A 9-Month-Old Boy with a 3-Week History of Fever

Robert Listernick, MD

This 9-month-old boy was evaluated for a 3-week history of fever. Initially, he started having fever 5 weeks before admission and was unable to receive his flu shot at the 9-month visit because of low-grade fever. Three weeks before admission, his fever became higher and he received amoxicillin for otitis media. Daily fever with rhinorrhea continued and he received two doses of ceftriaxone. Two days before admission, there was no improvement in the fever and a third dose of ceftriaxone was doubled. He continued to have cough, fever, decreased intake, and decreased activity; the day of admission, he was sent to the emergency room for evaluation for possible Kawasaki disease. Review of systems was remarkable for ill-defined “eye redness.”

Birth history was unremarkable. Family history is quite remarkable. The mother was diagnosed with non-Hodgkin’s lymphoma shortly after delivery, and she was at this time being treated as an inpatient for Aspergillus pneumonia.

On physical exam, he was an alert, cranky boy who was easily consoled. Weight was in the 60th percentile, length in the 75th, head circumference in the 10th. Initial temperature was 100.5°F, pulse 160, respiratory rate 38, and blood pressure 96/50. There were no rashes. On HEENT examination, he had mild bilateral conjunctival injection. Tympanic membranes were normal. Neck was supple without significant adenopathy. Lungs were clear. S1 and S2 were normal. There was II/VI vibratory, systolic ejection murmur heard best at the left lower sternal border. Abdomen was soft and non-tender. Liver was palpable 3 cm below the right costal margin and spleen was palpable 2 cm below the left costal margin. Genitalia were normal. He had full range of motion of his extremities. There was slight erythema and puffiness on the dorsum of his feet. Neurologic exam was unremarkable.

Significant laboratory testing on admission included hemoglobin 7.9 g/dL with MCV 70; white blood cell count 15,000/mm³ with 30% neutrophils, 26% bands, 31% lymphocytes; platelet count 290,000. Chem14 was remarkable for albumin 2.6 g/dL, ALT 160 IU/L, and AST 131 IU/L. C-reactive protein was 10 mg/dL and sedimentation rate was 77 mm/hour. Urinalysis was unremarkable save for three to five red blood cells and three to five white blood cells per high-powered field. Chest X-ray was normal.

Robert Listernick, MD, moderator: Gestalt?

Evan Anderson, MD, pediatric infectious disease physician: The initial concern in the emergency department was for Kawasaki disease (KD). Certainly, there were some supportive clinical features, including the prolonged fever, conjunctival injection, red, puffy feet, elevated inflammatory markers and mildly elevated serum transaminases. He was quite cranky and the abdominal examination was difficult. The splenomegaly was not reliably identified. If present, it would have been unusual for KD. Overall, I saw no urgency in treating him with intravenous immunoglobulin, as the diagnosis of KD was shaky at best.

Stanford T. Shulman, MD, pediatric infectious disease physician: The diagnosis of incomplete KD can be quite challenging, particularly in infants. At times, we will treat a child with intravenous immunoglobulin and aspirin, even if we are not sure of the
We've seen some false positive mild data are limited, we believe that a grain of salt. Although published an intra-abdominal abscess was definitely on our list, given his overall appearance and his laboratory testing.

Ben Katz, MD, pediatric infectious disease physician: If this child were older, I would consider Epstein-Barr virus (EBV) or cytomegalovirus (CMV) infection, given the fever, hepatosplenomegaly, and transaminases infection. However, overall ill appearance and his elevated inflammatory markers argue against these diagnoses.

Dr. Listerick: How would you establish the diagnosis of EBV infection in such a young child?

Dr. Katz: I would perform EBV-IgM and EBV-IgG testing. The sensitivity of the heterophile test at this age is very low. However, it’s important to note that if you are planning to treat any child with intravenous immunoglobulin, it’s essential to either send whatever serologic testing you need or save some serum prior to treatment. Obviously, IgM testing would not be affected.

Dr. Listerick: Moving forward, he remained febrile for the first 2 days after admission. Echocardiography revealed that the right coronary artery appeared diffusely dilated; there was no pericardial effusion, but a small right pleural effusion was noted. Cardiac function was normal.

Dr. Anderson: We considered all of these diagnoses, as well as the possibility of endocarditis leading to septic emboli in the spleen. That said, we felt that endocarditis was unlikely, given his age, the lack of a pathologic murmur, and the absence of vegetations on the echocardiogram.

Dr. Katz: I’d like to point out that since the term “granulomatous hepatitis” has been suggested, the differential diagnosis is quite broad and reads like the index to an infectious disease textbook. There are also noninfectious causes, such as sarcoidosis.

Dr. Listerick: For what it’s worth, I’ve seen several young children present in similar fashion with similar ultrasound findings, who had Bartonella infections (cat-scratch disease). How does the mother’s unfortunate diagnosis come into play?

Elaine Morgan, MD, pediatric oncologist: She has an unusual peripheral T-cell lymphoma. There are rare reports of transplacental transmission of a variety of malignancies, most commonly melanoma and choriocarcinoma. I have never seen transplacental transmission of lymphoma; I found a single case report describing this.

Dr. Anderson: It has been described in human T-cell leukemia virus (HTLV)-associated malignancies, although it’s difficult to assess whether it was the HTLV infection that was transmitted or the actual malignancy. It’s important in difficult cases such as this one to go back and repeatedly ask questions of the family and perform repeated physical examinations. We could never document any unusual exposures, such as to animals. We did find out that he had eaten some dog food, which raised the possibility that he might have a Salmonella infection.
Dr. Listernick: I found an interesting case report of granulomatous hepatitis caused by *Pasteurella*. Regardless, on the third hospital day, blood culture started growing gram-negative rods and systemic antibiotics were begun. That evening, the child had a generalized seizure. Lumbar puncture was unremarkable. The next morning, he developed increasing abdominal distension and tenderness. Computerized tomography (CT) of the abdomen was performed, and he was evaluated by the surgeons.

Dr. Anderson: When the blood culture became positive, we wondered about an intra-abdominal infection, such as perforated appendicitis, which would be one of the more common reasons for gram-negative bacteremia.

Dr. Katz: Also, given the long duration of his symptoms, we considered other gram-negative organisms that would give a more subacute presentation such as brucellosis or tularemia. He had no history of any potential exposure to these agents.

Ram Yogev, MD, pediatric infectious disease physician: Let’s not forget that, although rare, 90% of splenic abscesses are diagnosed after at least 2 weeks of symptoms. One has to have a very high degree of suspicion to diagnose them earlier.

Dr. Shulman: Given his abdominal exam, we should not forget the possibility of *Clostridium difficile* colitis in someone who has received prolonged oral antibiotic therapy. Also, intermittent antibiotic therapy is a great way to induce *Salmonella* sepsis if a patient is colonized with *Salmonella*. During the modern world’s largest epidemic of salmonellosis in Chicago 25 years ago, which was related to contaminated milk, we observed the phenomenon of patients receiving oral antibiotics for “fever” who subsequently developed *Salmonella* sepsis.

Dr. Listernick: Let’s see the CT scan.

Dr. Norman: There were several new findings. First, there were scattered nodules in the right lower lobe of the lung. The low density lesions were observed again throughout the spleen. In addition, there appeared to be a small intestinal intussusception in the right lower quadrant of the abdomen. We often see small intestinal intussusceptions on CT scans that
are of no consequence unless the patient is having signs and symptoms of an intestinal obstruction.

**Ravi Radhakrishnan, MD, pediatric surgeon:** I examined the child at this point. His abdomen was tender and distended, although he didn’t have any frank peritoneal signs. Because of the combination of the physical and radiographic findings, as well as the positive blood culture, we felt that he needed an exploratory operation once he was vigorously fluid resuscitated and his hematologic abnormalities (anemia, prolonged prothrombin time) were corrected. We certainly thought that he had ischemic bowel or a perforated viscous. He received blood and fresh frozen plasma and went to the operating room the next morning.

**Dr. Listerick:** What did you find during the operation?

**Dr. Radhakrishnan:** We made a laparotomy incision to fully explore the abdomen. Although we were expecting to find abnormal intestines, the peritoneal cavity had some clear serous fluid with entirely normal nonischemic bowel. The liver looked congested and the spleen was a bit enlarged and studded with multiple small white nodules. We performed a splenic biopsy.

**Reema Jaffar, MD, pediatric pathologist:** These nodules have defaced the architecture of the spleen. On high magnification, each nodule has central fibrinoid coagulated necrosis surrounded by pale-looking histiocytes; they are all granulomas. The stains for acid-fast bacilli and fungi were negative. The striking degree of necrosis and the extent of the granulomas were together highly suggestive of chronic granulomatous disease (CGD).

**Dr. Listerick:** Flow cytometry on the child and mother confirmed the diagnosis of X-linked CGD.

**Dr. Shulman:** This is an extremely unusual presentation for CGD, which usually presents in a more indolent fashion. Typical presentations of CGD include: recurrent staphylococcal lymphadenitis, liver abscess, or infection in one or more organs with unusual organisms such as *Aspergillus*, *Serratia* species, or *Nocardia*.

**Rami Fuleihan, MD, pediatric immunologist:** Approximately 60% of CGD cases are inherited in an X-linked recessive fashion, whereas 20% to 40% have an autosomal recessive form. In both, the biochemical defect leads to an inability of phagocytes to generate superoxide anions, leading to ineffective intracellular killing of ingested bacteria and fungi. Most of these children present at younger than 5 years of age.

**Dr. Listerick:** Is there specific therapy for CGD?

**Dr. Fuleihan:** When the patient is this sick, the treatment is antibiotics or antifungals to treat the specific infection. There has been limited experience with neutrophil transfusions to help fight overwhelming infections in these patients. Prophylactically, these patients are maintained on Bactrim and interferon-gamma and usually itraconazole. We generally don’t use interferon-gamma when the patient has a serious active infection. Stem-cell transplantation has been successful in some patients, but this still remains a controversial therapy.

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**Key Learning Points**

1. Some patients who do not fulfill all the criteria for Kawasaki disease (KD) may be diagnosed with “incomplete KD,” often based on abnormal echocardiographic results. It’s particularly important in these patients to continually consider alternative diagnoses, even if the decision is made to treat them for KD with intravenous immunoglobulin and aspirin.

2. Differential diagnosis of granulomatous hepatitis is broad, including a number of bacterial diseases (*Bartonella* infections, tuberculosis, tularemia, brucellosis; fungal infections; and rheumatologic diseases (sarcoidosis).

3. Typical presentations of CGD include: recurrent staphylococcal lymphadenitis, liver abscess, or infection in one or more organs with unusual organisms such as *Aspergillus*, *Serratia* species, or *Nocardia*.

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