ILLUSTRATIVE CASE

A Case of Fever of Unknown Origin

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A 12-month-old previously healthy girl was admitted after having 8 days of intermittent fever and rash; she also developed bilateral hand swelling the day of admission. Her rash consisted of erythematous macules over her arms, torso, back, and face. She had no evidence of conjunctival injection, lymphadenopathy, or mucositis. On admission, she was febrile at 39.1°C, her white blood cell (WBC) count was 34 400/mm³, platelet count (PLT) 703 000/mm³, and C-reactive protein (CRP) was >15 mg/dL. Her albumin was 3.1 g/dL. It was also noted that she had normocytic, normochromic anemia.

Question What is the clinical diagnosis? Does the patient have incomplete Kawasaki disease (KD)?

Discussion

KD is a clinical diagnosis and therefore largely a diagnosis of exclusion. The classic diagnosis of KD is based on the presence of ≥5 days of fever and the presence of 4 of 5 principal features, including polymorphous exanthem, bilateral bulbar conjunctival injection without exudate, mucositis, cervical lymphadenopathy (>1.5 cm diameter), and changes in extremities. Current recommendations suggest following the algorithm set forth by the American Heart Association (AHA) when the classic pattern of KD is not present.1 Supplemental laboratory criteria include albumin ≤3 g/dL, anemia for age, elevation of alanine aminotransferase, PLT after 7 days ≥450 000/mm³, WBC count ≥15 000/mm³, and urine ≥10 WBCs per high-power field. Given our patient’s clinical presentation, she did not meet classic criteria but was consistent with incomplete KD via the algorithm given her supplemental criteria. She met criteria for anemia, WBC, and PLT counts.

Case Continuation

The next day of our patient’s admission, we consulted with our infectious disease team. After reviewing her case and evaluating the patient, they also concurred with our presumptive diagnosis of incomplete KD. She was started on intravenous immunoglobulin (IVIG) and high-dose aspirin therapy per the recommended treatment protocol. She tolerated the IVIG therapy. A transthoracic echocardiogram (TTE) was obtained, which showed no evidence for coronary artery aneurysm (CAA) and was otherwise unremarkable. She remained afebrile for the next 3 days. Her blood cultures demonstrated no growth. Over those 3 days, she showed continual clinical improvement, and her inflammatory markers trended down. She was deemed stable for discharge and was scheduled to follow up with pediatric cardiology. Her aspirin was also deescalated to standard low-dose therapy, which she continued until her follow-up with cardiology.

A month after discharge, she was seen by pediatric cardiology and had a repeat TTE. Both the examination and TTE were essentially normal with no evidence for CAA or other structural or functional abnormalities. At this time, her low-dose aspirin therapy was discontinued.

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She continued to follow up regularly with her primary care provider, who grew concerned because of persistent anemia on repeated laboratory draws. A month after she was cleared by cardiology, the laboratory work showed her hemoglobin was 7.0 g/dL, and her PLT was 900,000/mm³. Her parents were concerned at this time because they reported that she had again developed fever and rash. Additionally, she seemed to be in pain every time they tried to move her. She was admitted for these concerns, and her inflammatory markers remained grossly elevated: C-reactive protein 21 mg/dL, erythrocyte sedimentation rate 100 mm/h, WBC 30.5, PLT 886,000/mm³, and hemoglobin/hematocrit 6.3 g/dL and 21.2%, respectively. Her rash was erythematous and more prominent on her torso. It was more noticeable with her fevers, which had remained relatively low grade with the maximum temperature reaching 38.8°C.

Given her low blood counts and thrombocytosis, pediatric hematology/oncology was consulted. Multiple laboratories looking for an underlying cause of anemia were drawn including direct Coombs, interleukin (IL)-2, enzyme-linked immunosorbent assay, fibrinogen, triglycerides, haptoglobin, Ebstein-Barr virus profiles, and cytomegalovirus profiles, all of which came back within normal limits. Blood cultures were also drawn on admission and did not show any growth. She ultimately had a bone marrow aspiration that also showed no abnormalities. Hemophagocytic lymphohistiocytosis and juvenile myelomonocytic leukemia were ruled out. She was transfused with packed red cells for her anemia.

On day 2 of her hospitalization, she refused to bear weight or walk at all. X-rays of the hips and femurs were obtained, which showed mild asymmetry of the capital femoral epiphyses. Ultrasound was also done over both hips, which showed a bilateral joint effusion with capsular distension on the right side (Fig 1). Both orthopedics and infectious disease were consulted due to concern of septic arthritis. She had an incision and drainage of the right hip with orthopedics. A large amount of purulent material was expressed from the joint and cultured. The synovial fluid analysis showed a cell count of 54,000/mm³, glucose of 65 mg/dL, and protein of 3.5 g/dL. She was started on intravenous cefazolin and vancomycin. The Gram stain was negative, cultures did not show any growth, and the antibiotics were discontinued after 3 days when it was determined there was no evidence of infection.

On day 4 of her hospitalization, we drew rheumatologic laboratories. These laboratories included antinuclear antibody (ANA), rheumatoid factor (RF), complement 3 and 4, antinuclear cytoplasmic antibody (ANCA), and anti-double stranded DNA antibody (anti-dsDNA), all of which came back within normal limits. She improved after the drainage of her right hip and began to bear some weight, but her symptoms did not resolve with the antibiotics, and her inflammatory markers remained inappropriately elevated.

**Question** On the basis of these laboratory and radiologic findings, what are the next steps in management? What is the correct diagnosis?

**Discussion**

The presumptive diagnosis of incomplete KD at the initial admission was based on our patient meeting the criteria as defined by the American Heart Association algorithm and her positive clinical response to IVIG. However, there have been multiple reports in the literature of patients responding to IVIG initially and then relapsing back into symptoms as has been described in our case. These patients usually have an underlying rheumatologic diagnosis such as systemic-onset juvenile idiopathic arthritis (SoJIA). Both incomplete KD and SoJIA can
begin as febrile illnesses with rash in young children and similar laboratory and clinical patterns. This makes a clear delineation in diagnosis difficult for clinicians, especially given the limited time window for initiation of IVIG in cases of KD. This is important because incomplete KD is not a milder form of KD and engenders patients to the same sequelae as classic KD. The diagnosis of SoJIA is based on internationally recognized classification criteria. SoJIA is defined by the presence of arthritis in ≥1 joints with or preceded by fever for at least 2 weeks (characteristically quotidian); presence of ≥1 of evanescent erythematous rash, generalized lymph node enlargement, or hepatomegaly and/or splenomegaly; and exclusion of all other causes. The Childhood Arthritis and Rheumatology Research Alliance has developed 4 standardized initial treatment approaches for systemic juvenile idiopathic arthritis. Until recently, the treatment modalities in SoJIA included mainly corticosteroids and methotrexate. However, methotrexate and anti–tumor necrosis factor seem to be less effective for SoJIA than for other JIA categories. Two cytokines (IL1 and IL 6) have been the mainly implicated in the etiopathogenesis of SoJIA and are the target of modern biologic treatment. A recent multicenter study suggested that anakinra (IL-1 receptor antagonist) can be used as a first-line drug for rapid resolution of systemic symptoms and arthritis. Canakinumab (anti-IL-1 antibody), rilonacept (or IL-1 Trap), anti-IL-6 receptor antibody (tocilizumab) are newer drugs used for the treatment of active SoJIA.

**Case Resolution**

Our patient had a magnetic resonance imaging scan of her hip that did not show evidence of arthritic or destructive changes in the joint space. With the paucity of findings suggestive of underlying infectious or hematologic etiologies, in addition to the findings of daily cyclic fevers, salmon-colored rash, joint pain, effusions, significant leukocytosis, anemia, thrombocytosis, and elevated inflammatory markers, the patient was thought to have an underlying autoimmune condition, most likely SoJIA. She was started on naproxen 50 mg twice daily. For >72 hours before discharge, she remained afebrile and had a significant clinical improvement overall. The rash ultimately dissipated, and she was able to ambulate on her right leg without difficulty. She was later started on steroids and anakinra.

**Question** How do we distinguish SoJIA from incomplete KD?

**Discussion**

Their presentations of prolonged fever with erythematous rash and similar laboratory findings can lead to confusion as evidenced in our case. The dilemma of distinguishing these 2 entities is challenging because neither have definitive laboratory tests. The major dilemma most clinicians face is whether to initiate IVIG when incomplete KD is suspected. As discussed previously, incomplete KD carries the same sequelae and risks as classic KD. Exposing patients to IVIG carries adverse effects, although most are mild and transient including headaches, flushing, fever, chills, diarrhea, blood pressure changes, and tachycardia. However, acute renal failure, immunoglobulin A–deficiency anaphylaxis, and thromboembolic events are possible although rare. Proper hydration and slow infusion rates minimize these risks.

There have also been reports of proposed associations of specific qualifiers to each disease. Two examples of these include early age of presentation favoring KD and hyperferritinemia favoring SoJIA. Newburger et al reported that some children with SoJIA present with transient coronary artery dilation similarly to those affected by KD. Pericarditis, myocarditis, and rarely endocarditis may be present as complications of SoJIA. The initial episode of KD being evolving SoJIA or acting as a trigger for SoJIA is not unknown. The occurrence of lupus after KD has also been reported. Newer studies in the literature have aimed to distinguish SoJIA from incomplete KD by studying the pathophysiology and cytokine component of the diseases. There appears to be some promise revolving around the measurement of IL-18. A protein produced by neutrophils, myeloid reactive proteins, is present at high serum levels in SoJIA, much higher than in other inflammatory illnesses. Further studies are needed to identify biomarkers that can help differentiate the diseases. Our case reinforces the importance of an evaluation by a pediatric rheumatologist of any patient with KD who develops unusual or persistent clinical and laboratory findings.

**WHAT IS FEVER OF UNKNOWN ORIGIN? WHAT ARE THE COMMON CAUSES?**

In 1961, Petersdorf and Beeson described for the first time fever of unknown origin (FUO) as fever lasting >3 weeks, with temperature higher than 38.3°C and the cause remaining unidentified despite 1 week of evaluation in the hospital. The definition of definitions of FUO in pediatric literature varies widely, for example: (1) fever >10 days without an apparent cause, (2) fever for ≥8 days, the cause of which remains undiagnosed despite careful and thorough history and physical examination and screening laboratory evaluation, (3) outpatient fever for 5 weeks or inpatient fever for 1 week, (4) temperature ≥38.5°C on >4 occasions for >2 weeks in any setting. The temperature and duration of fever and the setting for defining FUO has varied widely. The most common etiologic categories for FUO are infections, collagen tissue diseases, and malignancies. About one-fifth of the cases are rheumatological. This case illustrates the importance of rheumatological workup in an inpatient setting in a child with FUO.

**Conclusions**

As described here, incomplete KD can present later as systemic onset JIA. A high index of suspicion is required because KD and SoJIA have similar clinical presentations without a specific diagnostic test. Additional studies should be performed to identify biological markers to differentiate between the 2 diseases at an early stage.

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