.*9 Our patient’s serum was PCR positive and antibody positive for *L donovani* complex. *L donovani* was detected in his bone marrow by immunohistochemistry but not by PCR.

Treatment of VL is dependent on the species and strain of *Leishmania*, the geographic region in which the infection was acquired, and host factors such as age and immune status.8 Liposomal amphotericin B is the only US Food and Drug Administration–approved drug for treatment of VL in the United States and results in close to a 100% cure rate when administered at a high cumulative dose.28 Liposomal amphotericin is preferred in several other countries; however, worldwide treatment varies by country, depending on the availability and cost of each drug. Other drugs used to treat VL include miltetosine and pentavalent antimonial drugs (eg, sodium stibogluconate or meglumine).29,30 The US Food and Drug Administration currently recommends a series of 3 mg/kg doses on days 1 to 5, 14, and 21 for a total dose of 21 mg/kg.28 Fever should resolve within 1 to 2 weeks, and hepatosplenomegaly should resolve in ~1 month.29

Treatment success is determined by resolution of clinical and laboratory findings, as antibody testing may remain positive for up to several years.29 Patients who respond clinically to amphotericin B should be managed for at least 1 year, as relapses can occur despite adequate treatment.29 Most relapses occur between 6 and 12 months after treatment, but relapses have been observed up to 18 months posttreatment.31 For patients who relapse, a dose increase to 30 to 40 mg/kg total may be warranted. There are no trial data to determine the optimal regimen.32

A small subset of patients successfully treated for VL can later develop diffuse maculopapular or nodular skin lesions called post-kala-azar dermal leishmaniasis.6 It is poorly understood and generally occurs in patients infected with *L donovani*, like our patient, but most cases have been reported in patients who became infected in Sudan or India.8 Our patient had a rapid response to treatment with amphotericin B; his blood counts started to improve (Table 1), and his fevers resolved within 24 hours. The patient then completed his amphotericin B treatment as an outpatient and was managed by infectious disease and hematology with no relapses or skin lesions for 18 months. He had resolution of his abdominal distention and splenomegaly and normalization of his blood counts within 2 weeks (Table 1). He and his family were later screened for *L donovani* with serum PCR testing, which was negative.

With our case, we illustrate the multidisciplinary approach necessary to create a broad differential diagnosis in the face of a less common disease entity and the importance of a detailed travel and exposure history, and we highlight how our understanding of pathophysiology can guide effective clinical decision-making.

**ACKNOWLEDGMENTS**

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**ABBREVIATIONS**

AFB: acid-fast bacterial
ALL: acute lymphoblastic leukemia
CMV: cytomegalovirus
CT: computed tomography
EBV: Epstein-Barr Virus
ED: emergency department
HLH: hemophagocytic lymphohistiocytosis
LSD: lysosomal storage disease
PCR: polymerase chain reaction
VL: visceral leishmaniasis
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