An 11-Year-Old Boy with Fever

Robert Listernick, MD

An 11-year-old boy was admitted for fever, ranging from 100°F to 103°F, for 4 weeks. When febrile, he had “cold teeth that are chattering,” and became drenched in sweat. He had been tired and often took naps after school. His mother noted that he had decreased energy and reduced oral intake. He had a documented 8-kg weight loss during the previous 6 months. There was no history of vomiting, diarrhea, hematochezia, or other symptoms. He had not missed any school during the last 4 weeks. There had been no exposures to unusual foods, animals, foreign visitors, or anyone with tuberculosis risk factors. He had not traveled outside of Chicago.

His past medical history was remarkable in that he had possible Kawasaki disease at age 4 years. This illness was characterized by prolonged fever, mildly red eyes and oral mucosa, microcytic anemia, thrombocytopenia, and splenomegaly. Echocardiogram revealed a possibly minimally dilated right coronary artery on presentation. Although his fever improved initially after receiving intravenous immunoglobulin and aspirin, he continued to have intermittent fevers and arthralgias for the next several months. The diagnosis of juvenile idiopathic arthritis was entertained, but his fever and other symptoms ultimately improved and he didn’t return for follow-up. He remained well for the ensuing 7 years. Repeat blood count several months later had normal hemoglobin without microcytosis.

His family history was remarkable in that his father reportedly had aplastic anemia as a teenager and had a stem cell transplant.

On exam, he was a well-appearing boy. His weight was greater than the 95th percentile and height in the 80th percentile. Temperature was 97.8°F, pulse 102, respiratory rate 22, and blood pressure 110/60. HEENT exam was unremarkable. Neck was supple without significant adenopathy. Lungs were clear. S1 and S2 were normal without murmurs or rubs. Abdomen was soft and non-tender without masses or organomegaly. He was Tanner 1. He had full range of motion of all joints without pain or swelling. There were no rashes. Neurologic exam was normal. Rectal examination was normal; stool hemoccult testing was negative.

Laboratory evaluation on admission: hemoglobin 8.3 g/dL with MCV 68, white blood cell count 15,000/mm³ with 85% neutrophils; platelet count 210,000/mm³. RDW was 14.5% (normal 12.5%-16%). CRP was 8 mg/dL and ESR 97 mm/hour. Urinalysis, serum chemistries, and chest X-ray were normal, save for albumin 3.3 mg/dL. PPD was negative. Blood and urine cultures were negative. Echocardiography was normal.

Robert Listernick, MD, moderator: Did he have Kawasaki disease (KD) 7 years ago?

Ben Katz, MD, pediatric infectious disease physician: Obviously, there’s no way to rule out KD because we don’t have a specific diagnostic test. Certainly, splenomegaly and microcytic anemia are not typical features. We occasionally see thrombocytopenia, which is a bad prognostic sign for the development of coronary artery disease. I believe at the time it was reasonable to treat him with intravenous immunoglobulin. However, if his symptoms persisted or if he developed further atypical symptoms for KD, such as arthritis, it would have been reasonable to consider al-
alternative diagnoses, such as juvenile idiopathic arthritis (JIA).

Michael Miller, MD, pediatric rheumatologist: Systemic JIA, the subtype most likely to be confused with KD, is characterized by daily fever lasting more than 2 weeks in association with systemic inflammatory signs, such as a characteristic erythematous “evanescent” rash, lymphadenopathy, hepatosplenomegaly, and serositis. To confirm the diagnosis of JIA, the child must have arthritis for a minimum of 6 weeks; however, the arthritis may develop months after the onset of inflammatory symptoms.

Dr. Listernick: I was impressed by the history because it seemed he might be having a clinical illness similar to what he had 7 years earlier. Does recurrent KD exist?

Julie Stamos, MD, pediatric infectious disease physician: It’s well described in the literature, but in my experience, recurrences account for less than 1% of all cases, and the recurrent episode is generally within 1 to 2 years after the original episode.

Dr. Listernick: What about the father’s history of aplastic anemia?

Robert Liem, MD, pediatric hematologist: There’s nothing about this boy’s microcytic anemia that I can relate to the father’s aplastic anemia. As far as I can tell, the father didn’t have any syndrome, such as Fanconi anemia, to account for it. It’s possible that the aplastic anemia was related to exposure to non-A-E hepatitis. Or perhaps he received oral chloramphenicol in Mexico, a known risk factor for its development.

Dr. Listernick: Does this boy have a fever of unknown origin (FUO)?

Robert Tanz, MD, general academic pediatrician: There’s no strict definition of FUO in children. Two conditions need to be met: fever for a prolonged period of time and the physician needs to have been actively looking for the cause of the fever. The agreed-upon time period generally ranges from 7 to 10 days. With this definition, I would agree that this boy has FUO.

Dr. Listernick: What questions might you ask the family of a child with FUO that you might not ask if the child had a simple fever?

Dr. Tanz: Information about unusual exposures — foreign travel and foreign visitors, animals or pets, and unusual foods, such as raw milk or uncooked meats. In addition, a detailed history of possible tuberculosis exposure — exposure to incarcerated people, homeless individuals, or anyone with a chronic cough.

Dr. Listernick: Once you’ve asked those questions, assuming nothing points you in a particular direction, how would you proceed?

Dr. Tanz: It’s important to be methodical so nothing is missed. Initially, I would have done what you outlined in the presentation — CBC with differential, inflammatory markers, urinalysis, liver function testing, chest X-ray, and PPD. Also, I would make sure to obtain blood and urine cultures and, if the child was having diarrhea, stool cultures.

Dr. Listernick: I agree. A common mistake I’ve seen is forgetting to obtain blood cultures. So, we can start with the abnormal CBC.

Dr. Liem: He is a prepubertal 11-year-old with microcytic anemia and elevated inflammatory markers. Dietary iron deficiency would be unusual in this situation. If his anemia were from pure iron deficiency either due to poor absorption, such as in celiac disease, or increased losses caused by inflammatory bowel disease (IBD), I would have expected an elevated RDW, indicating a wide range of red blood cells of differing width. The normal RDW raises the possibility of the anemia of chronic disease.

Dr. Listernick: Do we understand the pathophysiology of the anemia of chronic disease?

Dr. Liem: It’s complicated, but in the last 10 years, a peptide hormone called hepcidin has been identified. It is released from the liver in chronic inflammatory states and may limit absorption of iron from the jejunum, as well as release of iron from macrophages.

Dr. Listernick: Can we accurately differentiate between these two types of anemia?

Dr. Liem: Besides looking at the RDW, the gold standard for diagnosing the anemia of chronic disease is the identification of stainable iron in the bone marrow on biopsy. Short of that, the serum soluble transferrin receptor is a fairly sensitive discriminating test; it’s elevated in iron...
deficiency and normal in chronic inflammatory states.

Dr. Listernick: Despite the lack of diarrhea, the combination of weight loss, microcytic anemia, and elevated inflammatory markers raised the possibility of IBD. Computerized tomography (CT) of the abdomen was normal, save for mild splenomegaly, which had not been appreciated on examination.

Jeff Brown, MD, pediatric gastroenterologist: If this child had Crohn’s disease presenting with microcytic anemia, he should have had significant abdominal pain and grossly bloody stools, or at least hemoccult-positive stools. Their absence is a huge strike against Crohn’s disease. These children also have clear-cut iron deficiency with wide RDW. Also, if a child has Crohn’s disease with very high inflammatory markers, such as sedimentation rates over 90 mm/hour, I would expect him to be much sicker, and to have a very low serum albumin. Finally, the platelet count in these children is generally very elevated, another sign of chronic inflammation; this child’s wasn’t.

Ellen Benya, MD, pediatric radiologist: We often see significant bowel wall thickening and other inflammatory changes on the CT scans of children who have Crohn’s disease; his scan was absolutely normal.

Dr. Listernick: Would you have performed endoscopy on this child?

Dr. Brown: Endoscopy is safe, with only a very small risk of perforation. If the primary physician wanted it done, I would have said that it was very low yield, but I probably would have done it so the diagnosis could have moved forward.

Dr. Listernick: Upper and lower endoscopies were both absolutely normal. ANA, C3, C4, rheumatoid factor, and ANCA were all negative. Could he still have a rheumatologic disease?

Dr. Miller: Yes. Polyarteritis nodosa, a systemic vasculitis of small and medium-sized arteries defined by the presence of at least three of 10 criteria: weight loss of more than 4 kg, livedo reticularis, myalgias,
testicular pain, mononeuropathy or polyneuropathy, elevated diastolic blood pressure, elevated BUN and creatinine, infection with hepatitis B virus, abnormal arteriogram, or the presence of arterial vasculitis on biopsy. ANCA is rarely positive in polyarteritis nodosa.

**Dr. Listerick**: This child doesn’t meet the case definition.

**Dr. Miller**: It’s a difficult diagnosis to suspect and make early in the course of the disease. I would have considered performing abdominal aortography looking for evidence of vasculitis. I’m not sure whether CT or magnetic resonance angiography has sufficient sensitivity to supplant the need for conventional angiography.

**Dr. Listerick**: His current illness is remarkably similar to the illness 7 years ago. What about the possibility of an underlying immunodeficiency syndrome as the cause?

**Ramsay Fuleihan, MD, pediatric immunologist**: We discussed possible conditions that might predispose him to recurrent hemophagocytic syndrome (HS). Although he had splenomegaly, he really didn’t have many features of HS, such as cytopenias, other than anemia, rash, or hypofibrinogenemia. Ultimately, his soluble IL-2 receptor assay was normal, making HS unlikely. One condition that may lead to recurrent HS is X-linked inhibitor of apoptosis protein (XIAP), which causes a form of X-linked lymphoproliferative syndrome. These children can present with either HS, which may be recurrent, or dysgammaglobulinemia.

**Dr. Listerick**: Flow cytometry for XIAP was normal.

**Dr. Katz**: Did you do a CT scan of the chest looking for significant adenopathy or small mediastinal masses?

**Dr. Listerick**: No, but that’s a good point. I probably should have when I did the CT of the abdomen. What do you think about the utility of bone marrow biopsy in this situation?

**Elaine Morgan, MD, pediatric oncologist**: The peripheral smear is not suggestive of an infiltrative process or myelodysplasia; the white blood cell and platelet counts are normal. The literature suggests that the utility of bone marrow examination in children with FUO is very low. However, if bone marrow biopsy were performed, it should be cultured for bacteria, viruses, fungi, and mycobacteria.

**Maria Proytcheva, MD, pediatric hematopathologist**: Microcytic anemia is a classic, albeit rare, presenting laboratory finding in Hodgkin’s lymphoma.

**Dr. Morgan**: Although one might see microcytic anemia, the absence of lymphadenopathy or significant hepatosplenomegaly would be very unusual. Isolated bone marrow involvement in Hodgkin’s lymphoma in a child would be reportable.

**Dr. Listerick**: Before we discuss the possibility of bone marrow biopsy, is there a role for further imaging? Gallium scan?

**Dr. Benya**: Gallium-67 binds to transferrin, leukocyte lactoferrin, and other inflammatory proteins. It’s deposited in areas of increased inflammation and vascular permeability. It’s extremely useful in identifying areas of infection or metastatic disease. However, it involves a high radiation dose and requires 72 hours to complete the test.

**Dr. Listerick**: What about positron emission tomography (PET)?

**Dr. Benya**: PET scans, particularly when coupled with either CT or MRI, provide metabolic and anatomic information. Radiolabeled glucose analog is injected and taken up by highly metabolically active cells, which we can image with the scanner. Followed by a low-dose CT scan, we can “fuse” the images and visualize the anatomy of metabolically active areas.

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**Key Learning Points**

1. The definition of fever of unknown origin (FUO) in children includes duration of fever for a prolonged period, usually at least 7 to 10 days, while the physician has been looking actively for the cause of the fever.

2. Systemic juvenile idiopathic arthritis (JIA) is characterized by daily fever lasting more than 2 weeks in association with systemic inflammatory signs, such as a characteristic erythematous “evanescent” rash, lymphadenopathy, hepatosplenomegaly, and serositis. To confirm the diagnosis of JIA, the child must have arthritis for a minimum of 6 weeks.

3. In taking a history about a child with FUO, information about unusual exposures is critical, including exposure to foreign travel and foreign visitors, animals or pets, and unusual foods, such as raw milk or uncooked meats. In addition, detailed history of possible tuberculosis exposure — exposure to incarcerated persons, homeless individuals, or anyone with a chronic cough — is important.
This child had PET-CT imaging. There were two foci of increased metabolic activity — in the left supraclavicular area/lower neck, and a smaller area next to the abdominal aorta near the liver. Both looked like regional lymphadenopathy. There was also mild increased activity in the spleen.

**Dr. Listernick:** I didn’t find the supraclavicular adenopathy initially. Either it appeared over the course of several weeks, or it was easier to identify once one knew what region to concentrate on based on the PET scan. He had a bone marrow and lymph node biopsy. Let’s see the pathology.

**Dr. Proytcheva:** Looking at the bone marrow biopsy first, there was a great deal of iron, confirming that his anemia was due to chronic inflammation. There was increased fibrosis and significant lymphohistiocytic infiltrate. These features are common in Hodgkin’s lymphoma, but I could not find any definite Reed-Sternberg cells and the immunophenotyping of the cells was not consistent with Hodgkin’s lymphoma or any non-Hodgkin’s lymphoma.

The lymph node had a dense ring of fibrosis around it that appeared to be infiltrating deeper into the parenchyma. Although a few of the areas looked like what we see in nodular sclerosis-type Hodgkin’s lymphoma, once again I could not find any Reed-Sternberg cells, and the immunophenotyping was not consistent with this diagnosis. We were stuck and we sent out the slides around the world. A firm diagnosis was suggested by a well-respected expert pathologist in Hong Kong — inflammatory pseudotumor of lymph nodes.

**Dr. Morgan:** Most of the literature on inflammatory pseudotumor of lymph nodes has been written by pathologists, so the clinical details are sketchy at best. These individuals tend to have isolated lymphadenopathy associated with systemic inflammatory symptoms, as this boy had. Splenic involvement is common. Spontaneous resolution or resolution after excision of lymphadenopathy appears to be the norm. There is very little information in the literature about bone marrow involvement. This pathology is quite distinct from what used to be called “inflammatory pseudotumor,” which involved an isolated mass in virtually any organ of the body, generally with systemic inflammatory symptoms. This is now termed “inflammatory myofibroblastic tumor.”

**Dr. Listernick:** In some ways, this is very satisfying because we have a definitive pathologic answer from a world expert. On the other hand, the bone marrow involvement is disturbing and he’s still symptomatic. I’m still concerned about the history 7 years ago. We’re going to have to watch him very carefully. Thank you, everyone.

**FOLLOW-UP**

**Dr. Listernick:** Two weeks after removal of the lymph nodes, he had no more fever, had gained 1.3 kg, and his hemoglobin had risen to 9.1 g/dL.

Six months later, he has gained 15 kg and remains asymptomatic. I don’t believe we are yet out of the woods, but I will keep the readers informed of his progress and if there are any changes in the diagnosis.

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**correction**

In the August issue of *Pediatric Annals*, a key learning point in the Firm Rounds column (page 389) read, “Measurement of soluble transferring receptor is helpful in distinguishing between iron deficiency anemia (low) and the anemia of chronic inflammatory conditions (normal).” The sentence should have read, “anemia (high).” *Pediatric Annals* regrets the error.