CLINICAL VIGNETTE

"Headache, Fever, Transaminitis and Pancytopenia: Possibly HLH?"

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Case Presentation

A 22-year old woman with history of allergic rhinitis and migraines, presents to clinic with new onset headache. She reports the headache is similar to her migraines and is throbbing in nature, right-sided, constant and severe for the past 4 days. She denies any aggravating or alleviating factors, fevers, chills, neck pain, cough, or chest pain. No light or sound sensitivity, nausea, change in appetite, or lightheadedness was noted. She takes no medications, no known allergies, no prior surgeries and family history is only notable for hypertension. She was given analgesics and asked to return to clinic if symptoms did not improve. Two days later, the patient developed worsening headache, neck stiffness, night sweats and fever up to 38.6 C, and was directed to the emergency room.

In the emergency room, the patient had a temperature of 38 C, BP 180/87, pulse 124, oxygen saturation 95% on room air. On examination, she appeared well developed, without distress. Her neurologic examination was normal with supple neck and absent Brudzinski's and Kernig's signs. Cardiopulmonary and abdominal exams were normal. Her skin was warm and dry. Initial laboratory testing was notable for white blood cell count of 1.6 x 10^3/UL, absolute neutrophil count of 1 x 10^3/UL, Hgb 11.8 g/dL, Platelets 80 x 10^3/UL. Creatinine was normal at 0.8 mg/dL, but she had elevated liver chemistries with alkaline phosphatase of 122 U/L, AST 147 U/L and ALT 192 U/L. Total bilirubin, PT and PTT were all normal. D-Dimer, was elevated at >10,000 ng/mL, with low haptoglobin <8 mg/dL, but fibrinogen was normal at 47 mg/dL. C-reactive protein was elevated at 1.6 mg/dL, lactase dehydrogenase elevated at 410 U/L, but sedimentation rate was normal at 3 mm/hr. Triglycerides were elevated at 293 mg/dL. COVID-19 PCR was negative. Chest x-ray was negative for consolidation or pulmonary edema. In the emergency room, the patient underwent a lumbar puncture, that showed clear/colorless CSF, 0 RBC and 0 WBC. CSF gram stain, protein, glucose, viral cultures (including HSV, CMV), bacterial and fungal cultures and PCR were all normal.

The patient was admitted to the medicine service for further evaluation. She continued to complain of severe right-sided headache, nausea and fever, that improved slightly with ibuprofen. She declined opiates for analgesia. CT brain was unremarkable for acute intracranial process. CT of the chest, abdomen and pelvis only noted mild hepatosplenomegaly. Over the next few days of hospitalization, pancytopenia continued to worsen. On day 5, the patient's WBC dropped to 1.33 x 10^3/UL, with absolute neutrophil count of 3.3 x 10^3/UL. Hemoglobin decreased to 10.9 x 10^3/UL and platelets decreased to 62 x 10^3/UL. Ferritin was elevated at 1216 ng/mL, but iron and iron saturation were normal. The primary team consulted rheumatology, hematology/oncology, infectious disease and gastroenterology. She underwent extensive serologic testing for autoimmune disorders, viral, bacterial, mycobacterial and fungal infections- all which were normal. On day 6, she underwent bone marrow biopsy, which showed slightly hypocellular bone marrow with trilineage maturation, no excess blasts and normal flow cytometry. Soluble IL-2R (CD25) was checked due to suspicion of hematophagocytic lymphocytosis (HLH), and returned elevated at 1,051 U/mL. Infectious disease recommended Doxycycline 100mg for empiric rickettsial infection given recent travel to Arizona, but rickettsial antibody testing was ultimately normal.

Additionally, the patient's liver function tests continued to rise, with alkaline phosphatase peaking at 159 U/L, AST 696 U/L, and ALT 1000 U/L. Her bilirubin, INR and PTT remained normal. The patient had denied any history of alcohol, herbal supplements, or recreational drugs, which her family confirmed. Liver biopsy was scheduled, but by day 7 the patient's liver function tests began to spontaneously improve, and the biopsy was cancelled. As the patient's liver function tests normalized, so did her blood counts. Doxycycline was continued despite the team's low suspicion for rickettsial disease. By day 10, the patient was discharged with complete normalization of her laboratory abnormalities. Fever, headache and nausea also resolved by discharge. The patient had repeat labs a month later and all tests remained in normal range.

Case Discussion

As our patient's pancytopenia and liver failure worsened, hematophagocytic lymphohistiocytosis (HLH) rose to the top of the differential diagnosis. HLH is a syndrome of excessive immune activation of lymphocytes and macrophages, which then infiltrate the bone marrow, liver, spleen and central nervous system leading to multiorgan failure and commonly death.[1] There are two forms of HLH: primary and secondary. Primary, or familial HLH, is an autosomal recessive disorder, and most commonly affects infants less than the age of 1. Genetic mutations impair the cytotoxic function of natural killer and cytotoxic T-cells. Macrophages and lymphocytes are activated and cytokine storm ensues.[1] Secondary HLH may

develop as a strong immunological activation of the immune system triggered from infectious, oncologic or rheumatologic processes, although an associated disease process is not always identified.[2] Ebstein Barr virus (EBV), HIV, herpes viruses, tick born bacteria and mycobacteria are the most common infectious causes of secondary HLH. Non-Hodgkin's lymphoma and other acute leukemias/lymphomas are the most common malignancies associated with secondary HLH. HLH complicates up to 13% of patients with juvenile idiopathic arthritis, presenting as macrophage activation syndrome, but can also occur in patients with systemic lupus erythematosus and rheumatoid arthritis.[1-3]

Typical presenting signs and symptoms of HLH are nonspecific, usually related to organ damage by immune activation. Fever of unknown origin, cytopenias, splenomegaly, acute liver failure, bleeding, rash and neurologic symptoms may all be indicative of HLH.[2,3] In 2006, the Histiocyte Society updated a set of clinical and laboratory criteria to diagnose HLH, named the HLH-2004.[2,] (See Table 1.) Additionally, genetic mutations in PRF1, UNC13D, STXBP2, RAB2JA, STX11, SH2D1A or BIRC4 are also diagnostic of HLH.[2,4]

Table 1. Diagnostic Guidelines for HLH

The patient must fulfil at least 5 of the following 8 criteria:

1. Fever >38.4C
2. Splenomegaly
3. Cytopenias (affecting at least 2 cell lines)
   a. Hemoglobin <9 g/dL
   b. Platelets <100 x 10^3/UL
   c. Neutrophils <1 x 10^3/UL
4. Hypertriglyceridemia and/or hypofibronogenemia
   a. Fasting triglycerides >265 mg/dL
   b. Fibrinogen level of <150 mg/dL
5. Hemophagocytosis in bone marrow, spleen or lymph nodes, and no evidence of malignancy
6. Low or absent natural killer-cell activity
7. Ferritin level of >500 U/L
8. Soluble CD25 level of >2,400 U/mL

The original HLH-1994 protocol for induction treatment has improved 5-year survival outcomes from 10% to 50%.[5] This protocol includes an 8 week induction with dexamethasone and etoposide. Cyclosporin has been studied in the HLH-2004 protocol, but results have not been clinically significant.[2] Allogenic hematopoietic stem cell transplant is the permanent treatment in primary HLH but effectiveness in adults and secondary HLH is still not proven.[6]

Our patient was actively worked up for secondary HLH. Infectious disease, rheumatology, gastroenterology, hematology/ oncology teams were all consulted, which led to extensive testing that was all normal. Our patient did meet 5 out of 8 HLH-2004 diagnostic criteria with fever, splenomegaly, cytopenias, hypertriglyceridemia, and elevated ferritin. However, her primary team and specialists did not feel the case was consistent with HLH, perhaps because her spontaneous recovery is not the typical course for HLH. Infection-associated HLH may recover spontaneously, but again, an infection source was never identified. On the other hand, if this was not HLH, what else could explain her clinical course? The patient similarly does not meet criteria for sepsis given absence of bacteremia or source of infection. Regardless, her case is an important reminder to consider HLH for patients presenting with acute liver failure, pancytopenia, fever and neurologic symptoms. Given its life-threatening nature, HLH should be recognized early. Fortunately, our patient had a remarkable recovery, but more than 50% of HLH cases are indeed fatal.[6]

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