A 20-Month-Old Boy with Fever for 23 Days

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A 20-month-old boy developed fever at home. He was seen on the second day of fever by his primary care physician, who noted the patient had an exudative pharyngitis and prescribed cefdinir. A rapid strep test was negative. He continued with fever and developed a blotchy red rash over his torso that extended to his axillae and then arms on day 5. The same day, he was seen by an otolaryngologist and switched from omnicef to amoxicillin for persistent tonsillitis.

His CBC demonstrated a hemoglobin of 11.4 g/dL; white blood cell count of 10,800/mcL; and platelet count of 368,000/mcL. The fever persisted and the patient’s parents reported to the primary care physician that the rash was worse with the fever; the child returned on day 7. The child was given IM ceftriaxone and admitted to the hospital near his home for further evaluation. A repeat CBC was not significantly changed. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) serologies and influenza studies were negative. Chemistries were notable for normal liver function tests, a lactate dehydrogenase (LDH) of 326 IU/L (mildly elevated) and an albumin of 2.5 g/dL.

CME EDUCATIONAL OBJECTIVES

1. Delineate the differential diagnosis of daily fever with rash in a young toddler.
2. Explain the evaluation of an ill child presenting with daily high fever and progressive rash.
3. Outline the differentiating characteristics between macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH).

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Figure. Laboratory abnormalities. Source: Klein-Gitelman MS. Reprinted with permission.
The patient received IV ceftriaxone in the hospital for several days; his blood cultures were negative. He then received a dose of IV steroid on day 9 and was discharged home on a course of oral prednisone. The rash improved after the steroids were given; however, the fever persisted. On day 15, the patient was referred to another medical center for the possible diagnosis of Kawasaki disease. At the time of admission, his hemoglobin was 7 g/dL; white blood cell count was 29,200/mcL with platelets 522,000/mcL. Other laboratory abnormalities included erythrocyte sedimentation rate (ESR) 105 mm/hr, C-reactive protein 24.7 mg/dL, normal cerebrospinal fluid studies, and a negative polymerase chain reaction (PCR) for enteroviruses.

Because of persistent fever and rash along with abnormal CBC and inflammatory markers, the patient was treated presumptively for possible Kawasaki disease. He received intravenous immunoglobulin (IVIG) and aspirin, and he also was started on IV antibiotics for a possible pneumonia on chest radiograph. Echocardiogram was notable for a small pericardial effusion and possibly dilated coronary vessels.

A pleural effusion was noted on repeat chest radiography, as well as infiltrate versus atelectasis, at which time antibiotics were discontinued. The fever and rash continued. The patient was given a second dose of IVIG on day 18 of his illness. Two days later, the patient received IV methylprednisolone 30 mg/kg due to persistent fever and concern about the pericardial effusion on echocardiogram. His CBC was notable for an improved white blood cell count of 10,400/mcL and his C-reactive protein had improved to 8.4 mg/dL while albumin dropped further to 1.9 g/dL. Other studies obtained at this time included aldolase, which was mildly elevated at 10.5 U/L (normal <8.1), ferritin elevated at 2,929 ng/mL, a normal triglyceride of 97 mg/dL and a positive nasal swab for methicillin-resistant Staphylococcus aureus (MRSA).

Studies to assess for other diagnoses were sent to an outside laboratory. The patient was edematous and received albumin and furosemide, as well as linezolid for a new left lower lobe infiltrate on chest radiograph.

His fever resolved on illness day 20; antibiotics and aspirin were continued. However, the fever recrudesced on day 25 and the patient was transferred to a third medical center for further evaluation.

At the time of admission, a review of systems was notable for dry, cracked lips, swelling and redness of the skin around the eyes, but no conjunctival injection. The patient’s past medical history was notable for anemia treated with oral iron in the past. His family history was notable for Hashimoto’s thyroiditis; a maternal uncle with a congenital heart defect; and a paternal great aunt with Kawasaki disease.

On physical examination, the patient was irritable. His vital signs were notable for a heart rate of 132 beats per minute; a respiratory rate of 30 respiratory per minute; and a temperature of 103.1°F. Physical examination did not reveal conjunctival injection, cracked lips, or strawberry tongue. His cardiovascular exam was unremarkable. His neurologic exam was notable for irritability.

The initial impression at the third hospitalization was that the patient did not meet criteria for Kawasaki disease, as he only had had fever and rash. On review, previous echocardiograms were considered unremarkable. The differential diagnosis included viral infection, drug allergy, bacterial infection, rheumatologic disease, or malignancy. Consultations were requested by the admitting team.

The oncology service evaluation noted that the illness presentation and laboratory studies were inconsistent with a malignancy. The rheumatology service evaluation noted the pattern of spiking fevers with worsening rash. Further laboratory evaluation was suggested by the rheumatology service, as well as continuing treatment with high-dose IV steroids. During the next several days, the fevers became persistent throughout the day. Some of the previous laboratory results were repeated and results from specialty laboratory studies led to the initial diagnosis.
Initial Diagnosis:

Macrophage Activation Syndrome (MAS)/Hemophagocytic Lymphohistiocytosis (HLH): reactive vs familial (MAS-HLH).

MAS and HLH are described separately in the literature but represent the same spectrum of macrophage/T-cell disorders.

DISCUSSION

The rheumatology consultant noted that the patient had a pattern of daily fever spikes in the evening with rash. However, the rash was not the typical salmon pink macular rash of systemic onset juvenile arthritis. In time, the fever became more persistent. The patient had a physical exam absent of objective signs of arthritis (joint swelling or loss of the normal range of motion with tenderness).

Initial laboratory data revealed leukocytosis, anemia, and thrombocytosis. Although these can be seen in systemic onset juvenile arthritis, the necessary finding of arthritis at the time of illness was missing. Of note, before all exams by a pediatric rheumatologist, the patient had received both IVIG and steroids; this could have modified arthritis that then was unappreciated on physical examination.

Helpful laboratory studies 3 days after admission to the third hospital (illness day 29) included ferritin of 56,667 ng/mL, neopterin 50.3 nmol/L (normal, <10), LDH 639 IU/L (normal, <400 IU/L with AST 77 IU/L (normal, 22 to 59), and a normal ALT 20 IU/L. Other laboratory abnormalities included a very high D-dimer level at 16.6 mcg/mL fibrinogen equivalent units (FEU) (normal, <0.5), and prothrombin time of 16.6 seconds (normal, up to 15.5 seconds). CBC was notable for a normal white blood cell count of 6,470/mcL with hemoglobin 7 g/dL and platelet count 274,000/mcL, despite very high markers of inflammation.

Other studies can be obtained to support a diagnosis of MAS/HLH, including natural killer (NK) cell activity, soluble IL-2 receptor alpha and soluble CD163 levels. This patient had a genetic evaluation for PRF-1, MUNC13-4, STX-11, and RAB27A; he lacked any of the genetic mutations associated with familial HLH, although these mutations account for only approximately 40% of familial HLH cases.

The patient was treated for presumed reactive disease with a course of corticosteroids and cyclosporin. He responded quickly and was discharged to home 3 days after the initiation of therapy.

An entity termed histiocytic medullary reticulosis, dramatic and life-threatening, was described by Scott and Robb Smith in 1939. Currently known as HLH/MAS, two forms of disease are recognized: familial and reactive. Both forms of the disease are severe and potentially fatal.

The hallmark of the disease is excessive activation and expansion of macrophages and T cells leading to an overwhelming inflammatory state. Familial disease is fatal unless patients receive hematopoietic stem cell transplantation. Reactive hemophagocytosis is associated with viral and other infections (most often EBV), and malignancy.

MAS is the label given to this process when it is associated with autoimmune disease, most often systemic-onset juvenile arthritis, and has been well-recognized over the past 2 decades. It is interesting to note that the pediatric rheumatology literature describing systemic juvenile arthritis before the recognition of MAS often noted both severe hepatitis and disseminated intravascular coagulation syndrome.

Signs and symptoms of MAS include fever, rash, bruising and bleeding gums, hepatosplenomegaly, adenopathy, and mental status changes. The patient in this case had fever, rash, splenomegaly, adenopathy, and irritability consistent with mental status change. Laboratory abnormalities include cytopenias, normal or slightly elevated ESR, prolonged PT/partial thromboplastin time (PTT), abnormal fibrinogen, abnormal fibrin degradation products, low vitamin-K-dependent clotting factors, high neopterin, elevated liver function tests with lactate dehydrogenase (LDH) out of proportion to aspartate aminotransferase (AST) and alanine aminotransferase (ALT), high ferritin, high triglycerides, and well-differentiated macrophages phagocytosing other hematopoietic elements on microscopic examination of tissue samples, such as bone marrow or liver (see Figure, page e1).

Our patient had normal white blood cell and platelet counts in the setting of high inflammatory markers and red cell cytopenias, elevated PT, prolonged D-dimer, high neopterin, mildly elevated AST with a higher elevation of LDH, and massively elevated ferritin. He did not have high triglycerides.

Stéphan and colleagues described the first case series of children with rheumatologic diagnoses and MAS. Of the 24 patients described, 18 had systemic onset juvenile arthritis, whereas two each had systemic lupus, polycystic juvenile arthritis, and unclassified disease.

Median onset of MAS was 1 year after primary rheumatologic diagnosis with a range of 0 to 14 years and a mean of 3.7 years. All 24 patients had fever and splenomegaly; 14/24 had hepatomegaly; 12/24 had lethargy or pulmonary involvement; 10/24 were admitted to the ICU or had cardiac involvement. Adenopathy was found in eight patients, and four had kidney involvement. Triggers were identified in 14 patients; 11 patients had an infectious trigger with nine of those being viral. Three patients had a change in medication associated with MAS onset.
Most patients responded to treatment with corticosteroids, while seven nonresponding patients responded to salvage therapy with cyclosporine, which was based on the author’s experience with familial hemophagocytosis and other forms of macrophage activation. Two patients died.

It is often difficult to differentiate on clinical grounds between familial HLH, reactive HLH, and MAS as part of the presentation of an underlying autoimmune disease. Our patient appeared to have an infectious disease onset to his illness and did not fit criteria for arthritis, although he had been treated before evaluation by a rheumatologist.

Because we could not exclude familial disease, our patient had a genetic evaluation that was negative; however, the genetic analysis that is available likely identifies only 40% of the genetic abnormalities suspected in the familial form of the HLH syndrome. Criteria for diagnosis of MAS in the setting of rheumatologic disease were suggested by Ravelli and colleagues. This patient would not fit those criteria unless he had undergone a procedure to demonstrate hemophagocytosis, which was not performed.

In the setting of a patient who has already received therapies known to treat MAS and autoimmune disorders, a more certain diagnosis based on criteria is difficult. Because MAS has a high rate of morbidity and mortality, it requires rapid recognition and vigorous treatment. Patients who fail therapy with cyclosporin and corticosteroids can be placed on the HLH 2004 protocol, which includes etoposide or antithymocyte globulin.
Final Diagnosis:
Systemic Onset Juvenile Arthritis with MAS

Just more than 6 months after starting therapy for HLH/MAS, the patient was off all medications and doing well. However, almost 2 years after diagnosis, the child had a recurrence of fever, rash, and inflammatory markers. His CBC was notable for a white blood cell count of 24,700/mcL; hemoglobin 9.6 g/dL; and platelets 727,000/mcL. He had a mild elevation of LDH, ferritin, and prolonged D-dimer, which rapidly improved.

Physical examination was notable for a systolic murmur with a rub auscultated at the left sternal border, as well as swelling of both knees. Skin exam revealed a salmon pink rash typical of JIA on cheeks and torso. The patient now had evidence of classical findings of systemic onset juvenile arthritis. He had a brief hospitalization to monitor the pericardial effusion found on his echocardiogram and did well on methotrexate, naproxen, and a short course of oral corticosteroids.

CONCLUSION
MAS/HLH is a systemic inflammatory syndrome that can present as a prolonged fever syndrome. It is an important consideration for patients with prolonged fever as it requires early diagnosis and aggressive management to reduce the high risk of morbidity and mortality.

The familial form of the disease must be considered in the absence of an underlying disorder. Reactive forms of the disease can be secondary to intercurrent infection, malignancy or the onset of a rheumatologic illness, particularly systemic onset juvenile arthritis. Patients may have recurrent episodes or develop systemic disease after the initial episode.

REFERENCES