Hemophagocytic lymphohistiocytosis

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome of widespread inflammation due to massive amounts of cytokines released from activated macrophages. The most common trigger for HLH is infection from a virus, most commonly Epstein-Barr virus. Here we report an adult case of this rare and life-threatening syndrome.

KEYWORDS Epstein-Barr virus; hemophagocytic lymphohistiocytosis; hemophagocytosis; Kikuchi-Fujimoto disease; parvovirus B19

Hemophagocytic lymphohistiocytosis (HLH) causes excessive immune activation, which results in tissue destruction and eventual organ failure if left untreated.¹ Although HLH is predominantly a pediatric disease, it can be seen in adults of all ages.¹ Due to the irregular clinical presentation of HLH and its rarity, especially in the adult population, it is often diagnosed later in a patient's clinical course, leading to poor survival outcomes.^{2,3} Therefore, suspicion of this syndrome should lead to immediate initiation of treatment.² Here we report HLH in a 36-year-old woman.

CASE REPORT

A 36-year-old woman was admitted to the intensive care unit for septic shock and acute respiratory failure. Lab work showed a leukocytosis of $13.4 \times 10^9/L$, hemoglobin of 7.4 g/dL, and thrombocytopenia of $53 \times 10^9/L$. Her triglycerides were elevated to 367 mg/dL. Peripheral smear showed anemia with mild hypochromia, rouleaux, rare spherocytes, thrombocytopenia, mature white blood cells with toxic neutrophils, and absence of schistocytes. Computed tomography of the abdomen and pelvis showed hepatosplenomegaly and lymphadenopathy throughout the chest, abdomen, and pelvis.

Hematology-oncology was consulted for further evaluation. Upon review of her history, it appeared that our patient had presented with paranoid hallucinations, headaches, anorexia, and nausea and vomiting 2 months prior, resulting in an extensive workup, including brain magnetic resonance imaging, electroencephalography, lumbar puncture, and porphyria evaluation. The results were unremarkable. Human

immunodeficiency virus, rheumatoid factor, and antinuclear antibody testing were also negative. However, a surprising finding was discovered on her iron panel, which showed a ferritin level of 40,000 ng/mL. A bone marrow biopsy did not show immaturity, erythroid hypoplasia, malignancy, or evidence of hemophagocytosis; however, her presentation was highly suspicious for HLH. She also had an axillary lymph node biopsy, which showed necrotizing lymphadenitis with a positive polymerase chain reaction analysis for Epstein-Barr virus (EBV), favoring Kikuchi-Fujimoto disease. She was started on dexamethasone and clinically improved. Unfortunately, her steroids were discontinued early due to adverse side effects.

HLH was again suspected to be the culprit of her current presentation, because an extensive infectious workup could not explain her active fevers, cytopenias, and elevated ferritin. Dexamethasone was restarted and resulted in remarkable improvement. Possible triggers for her HLH were investigated. Malignancy was not identified. Polymerase chain reaction for EBV and parvovirus B19 demonstrated active replication. Her soluble CD25 eventually returned and was elevated at 9420 pg/mL. Her HLH was acquired in adulthood; therefore, genetic analysis for HLH subtypes was not performed. Unfortunately, 3 months later, our patient contracted a coronavirus, which precipitated a relapse of her HLH. Plans were made to start her on etoposide along with dexamethasone.

DISCUSSION

A common misconception in diagnosing HLH is that hemophagocytosis must be seen on immune tissue or bone

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marrow biopsies.^{3,4} In actuality, hemophagocytosis is not required for diagnosis.^{3,4} Instead, diagnosis involves either identifying an HLH-associated gene mutation or meeting five of the following eight criteria: fever $\geq 38.5^{\circ}\text{C}$; splenomegaly; hypertriglyceridemia; hemophagocytosis in bone marrow, spleen, lymph node, or liver; low or absent natural killer cells; ferritin >500 ng/mL; elevated soluble CD25; and peripheral blood cytopenias.⁵ Our patient met six of these criteria.

Kikuchi-Fujimoto disease is also a rare but benign disease that typically presents with cervical lymphadenopathy, fever, and a flu-like presentation.^{6,7} The pathogenesis of Kikuchi-Fujimoto disease is unknown but viruses are commonly implicated, including EBV and parvovirus B19.⁷ In one literature review, hepatosplenomegaly and a higher level of serum ferritin were more commonly seen in HLH-associated Kikuchi-Fujimoto disease.⁶ Kikuchi-Fujimoto disease differs from HLH in that it is usually self-limiting.⁷ In comparison, HLH that is left untreated has a high mortality rate.³

Our patient's ferritin level of 40,000 ng/mL was truly remarkable and led to the suspicion of this rare diagnosis.³ The most common trigger for HLH is infection from a virus, most commonly EBV.¹ Our patient was infected with both EBV

and parvovirus, and viruses are believed to have triggered this rare and life-threatening syndrome.

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