A Case of Pregnancy-associated Hemophagocytic Lymphohistiocytosis.

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Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of pathogenic immune activation characterized by clinical signs and symptoms of extreme inflammation.1

HLH can be primary (familial) or secondary acquired. Primary HLH is caused by genetic mutations affecting the cytotoxic function of T lymphocytes and natural killer (NK) cells and typically presents in young children. Secondary acquired HLH occurs in the setting of infections, malignant, rheumatologic, or metabolic conditions.2

In familial HLH certain mutations cause impaired cytotoxic function and lead to an uncontrolled inflammatory response with the activation of the kempner gamma (g) producing T cells. High levels of IFN g lead to macrophage activation and overproduction of proinflammatory cytokines, which can cause severe tissue damage and organ failure. Mutations have been found in the following genes: PRF1, UNC13D (MUNC13-4), STX11, STXBP2, and MUNC18-2.2

The diagnosis of HLH is often delayed due to the rarity of the disease, the complexity of diagnosis criteria and the varying patterns of presentation seen in different patients. Any five of a combination of eight clinical and laboratory signs and symptoms of extreme inflammation are fulfilled.3

Five of the 8 criteria listed below are fulfilled:

1. Fever >38.5 °C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood)
4. Hemophagocytosis in the bone marrow aspirate
5. Low or absent NK-cell activity
6. Ferritin >500 ng/mL
7. HLA-DR or CD25 >2400 IU/mL
8. Pathologic mutations of PRF1, UNC13D, Munc18-2, Rab27a, SH2D1A, or BIRC4

In patients with known predisposition to HLH, recurrent disease, or no clear precipitating cause pregnancy status was of unknown risk.4

Because it was not clear-cut that HLH in our patient was viral-induced, maintenance treatments initially with dexamethasone pulses and etoposide and later with tacrolimus were considered.

As a result, she was put on limited activity and started on intermittent hemodialysis. By the time she received her third dose of etoposide bilirubin 10 mg/m2). Etoposide was initially held due to renal failure and elevated bilirubin. It was later started and continued up to the end of the third week.

A chest X-ray showed left lower lobe infiltrate suspicious of pneumonia. She became hemodynamically unstable. Her declining hemodynamic and respiratory status led to fetal distress. Within a few hours of admission, she developed hypoxic respiratory failure requiring mechanical ventilation. A large number of reported pregnancy-related HLH were triggered by viral infection: EBV, parvovirus, V2, and HIV.5

Inflammation is a key component of both native and adaptive immunity. A large number of reported pregnancy-related HLH were triggered by viral infection: EBV, parvovirus, V2, and HIV.5

In patients with known predisposition to HLH, recurrent disease, or no clear precipitating cause hematopoietic and stem cell transplant treatment is recommended. Maintenance therapy with desflurane pulses, cyclosporine daily, and etoposide should be considered after induction if stem cell transplant is not immediately feasible.2

It is of interest that in a few reported cases, patients’ symptoms resolved and laboratory parameters improved after delivery, raising the assumption that pregnancy may increase risk in predisposed patients.4 However, mutation analysis shows no evidence of familial HLH in our patient and hence she is unlikely to have active HLH. Because it was not clear-cut that HLH in our patient was viral-induced, maintenance treatments initially with dexamethasone pulses and etoposide and later with tacrolimus were considered.

References:

7. Figure 1: Mechanics of cytotoxic function revealed by HLH-associated gene mutations.
8. Figure 2: HLH-94 protocol for the treatment of HLH.
9. Figure 3: Bone marrow biopsy demonstrating hemophagocytosis.