An 18-Year-Old with Recurrent Fever, Night Sweats, and Lymphadenopathy

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An 18-year-old male college student presented to our children’s hospital with fever, night sweats, and lymphadenopathy for more than 1 week. He had been feverish, with temperatures as high as 102°F. He also had fatigue, decreased appetite, dry cough, myalgias, and headache for the past 5 days. He had similar symptoms 2 years prior and was diagnosed as having systemic juvenile idiopathic arthritis (SJIA). He received corticosteroids for a period of 5 months after the diagnosis was made. Despite completing this treatment, he would periodically have recurrent episodes of symptoms; however, he did not seek care as they would usually subside after a few days. He became concerned with this episode because the symptoms did not subside as they had previously.

Past medical history was significant for SJIA and attention-deficit/hyperactivity disorder. His only prescription medication was 30 mg/d of dextroamphetamine. He reported no drug allergies. Family history was significant for Crohn’s disease in his sister, spinal cancer in his father, and Burkitt’s lymphoma in a maternal uncle. He admitted to prior marijuana use and occasional alcohol consumption but denied tobacco use. He was exposed to a cat and rabbit prior to this illness but denied any scratches. He denied recent international travel but reported having a tick bite 3 months prior during a visit to the southeast United States.

He was afebrile on presentation with mild tachycardia. He appeared mildly ill, diaphoretic, and uncomfortable. He had right-sided nontender anterior cervical lymphadenopathy, palpable splenomegaly 2 cm below the left costal margin, and a circular erythematous patch of dry skin on the right upper thigh. No hepatomegaly was palpated. The rest of the examination was unremarkable. A complete blood count revealed thrombocytopenia with platelets of 129,000 uL and atypical lymphocytes on blood smear. Transaminitis was present, with aspartate aminotransferase of 472 U/L and alanine aminotransferase of 483 U/L. Gamma-glutamyl transferase and lactate dehydrogenase were both elevated (248 U/L and 1185 U/L, respectively). International normalized ratio was also mildly elevated at 1.3. D-dimer and fibrinogen levels were normal. C-reactive protein was elevated at 7.9 mg/dL. Monospot testing was negative. Given his history of SJIA, iron studies were obtained and his serum ferritin level was very elevated at 2,904 ng/mL. Computed tomography (CT) of the abdomen and pelvis showed a prominent spleen but otherwise was unremarkable. A CT scan of the brain without contrast showed a prominent spleen but otherwise was unremarkable. A CT scan of the brain without contrast was unremarkable. A right upper quadrant ultrasound showed hepatomegaly and diffuse gallbladder wall thickening of uncertain etiology. Additional testing was performed and revealed the diagnosis.

For diagnosis, see page 147

Editor’s note: Each month, this department features a discussion of an unusual diagnosis. A description and images are presented, followed by the diagnosis and an explanation of how the diagnosis was determined. As always, your comments are welcome via email at pedann@Healio.com.
Epstein-Barr virus (EBV) serology was obtained and the results were as follows: EBV early antigen immunoglobulin G (IgG) was positive, EBV nuclear antigen IgG was negative, EBV viral capsid antigen IgG was positive, and EBV viral capsid antigen immunoglobulin M (IgM) was positive. These results were consistent with acute primary EBV infection. The very elevated ferritin level, along with his other symptoms, raised concern for a hemophagocytic syndrome. Triglycerides were checked and found to be normal. A bone marrow biopsy was ultimately performed, and a small number of marrow macrophages with hemophagocytosis (Figure 1) was observed. Subsequent testing of soluble interleukin-2 receptor was elevated with a value of 15,740 pg/mL (0-1033 pg/mL).

Given that this patient had a history of SJIA and now had confirmed EBV infection, the diagnosis of macrophage activation syndrome (MAS) was made. We chose to start the patient on dexamethasone therapy according to the standard hemophagocytic lymphohistiocytosis (HLH) protocol (HLH-2004 Initial). Over the next several weeks, he began to show clinical improvement along with improvement of his serum ferritin, liver transaminases, and platelet count.

Diagnosis:
Macrophage Activation Syndrome

DISCUSSION
MAS is one of the life-threatening extra-articular complications of rheumatic disorders that results from uncontrolled activation and proliferation of T cells along with excessive activation of macrophages. MAS was first described in 1985 by Hadchouel et al. in patients with SJIA. MAS is a subset of HLH induced by chronic rheumatologic diseases, frequently by SJIA. Acquired MAS is typically triggered by infections, neoplasms, immunodeficiencies, and rheumatic diseases. The clinical presentation of MAS is generally acute and can be dramatic. Patients can become acutely ill with unremitting high fever, hepatosplenomegaly, lymphadenopathy, profound pancytopenia, and elevated serum liver enzymes. Central nervous system dysfunction occurs frequently as well. The pathognomonic feature is the presence of numerous well-differentiated macrophages actively engaged in the phagocytosis of hematopoietic cells in the absence of malignancy. MAS is a rare complication (a published incidence of 7% in patients with SJIA), and can be mild (as in our case) but can also be associated with high mortality.

In one study, 53% of patients with SJIA had bone marrow aspirate findings suggestive of MAS. Only 25% of these were diagnosed with MAS clinically. The authors also point out that the International League of Associations for Rheumatology criteria for diagnosing SJIA include findings that are hallmark components of MAS as well. Specifically, these include high fever, hepatosplenomegaly, and lymphadenopathy. Patients with SJIA also may have mildly elevated D-dimer, prothrombin time, and ferritin level. These findings suggest that current ap-

Figure 1. Hemophagocytosis within the bone marrow aspirate (black arrow).
proaches used to identify MAS may not be sensitive enough.

EBV has long been associated as a potential trigger for MAS, along with varicella-zoster virus, hepatitis A, and coxsackie B. Our patient demonstrated clinical and laboratory findings consistent with active primary EBV infection in addition to histologic evidence of MAS. Histiocytes ingesting blood elements is characteristic of virus-associated hemophagocytic syndrome (VAHS). Generally, VAHS is associated with primary EBV infection (as in our case). In addition to the customary laboratory findings of MAS, hyperferritinemia and hypereytoxokininemia (such as increased serum levels of interferon-gamma) are commonly found in this syndrome.

The described treatment strategy for MAS historically has consisted of high doses of corticosteroids with transition to cyclosporine A in severe or steroid-resistant cases. Conflicting results have been published regarding the use of high-dose intravenous immunoglobulins, cyclophosphamide, plasma exchange, and etoposide. The success reported with cyclosporine A is poorly understood at present, but is believed to be the result of immunosuppression due to the suppression of the early steps in T-cell activation, leading to failure to activate the transcription of early genes such as those encoding for cytokines. As very few cases of MAS have been reported, no treatment protocol for MAS has been previously established. In our case, our patient responded well to monotherapy using dexamethasone according to the established HLH-2004 protocol.

CONCLUSION

MAS is a potentially fatal systemic disorder that results from uncontrolled activation and proliferation of T cells along with excessive activation of macrophages. It typically presents with persistent high fever, hepatosplenomegaly, lymphadenopathy, severe cytopenias, serious liver disease, and central nervous system inflammation. MAS is reported in 7% of patients with SJIA. EBV has also been associated with VAHS. This article describes a case of MAS in a young patient with acute EBV infection who responded well to monotherapy with corticosteroids.

REFERENCES