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Case Report

# CMV Induced HLH in a Patient with Granulomatosis with Polyangiitis

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**Abstract**

Hemophagocytic lymphohistiocytosis [HLH] is a rare condition marked by over-activation of the immune system leading to uncontrolled systemic inflammation. It is characterized by cytokine storm with over-activation of T-cells and macrophages, leading to tissue damage, multi-organ failure [1]. HLH presents a wide array of symptoms that are not easily differentiated from systemic inflammatory response and as such the diagnosis is often delayed. Mortality rates are high, ranging from 40%-70% [2]. To confirm the diagnosis, the HLH-2004 criteria are used. The criteria include molecular diagnosis and/or clinical and laboratory diagnosis [1]. HLH can be associated with rheumatologic conditions and triggered by infection. In this case report we highlight a middle-aged woman with a rare cause of HLH: cytomegalovirus-induced HLH in a patient with granulomatosis with polyangiitis.

**Keywords**: Hemophagocytic lymphohistiocytosis; Immune System; Granulomatosis; Polyangiitis; Inflammation

## Introduction

HLH could be primary or secondary. Primary HLS is triggered by a genetic mutation, and secondary HLH is triggered by external factors including viral infection, malignancies, autoimmune disease, and organ transplant [3]. Viral infections are a well-known cause of secondary HLH. Cytomegalovirus (CMV) is a virus in the herpes family known to cause HLH in rare cases. The ability to recognize the characteristic clinical traits and perform specific HLH diagnostic workup are key factors to ensure targeted diagnostic work and treatment intervention for this patient group [4]

### Case Presentation

An older adult female in her 50s with a history of granulomatosis with polyangiitis on azathioprine, and chronic kidney disease (CKD) presented to the Emergency Room (ER) complaining of fevers, weakness, and fatigue of 2 days. She was found to be hypotensive, tachycardic, with CBC showing bicytopenia (leukopenia and thrombocytopenia). Blood cultures were collected, and she was started on vancomycin and cefepime empirically.

Her hospital course was remarkable for persistent fevers despite antibiotic therapy, with a Tmax of 102.4. Further work-up showed positive CMV titers by PCR. The infectious disease team was consulted, and she was started on ganciclovir. CT of the chest, abdomen, and pelvis was done to evaluate for infectious source and revealed splenomegaly with spleen measuring 14 cm and mild cirrhotic liver morphology. Additional labs reviewed extremely elevated ferritin at 2948, low fibrinogen of 132, and worsening bicytopenias.

There were concerns for HLH, so IL-2/CD25 test, and IL 18 level were ordered, as well as a bone marrow biopsy. She continued to have high-grade fevers, despite continued antimicrobial therapy.

Although bone marrow biopsy showed no hemophagocytosis, she was started on steroids, with resolution of her fevers, and improvement in thrombocytopenia. Her IL 18, and IL-2R came back significantly elevated. She improved with steroid treatment and was discharged in stable condition.

**Investigation**

CT chest abdomen pelvis with contrast showing;

The liver has a mildly cirrhotic morphology. Enlarged spleen measuring 14.0 cm, small volume of ascites. (Figure 1)

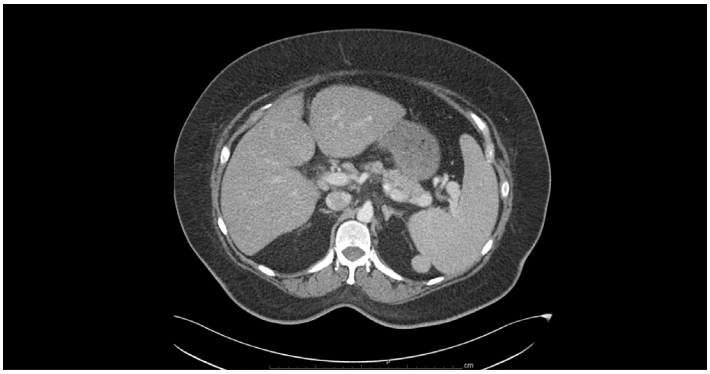

**Figure 1:** CT Chest Abdomen Pelvis.

**Treatment**

Following evaluation by Hematology-Oncology, she was started on dexamethasone.

**Outcome and follow-up**

Her fever subsided with improvement in bicyopenia after the initiation of steroids. She was subsequently discharged home on valganciclovir and Decadron taper. At 2-month post discharge, her CMV viral load continued to down trend to less than 50.

**Discussion**

HLH is driven by an overactivation of the immune system [1] and in most cases, can be fatal without treatment. [2] HLH can occur as a consequence of multiple genetic abnormalities or environmental triggers.

Epstein-Barr virus (EBV), a ubiquitous and predominantly B-lymphotropic human herpesvirus, is the most implicated trigger for secondary HLH [2] Other virus-induced HLH reported in case reports include CMV, COVID-19. Among rheumatological diseases, systemic lupus erythematous, adult-onset still disease, and ankylosing spondylitis are strongly associated with HLH [1,4]. There are only a few reported cases of CMV induced HLH in the literature and CMV induced HLH in patients with GPA is rare. One case-based systematic review reviewed 74 patients with CMV-induced HLH, 10 of these patients had autoimmune diseases, and only 1 patient (1.4%) had GPA [5]. One case report highlighted a presentation of HLH in an elderly male after initiation of rituximab following a new diagnosis of GPA, although it was not induced by CMV, unlike our patient.

HLH is often a diagnostic challenge especially when there are coexisting rheumatologic conditions [1]. A bone marrow biopsy negative for hemophagocytosis does not rule out HLH. A high index of suspicion is therefore necessary for early diagnosis and initiation of therapy. Timely diagnosis is critical to start therapy before damage by hypercytokinemia becomes irreversible [6].

**Learning Points/Take-home message.**

- This is a rare case of CMV-induced HLH in an immunosuppressed patient. HLH is characterized by cytokine storm with over activation of T-cells and macrophages, leading to tissue damage, multi organ failure.
- Mortality rates are high, ranging from 40%-70%, hence prompt diagnosis and treatment initiation is vital.
- We urge readers to have a high index of suspicion of HLH in immunocompromised patients presenting with sepsis with unknown etiology and not responding to antibiotic therapy.
- A multidisciplinary team approach is required for prompt diagnosis and treatment. Teamwork between the internist, infectious disease, and hematology-oncology is crucial to achieve safe and timely patient care.

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