A Case of Hemophagocytic Lymphohistiocytosis (HLH) Secondary to Cytomegalovirus Infection in an Immunocompetent Patient

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Introduction

- Hemophagocytic lymphohistiocytosis (HLH) is a severe life-threatening disorder due to uncontrolled and persistent immune response.
- They are associated with primary genetic abnormalities but can also be triggered by infectious, neoplastic, or autoimmune causes[1].
- Literature on CMV-induced HLH is limited and poorly characterized[2].
- Here, we present such a case of HLH from undiagnosed CMV infection in an immunocompetent patient.

Case Presentation

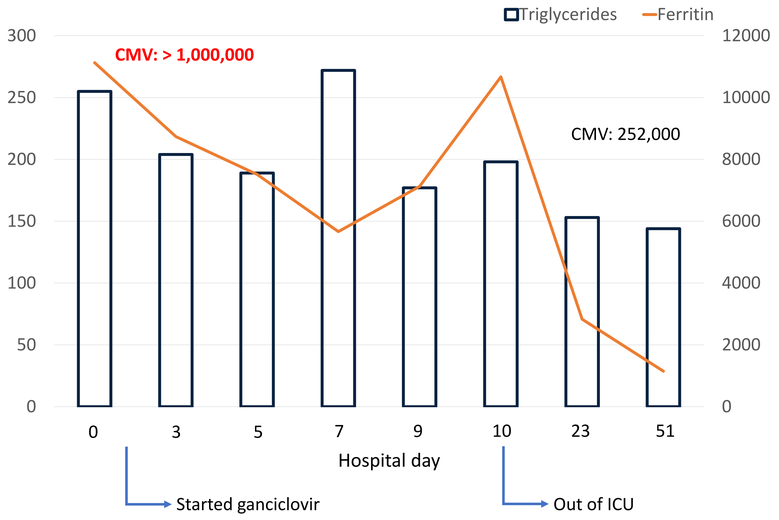
- Patient is a 25 year old female who presents to outside hospital for shortness of breath, fever, and myalgias, and was transferred to our facility due to concerns for myelodysplastic syndrome.
- Of note, she has history of antiphospholipid antibody syndrome and Trisomy 8 noted on prior bone biopsy. Before transfer, she was treated for pneumonia that did not improve and ultimately required BIPAP. Additionally, she developed diffuse maculopapular rash and malar rash, nephritic syndrome, and pancytopenia.
- Pertinent outside labs:
  - WBC 1.1, platelets 58, ferritin of 12,000 and positive anti-cardiolipin antibody. Triglycerides within normal limits.
  - Negative ANA, ANCA, histone antibody, HSV, VZV, Tularemia, anti-Smith, SSA, and SSB antibodies, and normal C3/C4
  - No splenomegaly on CT.
  - Renal biopsy sample only showed 1 glomerulus which had no fibrosis.
  - Skin punch biopsies of the maculopapular rash were consistent with drug reaction.
  - Two bone marrow biopsies showed normocellular, multilineage dysplasia with left shift myeloid precursors and dysgranulopoiesis, megaloblastic changes, megakaryocytes.
- After transfer, repeat labs showed TG 255, ferritin 11,127. Splenomegaly also now noted on repeat imaging. Serologies were negative for HIV 1&2, Rickettsia, Aspergillus, Histoplasma, and Fungitell.
- Treatment with etoposide was initially considered. However, outside hospital relayed updated labs: **positive CMV, DNA PCR 664,000, viral load 5.82.**
- Facility repeat labs also showed **CMV of >1M**. Repeat bone marrow biopsy was done which showed **rare macrophages with cytoplasmic debris suspicious for hemophagocytosis**.
- Given these results, we redirected treatment plan from etoposide to dexamethasone 20mg daily and IV ganciclovir.
- She was discharged home on oral valganciclovir and dexamethasone taper, with close follow up with infectious disease and oncology.

Figures

Figure 1. HLH-2004 diagnosis criteria, American Society of Hematology (1)

Establishing the diagnosis of HLH
1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below)
Fever
Splenomegaly
Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood) Hemoglobin <90 g/L (hemoglobin ,100 g/L in infants ,4 wk) Platelets <100 x 10^9 /L Neutrophils ,1.0 x 10^9 /L)
Hypertriglyceridemia and/or hypofibrinogenemia Fasting triglycerides ≥3.0 mmol/L (ie, ≥265 mg/dL) Fibrinogen ≤1.5 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy.
Low or no NK cell activity (according to local laboratory reference)
Ferritin ≥500 mg/L
sCD25 (ie, soluble IL-2 receptor) ≥2400 U/mL

Figure 2. Trends in HLH laboratory values with anti-CMV therapy



Day 0: Requiring HFNC, start of high dose dexamethasone therapy
Day 1: Ganciclovir therapy started
Day 10: Oxygen requirements improved to only nasal cannula, downgraded from ICU
Day 11: Valganciclovir therapy started, and was stable to discharge from hospital

Discussion

- Primary HLH stems from inherited defects in cytotoxic T cells, NK cells, or inflammasome regulation. Secondary HLH arise from various causes like infections, malignancies, and impaired macrophage activation[1].
- Hallmarks of Hemophagocytic Lymphohistiocytosis (HLH) includes excessive inflammation leading to tissue injury. Mechanism is likely from proliferation of activated macrophages and lymphocytes that lead to downregulation of T cells and NK cells[3]. Multi-organ failure is common, often with respiratory failure.
- Cytomegalovirus-induced HLH (CMV-HLH) is exceedingly rare. It is even rarer to have a patient meet all 8 criteria[2].
- Patient's **bone marrow biopsy was 70-80% cellular, macrophages suspicious for hemophagocytosis. No phagocytosis of nucleated cells was noted.** Flow was negative for blasts or any immunophenotypic abnormalities. Additional tests found **normal NK function, but CXCL9 titer was 18,718 and serum IL-2 level was 5862.**
- Serum IL2 level <2400 ruled out HLH in a 2017 retrospective study[4]. And elevated CXCL9 and IFN-ɣ titers were strongly associated with malignancy-induced HLH vs infection induced[5]. Serum ferritin is 90% sensitive for HLH, but serum CD25 is >90% sensitive and 80% specific for HLH[6].
- Although bone marrow biopsy was borderline, patient had already met 5/8 HLH criteria to make the diagnosis.
- Current standard therapy for HLH is etoposide and steroids[1].
- A recent systematic review of 67 cases of HLH-CMV found that 19/67 (28%) patients were only treated for CMV infection and showed clinical improvement[7].
- This patient started to improve clinically when inciting factor of HLH was treated with ganciclovir.
- Antiviral drugs may play a key role in HLH-CMV treatment.

References

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