CLINICAL VIGNETTE

Hemophagocytic Lymphohistiocytosis: A Rare and Rapid Cause of End-Organ Failure

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Case Summary

A 64-year-old male with past medical history significant for insulin-dependent diabetes mellitus and hypertension was transferred from an outside hospital for higher-level care for idiopathic pancytopenia. Four months prior to transfer, he was found to have severe anemia and thrombocytopenia, requiring multiple hospitalizations. The patient had fever and mild splenomegaly during one of his admissions, which resolved. Two bone marrow biopsies were performed, both of which were unremarkable and normocellular. The patient became dependent upon multiple weekly platelet transfusions, monthly packed RBC transfusions, IV methylprednisolone, and IVIG. A third and final biopsy was done immediately prior to transfer, showing a hypercellular bone marrow with erythroid predominance and myeloid left shift, thus raising concern for myelodysplastic syndrome. Further testing of the bone marrow showed normal cytogenetics and karyotype.

Upon arrival to our hospital, his vital signs were stable, but he was ill-appearing with acute liver failure with jaundice, ascites, petechiae, ecchymoses, anasarca, and hematochezia. The anasarca was presumed to be a result of corticosteroid use. Laboratory testing at admission was significant for: anemia (hemoglobin 8.9 g/dL), thrombocytopenia (platelet count 40,000/uL), hyperferritinemia (8756 ng/mL), prolonged aPTT (52.5 seconds), hypoalbuminemia (1.6 g/dL), hyperbilirubinemia (direct 9.9 mg/dL, total 12.4 mg/dL), elevated alkaline phosphatase (621 U/L), elevated aspartate aminotransferase (78 U/L), elevated alanine aminotransferase (92 U/L), and elevated lactate dehydrogenase (339 U/L).

Because of the liver abnormalities, he was evaluated for autoimmune hepatitis with abdominal ultrasound and assays for anti-nuclear antibodies, anti-smooth muscle antibodies, and anti-mitochondrial antibodies. There was no hepatosplenomegaly, and only the anti-smooth muscle antibody titer returned marginally positive, at 1:20, effectively ruling out autoimmune hepatitis.

Though the patient was afebrile on transfer with no hepatosplenomegaly, the elevated transaminases in the context of cytopenias raised the suspicion for hemophagocytic lymphohistiocytosis (HLH). No triggering condition was identified, and outside CT showed no evidence of malignancy. Additional labs included elevated triglycerides (614 mg/dL) and elevated soluble CD25 IL2 6274 U/mL with normal fibrinogen. Transjugular liver biopsy and PET-CT were obtained to assess for hemophagocytosis or underlying malignancy, a common finding in adult HLH.

On hospital day 7, the patient was found asystolic, likely due to hemoptysis and aspiration. The patient's previous DNR request was honored, and he expired. Later that day, the liver biopsy results returned and showed hemophagocytosis, which with the findings of cytopenia, hyperferritinemia, hypertriglyceridemia, and elevated soluble CD25 met the diagnostic criteria for HLH. The biopsy demonstrated large ALK-, CD30+ anaplastic cells. This was suggestive of an underlying lymphoproliferative disorder such as anaplastic large cell lymphoma, which was further corroborated by a PCR analysis showing a clonal T-lymphocytic population in the specimen.

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon and life-threatening disease characterized by excessive immune activation, inflammation, and tissue destruction mediated by lymphocytes and macrophages. The resulting cytokine storm from aberrant macrophage activation results in rapid end-organ failure, if left untreated.[1]

The two forms of HLH, primary and secondary, are difficult to distinguish, as both have similar clinical findings and may have overlapping ages of onset. Primary HLH (pHLH) results from mutations of HLH-related genes, inherited in either an autosomal recessive or X-linked recessive fashion.[2] Though triggers cannot always be identified, episodes of pHLH are sometimes triggered by episodes of infection. pHLH was historically believed to be a primarily pediatric disease, and as a result, most of the literature on HLH has been in pediatric populations. In recent years, it has been increasingly reported in adolescents and adults.[2,3] Secondary HLH (sHLH) is a sporadic form which can occur at any age and usually in the setting of severe infection, rheumatic disease, immunodeficiency, or malignancy.[2]

HLH requires rapid identification, as untreated HLH is associated with a mean survival time of less than 2 months.[1] However, it is often difficult to diagnose as it can present with non-specific clinical findings that may arise or resolve at

different points in the disease. Guidelines developed by the Histiocyte Society in 2004 state that HLH can be diagnosed either molecularly, or with five out of the eight diagnostic criteria: fever, splenomegaly, cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, low NK activity, hyperferritinemia, and elevated soluble CD25.[2] In addition, a recent retrospective study of 73 adult HLH patients by Otrock and Eby showed that the most common findings in their population were hyperferritinemia (100%), fever (95.9%), elevated lactate dehydrogenase (92.8%), hypoalbuminemia (91.8%), cytopenia (84.9%), transaminitis (83.6%), and elevated PT/PTT (82.2%). Interestingly, the absence of hemophagocytosis on biopsy did not rule out HLH as it was present in only 76.5% of patients in this study, and the finding has often been reported to be absent early on in the course of HLH.[1]

Though the diagnostic guidelines are helpful in the detection of HLH, they have their limitations, as they were developed for pediatric HLH, and many situations may arise that make a clear diagnosis difficult. For instance, though it is not listed as a diagnostic criterion, it is very common for patients with HLH to initially present with signs of end-organ failure, particularly liver dysfunction.[1,3] Thus, it is critical that a high index of suspicion for HLH be maintained, even in the face of common manifestations of HLH that may not be part of the formal criteria. Diagnosis can be further complicated by ongoing empiric and symptomatic treatment which may improve the patient's status and further mask the underlying condition, as in the case of our patient with multiple transfusions and IV corticosteroids.

In addition to early HLH-specific treatment, identification, and treatment of conditions that trigger HLH are important in improving patient outcomes and determining prognosis.[3] Adult sHLH can arise with malignancy, particularly lymphomas, and are associated with a significantly worse prognosis. One report suggests that, despite receiving treatment, patients with malignancy-associated sHLH have a mean overall survival of 1.13 months versus 47.03 months in those with non-malignancy-associated sHLH.[1] sHLH can develop during the course of cancer treatment or can mask the malignancy, serving as the reason for initial presentation, as in our patient. A CT scan performed by the outside hospital showed no evidence of malignancy. The patient expired before a PET-CT could be performed and before pathology reports of his liver biopsy returned, showing an underlying anaplastic large cell lymphoma, an aggressive non-Hodgkin peripheral T cell lymphoma. T/NK-cell lymphoma-associated HLH has been shown to have the worst 5-year overall survival (12.2% and 5%, in some studies) compared to all other subtypes of sHLH, despite CHOP treatment.[4,5] Only a small number of cases of HLH induced by anaplastic large cell lymphoma (ALCL) have been reported in pediatric populations, with even fewer reported incidents in adults, suggesting that this subset of malignancy-associated HLH is rare or underdiagnosed.

The biggest barrier to care for patients with HLH is often delayed identification, as HLH is both rare and difficult to confirm, given the variability in presentation between patients. One must consider HLH on the differential when a patient presents with unexplained fever, cytopenias, hyperferritinemia, and end-organ damage. Moreover, it is important to recognize that many patients will not meet all of the criteria necessary for an HLH diagnosis during one admission, as symptoms may arise and subside over the course of the disease and treatment. Thus, it may be appropriate to treat suspected HLH empirically with dexamethasone and etoposide when there is a strong degree of clinical suspicion, even in the absence of fulfilling five of the eight criteria.[2,3]

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