An Eight-Year-Old Child with Fever, Fatigue, Pallor, and Weight Loss

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An 8-year-old previously healthy Hispanic boy presented with fever and a 10-lb weight loss over the past 2 months. His fever has occurred almost daily, reaching 102°F. The fever was noted to be slightly higher and more frequent at nighttime, with occasional chills. He defervesced without the use of antipyretics.

Shortly after the fever began, the child developed an erythematous rash on his lower extremities. An unknown antibiotic produced resolution of the rash after 1 to 2 days. Several weeks before presentation, he developed a productive cough, green rhinorrhea, and post-tussive emesis. Results of blood tests performed at that time were normal, and he was symptomatically treated for a virus. However, the parents became concerned about the child’s increasing pallor and fatigue. When they returned to the pediatrician, a complete blood count (CBC) revealed anemia of an unknown degree. He was then referred to the emergency department (ED) for further evaluation.

The review of systems was notable for a decreased appetite and energy level. Otherwise, it was negative for diarrhea, constipation, and abdominal pain. Furthermore, he had no headaches, mental status changes, bruising, epistaxis, hematuria, or dysuria. History was also negative for travel and ill contacts. Over the past 5 months, there had been reconstruction at his school, and there was a rodent infestation at home.

The child took no medications and had an allergy to amoxicillin, with which he developed a rash. He was a full-term neonate, born in Los Angeles, Calif, delivered by cesarean section secondary to fetal distress and bradycardia, with a birth weight of 8 lb 9 oz. His mother received first-trimester prenatal care, with unremarkable study results. He had no prior hospitalizations or surgeries.

Family history was notable for hypertension in both the maternal and paternal grandparents and type 2 diabetes mellitus in the paternal grandmother. No childhood illnesses, cancers, or blood dyscrasias were noted. The patient had a regular diet with 4 to 5 glasses of milk per day. Immunizations were up to date by report, but the vaccination card was not available for review. The parents reported that the last purified protein derivative (PPD) was negative 2 years ago. The child lived with his parents, paternal grandparents, and 2 siblings (12-year-old brother, 3-week-old sister). There were no pets, smokers, or guns in the home. Overall, he had been doing well in the third grade but missed 2 complete days and 6 partial days in the past month because of illness.

On physical examination, his vital signs revealed the following: temperature, 39.3°C (axillary); heart rate, 133 beats/min; respiratory rate, 26 breaths/min; and blood pressure 113/62 mm Hg. His weight was 39.7 kg (90%), and height was 128 cm (50%). In general, he was pale and difficult to examine secondary to irritability and crying. HEENT examination results were notable for tacky mucous membranes and a cracked upper lip. Otherwise, the remainder of the HEENT and neck examination was unremarkable. The cardiac examination was notable for tachycardia, with a grade II to III/VI systolic ejection murmur at the left sternal border. The abdomen was moderately distended, with normoactive bowel sounds. The liver was palpable to 6 cm below the costal margin, and the spleen was palpable to 4 cm below the costal margin. There was mild right upper quadrant and epigastric tenderness to palpation, with voluntary guarding. The genitourinary examination result was normal. Extremities were warm and well perfused, and the neurologic examination revealed no focal neurologic deficits. His skin was without rashes, ecchymosis, or petechiae. However, the hairs on his legs were broken at the skin surface, without any underlying erythema.

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Initial laboratory studies were performed, including a type and screen, CBC, reticulocyte count, coagulation, and chemistry panels. These were notable for a total white blood cell count of 2.46/uL, with an absolute neutrophil count of 1400. The hemoglobin/hematocrit level was 6.8/21.8, and the platelet count was 119 × 10^3/μL. The reticulocyte count was 1.5%, the prothrombin time was 14.9 sec, and the partial thromboplastin time was 37 sec. A comprehensive metabolic panel was remarkable for a low albumin level of 2.6 g/dL and modestly elevated liver function test results. The uric acid level was 4.4 mg/dL, and the lactate dehydrogenase level was 1318 U/L. The erythrocyte sedimentation rate was 12 mm/hr, and the C-reactive protein level was 1.6. Urinalysis and chest x-ray results were negative.

Given the clinical presentation and laboratory results, it was determined that the child would need admission for further workup. He was empirically started on intravenous (IV) cefotaxime after blood and urine cultures were obtained. He was admitted to the pediatrics service, with hematology/oncology consultation. On hospital day 4, the results of a single study revealed the diagnosis.

### Differential Diagnosis

Prolonged fever, weight loss, and hepatosplenomegaly are concerning findings in a child. Initially, the broad differential diagnosis includes various malignancies and infectious diseases. Other broad categories include disorders of the rheumatologic and immunologic systems (Table 1) [1,2].

Of primary importance when such patients present to the ED is to evaluate for life-threatening etiologies, including malignancies. Of the most common, the leukemias and lymphomas can cause life-threatening metabolic abnormalities from tumor lysis syndrome. A similar clinical presentation could arise from solid tumors, such as hepatoblastoma, hepatocellular carcinoma, neuroblastoma, and rhabdomyosarcoma. Less commonly are locally invasive tumors from the stomach and pancreas. Even less common, especially given the child’s age, are metastatic tumors from primary lung, breast, or pancreatic cancers.

Several infectious diseases may present with prolonged fever and hepatosplenomegaly. Overall, the most common organism is Epstein-Barr virus (EBV), typically causing infectious mononucleosis. EBV commonly manifests with prolonged fever, exudative pharyngitis, hepatosplenomegaly, and lymphadenopathy. There may be additional central nervous system and hematologic involvement. Such presentations may be clinically indistinguishable from cytomegalovirus (CMV) and adenovirus infections. Laboratory diagnosis of EBV begins with the heterophil antibody test (monospot), which is more accurate in older age groups and later in the course of the illness. More accurate, however, are the serologic anti-body tests for EBV infection. Diagnosis of EBV infection is of clinical importance because potential life-threatening complications include splenic rupture [3].

In addition, one must consider tuberculosis in children with prolonged fever of unknown etiology. Although it is typically considered as presenting with fever, cough, night sweats, and chills, extrapulmonary manifestations may include meningitis or granulomatous inflammation of the lymph nodes, bones, joints, and skin. A positive tuberculin skin test is suggestive of possible infection, but the actual diagnosis needs isolation of the Mycobacterium tuberculosis organism from gastric aspirates, sputum, or other body fluids [4].

Oftentimes, a travel history would help in narrowing down the diagnosis or even suggesting a more exotic illness. This child initially presented without such a history. This would raise the possibility of malaria, tuberculosis, or parasitic infections. In addition, a dietary history is important to obtain. Infections such as listeriosis and brucellosis may be transmitted by ingesting unpasteurized dairy products. Further contact with animals could lead to infections such as psittacosis and cat-scratch disease.

Geographic location within the United States may also suggest certain infections such as histoplasmosis and coccidiomycosis. Histoplasmosis is endemic to the eastern United States, and humans may become infected from inhaling infected dust containing Histoplasma capsulatum, a dimorphic fungus. Clinical manifestations of histoplasmosis include fever, night sweats, weight loss, cough, and pulmonary infiltrates, lymphadenopathy, and skin lesions. Histoplasma capsulatum can cause a localized infection, chronic disseminated histoplasmosis, or progressive disease in patients with underlying chronic illness. Histoplasmosis is often diagnosed by serologic testing.

### Table 1  Differential diagnosis: prolonged fever, weight loss, and hepatosplenomegaly.

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and central United States, particularly in the Mississippi, Ohio, and Missouri river valleys. Whereas most symptomatic patients have pulmonary manifestations, those with progressive disseminated histoplasmosis may have prolonged fever, failure to thrive, and hepatosplenomegaly [5]. This entity is more common in children younger than 2 years. Symptomatic coccidiomycosis is endemic in the southwestern United States and certain regions of Central and South America. Although the primary infection is asymptomatic in 60% of children, the infection may disseminate to skin, bones, joints, and the central nervous system in less than 1% [6].

In all children with prolonged fever, weight loss, and pancytopenia, one must entertain the possibility of human immunodeficiency virus. The spectrum of disease presentation may include hepatosplenomegaly, lymphadenopathy, hepatitis, and failure to thrive. In addition, patients may present with opportunistic infections, malignant neoplasms, and ultimately, AIDS [7].

Lastly, hemophagocytic lymphohistiocytosis (HLH) is a syndrome of fever, splenomegaly, jaundice, and the pathologic finding of hemophagocytosis on bone marrow biopsy. Hemophagocytosis occurs when activated macrophages engulf and destroy blood cells and their precursors [8]. HLH can be of the acquired type, which includes infectious causes such as viruses, bacteria, fungi, and parasites. Alternatively, there is a malignant type of HLH. Treatment of HLH is involves treating the underlying infection, or chemotherapy in malignant cases [9,10].

**Case Progression/Diagnosis**

Once the patient was admitted, hematology/oncology and infectious disease consultations were obtained. The result of an EBV polymerase chain reaction was negative, and antibody titers only revealed a positive immunoglobulin G. Other titers were negative for leptospirosis, histoplasmosis, and coccidiomycosis. Tests for CMV and adenovirus were negative, as was a thick smear for parasites. Human immunodeficiency virus and PPD test results were both negative. Fibrinogen level was normal, and triglycerides and ferritin levels were elevated at 315 and 337 ng/mL, respectively. Because of the child’s persistent pancytopenia, with an unclear etiology, a bone marrow biopsy was then performed, revealing hemophagocytosis. Because of this pathologic finding, an initial diagnosis of HLH was given. Although there were no infectious causes to explain the HLH, intravenous immunoglobulin was empirically initiated. There was no response to the immunoglobulin, and the child remained persistently febrile, without improvement in his blood counts. Therefore, it was likely that this was the malignant type of HLH, and chemotherapy agents were considered for the treatment of HLH. That evening (hospital day 4), the microbiology laboratory reported the initial blood culture as positive for “tiny gram negative coccobacilli.” The initial and subsequent blood cultures yielded the organism *Brucella*.

Although an extensive history had been obtained in the ED, among the admitting ward team, hematology/oncology, and infectious disease physicians, no one had been able to elicit a possible source for the *Brucella*. After specific questions concerning travel, food, and animal exposures, the family recalled a visit by the maternal grandmother from Mexico 5 to 6 months prior. She had brought homemade unpasteurized cheese, otherwise known as *casero* cheese from her village in Mexico. Adult family members who had eaten the cheese were asymptomatic. No other children had ingested the cheese besides this patient. The grandmother was contacted in Mexico and reported that various villagers had recently experienced similar symptoms as our patient.

Therefore, it was thought that the *Brucella* infection had incited a hemophagocytic syndrome. Within a few days of starting intravenous gentamicin, the patient defervesced, and his anemia and leukopenia showed marked improvement. He was subsequently discharged on a 6-week course of oral doxycycline, with weekly CBC and erythrocyte sedimentation rate studies to be monitored by his pediatrician. He was also sent home with iron supplementation for a coexisting iron deficiency anemia. At a 1-month phone follow-up, he was doing well, without relapse.

**Brucellosis**

Brucellosis is also known as undulant fever. It is a zoonotic disease, which is largely transmitted by sheep, goats, camels, and less often by cows. Of the 6 *Brucella* species, the 4 affecting humans are *B. abortus, B. suis, B. melitensis*, and *B. canis*. [11] *Brucella* is endemic in the Mediterranean, western Asia, and parts of Africa and Latin America. It has not been reported in some regions, such as Canada. In the United States, there are a stable number of cases, approximately 100 per year. Half of these cases are in California and Texas. Of the reported cases in the United States, 50% of the patients are Hispanic persons, and less than 10% are children. The incidence is higher in spring and summer months [12].

**Pathogenesis**

Transmission of the *Brucella* organism, which is a gram-negative facultative intracellular organism, occurs by direct skin contact, inhalation, and ingestion. It is important to note that there is no person-to-person transmission of *Brucella*. Direct skin contact occurs largely with occupational exposures, such as with veterinarians, farmers, and butchers. The most infectious route is by inhaled aerosols, and *Brucella* is considered a class B bioterrorism agent. The most common route is by ingestion of unpasteurized dairy
products. The infective dose is only 10 to 100 organisms and grows best at an acidic pH of 6. It is most often transmitted through milk, butter, ice cream, and soft cheeses such as the casero and asadero Mexican cheeses. Brucella is less likely to be transmitted through hard cheeses and yogurt because of fermentation. Iron deficiency also increases susceptibility to infection [2,12,13].

**Clinical Presentation**

The incubation period for *Brucella* varies from 5 days to 6 months. The duration of illness also varies, from an acute course of 3 months to a chronic course of more than 12 months. In children, the illness is usually mild and self limited [4].

Patients often present with symptoms, including prolonged fever, headaches, arthralgias, weight loss, abdominal pain, and cough. Physical findings are generally nonspecific and include relative bradycardia, lymphadenopathy, hepatosplenomegaly, and purpura. Patients often present with osteoarticular abnormalities such as spondylitis and sacroilitis, and pain is often located at the knees, hips, ankles, and wrists [14].

**Diagnostic Tests**

To diagnose Brucellosis, laboratory studies include a serum agglutination test, where a positive result in acute infections is more than 1:160 in nonendemic regions and more than 1:320 in endemic regions. An enzyme-linked immunoassay is also available. However, the gold standard for *Brucella* identification is the blood culture. The yield of blood cultures is variable, and positive results can be obtained in 15% to 70% of cases, with the highest yield in acute infections. It is important to note that the *Brucella* organism is extremely slow growing, and the blood culture must be held for 3 to 4 weeks [4].

**Treatment and Outcome**

Complications of brucellosis include endocarditis, meningoencephalitis, osteomyelitis, pancytopenia, and HLH. Other complications include ocular lesions, pneumonitis, hepatitis, cholecystitis, and epididymo-orchitis [1].

The treatment of brucellosis requires 4 to 6 weeks of therapy. In children younger than 8 years, trimethoprim-sulfamethoxazole may be used, whereas children older than 8 years receive doxycycline. Rifampin must be added in all patients, to prevent relapse. For serious illness, parenteral gentamicin or streptomycin may be added in the first 1 to 2 weeks of therapy. For life-threatening complications such as meningitis and endocarditis, therapy is extended for several months. The mortality of brucellosis is less than 5%, and most cases resolve with treatment. The overall relapse rate is 5%, with most patients relapsing within the first 6 months. Therefore, patients must be closely observed from 6 months to 1 year [15].

An important aspect of brucellosis is the prevention of transmission. This largely involves the eradication and control of disease in host animals, hygienic precautions in occupational activities, and pasteurization of dairy products.

**Summary**

In summary, this case demonstrates the importance of the following:

1. Keeping in mind nonneoplastic causes of apparent malignancy;
2. The expanded spectrum of illness along border regions;
3. The importance of obtaining blood cultures for patients with prolonged fever or fever of unknown origin workups;
4. The need for specific questions in obtaining travel and ingestion histories; and
5. Remembering that the lack of travel does not exclude travel-related illnesses.

**References**


An eight-year-old child with fever, fatigue, pallor, and weight loss