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Case Report

Disseminated CMV Infection Associated Hemophagocytic Lymphocytosis in an Iatrogenic Immunocompromised Host

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Abstract

Hemophagocytic Lymphohistiocytosis (HLH) is a rare hematological condition that presents as a sequela of an underlying pathological process CMV has been documented to be a precipitant of HLH. We present the case of a 68-year-old immunocompromised female who developed multisystem organ failure which was later suspected to be secondary to HLH.

Hemophagocytic Lymphohistiocytosis (HLH) is critical condition precipitated by the generation of inflammatory cytokines and overactivation of macrophages and cytotoxic T cells. Symptoms primarily emerge in the setting of unbridled immune activation and lead to multiorgan failure that mirrors sepsis. HLH leads to a high morbidity and mortality, with one systematic review citing a pooled mortality rate of 41% despite treatment. Primary (genetic) HLH is caused by derangements in immune regulation due to variants in the *PRF1, UNC13D, STX11*, and *STXBP2* genes, and primarily affects children. In contrast, secondary HLH is precipitated by infection, malignancy, autoimmune disease, organ transplantation and immunosuppression. While these etiologies of HLH differ, the downstream pathophysiology converges and results in immune dysregulation and cytokine storm. Our case illustrates a 68-year-old woman who was transferred to the ICU with worsening fever, altered mental status and eventual respiratory failure.

Introduction

Hemophagocytic lymphohistiocytosis is a rare disorder that has become more recognized in adults with an incidence of 1.2 patients/million per year. The mechanism of HLH is secondary to defective $CD8^+$ T cell and/or Natural killer (NK) cell cytotoxicity that leads to persistent macrophage activation, engulfment of host blood cells, and cytokine storm. HLH is subdivided into primary and secondary types. Primary HLH is characterized by genetic mutations involved in the cytotoxic functions of immune cells. Secondary HLH can result from multiple etiologies such as underlying hematologic malignancy or viral infection and is managed by identifying and treating the underlying cause in addition to immunomodulation. Primary HLH can commonly be identified through molecular analysis.

Traditionally, the diagnosis of reactive HLH has been achieved through use of pediatric criterion known as the HLH-2004 criterion. The diagnosis requires the presence of 5 out of 8 criteria: (1) splenomegaly; (2) cytopenias in >1 cell lineages; (3) hypertriglyceridemia and/or hypofibrinogenemia; (4) biopsy demonstrating evidence of hemophagocytosis; (5) low or no NK cell activity; (6) hyperferritinemia; (7) soluble IL-2 receptor >2400; (8) fever. In 2014, Fardet et al. developed the H-score for diagnosis of reactive HLH by providing weighted scores to the above criteria in the absence of readily available cytokine data (NK cell activity and soluble Il-2 receptor levels) [1-5]. The score ranges from 0-337, with a score ≥ 250 yielding a 99% probability of HLH. A score less than 169 are typically used to rule out HLH [6].

Although Ebstein-Barr Virus (EBV) is the most common viral infection associated with HLH, cytomegalovirus (CMV) is also a known trigger. CMV-induced HLH is linked to immunosuppression by agents such as prednisone and can lead to a distributive shock presentation that can quickly lead to mortality if not recognized quickly [3].

Case Presentation

A 68-year-old female with a history of presumed Thrombotic Thrombocytopenic Purpura (TTP), hypertension, and insulin-dependent diabetes complicated by neuropathy and retinopathy was transferred to a tertiary medical center for refractory thrombocytopenia prior to transfer, she had been treated multiple cycles of steroids, plasmapheresis for 5 days, and rituximab weekly for 4 weeks. Her prior hospitalization was also complicated by anaplasmosis which was treated with 10 days of doxycycline. After transfer to our hospital, she was managed with high-dose prednisone for presumed TTP. She was also found to have CMV viremia of >20 million on qPCR and started on ganciclovir. Three days after admission, she developed worsening altered mental status, hypotension, and focal neurological deficits. She was then transferred to the ICU for acute hypoxic respiratory failure with increasing oxygen requirements necessitating intubation. Imaging was performed and showed pulmonary findings consistent with acute respiratory distress syndrome. She became febrile and developed increasing pressor requirements, prompting empiric management for septic shock. She quickly developed multi-system organ failure including hepatic and renal involvement. During her course, labs were notable for neutropenia,

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thrombocytopenia, ferritin of 19,774, hypertriglyceridemia reaching 1,484, elevated LDH to 1808, and profoundly elevated LFTs. There was low concern for active TTP at that time given repeat ADAMTS 13 activity was 95% during admission and absence of schistocytes on peripheral blood smear. Given her continued progressive end-organ dysfunction despite broad antimicrobial coverage, there became higher concern for infection-associated HLH. The diagnostic criteria met in this case included fever, cytopenia of 2 cell lines (thrombocytopenia, neutropenia), hypertriglyceridemia, and hyperferritinemia allowing for an H score of 213. Given the overall clinical context, the patient was treated for suspected CMV-associated HLH with high-dose dexamethasone and continued on ganciclovir. Despite these measures, she continued to develop electrolyte derangements and worsening metabolic acidosis which ultimately resulted in a PEA arrest.

Discussion

HLH is recognized as a cause for multisystem organ dysfunction resembling sepsis. In consideration of a viral trigger, EBV is noted to be more common than CMV [7,8]. Although anaplasmosis may also trigger HLH, our patient was appropriately treated for this with doxycycline during a prior hospitalization which makes this patient's CMV a more probable trigger. Cases of CMV typically arise in immunocompromised patients, whether secondary to HIV *vs.* medication induced immunosuppression. The underlying pathogenesis of CMV-induced HLH remains unknown; however given the presence of pulmonary involvement, it can be proposed that a local cytokine response in the lung can lead to rapid replication of CMV and a high mortality rate. Treatment for CMV induced-HLH is with valganciclovir/ganciclovir and initiation of corticosteroids [7-9]. Treatment of the infectious trigger is critical as prolonged immunosuppressive therapy without antiviral treatment presents a risk of reactivation/worsening of the underlying infection.

This case was notable as it emphasized the importance of early consideration of HLH given the high mortality rate and clinical similarity to sepsis which warrants different treatment [10]. It also highlighted the importance of early CMV recognition in immunocompromised hosts given the risk of latent CMV reactivation and necessity of rapid treatment initiation. CMV is notable for causing colitis, meningitis, and encephalitis in immunocompromised patients but can rarely trigger HLH as suspected in our case [11]. Finally, it emphasized the diagnostic limitations of the HLH-2004 criterion as it may be a challenge to perform a bone marrow biopsy in decompensating patients. Finally, another consideration for this patient would have been the initiation of etoposide. However, given her rapid clinical decline, treatment with etoposide was deferred as she was not clinically stable.

The H-score may be a more reliable tool for screening patients suspected to have HLH due to the ease with acquiring the required metrics. Moreover, this score is less restrictive and cost effective in providing a diagnosis. Its utility in clinical practice has shown a sensitivity of 93% and specificity of 86%. However, the score has its limitations as well. Given the lack of a gold-standard diagnostic method or pathognomonic finding for HLH, identification of patients in the original study who truly have HLH is difficult. Secondly, the presentation of HLH may vary widely, especially given the number of underlying processes that may precipitate it. Therefore, static cutoffs for lab values may not fully encapsulate the spectrum of presentations associated with HLH [6,12]

Notably, the underlying precipitant of HLH plays a major role in prognostication. Studies suggest that viral and autoimmune etiologies lead to improved survival rates compared to neoplastic etiologies interestingly, it appears that treatment-associated drug toxicities may contribute to the high mortality rate seen in HLH, particularly later in the course of the disease [13].

Conclusions

CMV-induced HLH is a rare manifestation of viremia in the immunocompromised patient. Our case highlighted the importance of clinical reasoning that must be present when initiating immunosuppressive therapy. Moreover, it served to highlight the risk of pulmonary involvement in unregulated immune activation. Moving forward, clinicians should perform a thorough medical review with special attention to immunosuppressive medications and foster awareness for other causes of multisystem organ failure such as HLH based upon clinical context, laboratory findings and integration of the H score in clinical management.

References

1. George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. J Blood Med. 2014;5:69-86.
2. Zhang K, Astigarraga I, Bryceson Y, Lehmberg K, Machowicz R, Marsh R, et al. Familial Hemophagocytic Lymphohistiocytosis. GeneReviews®. 2006.
3. Bonnecaze AK, Willeford WG, Lichstein P, Ohar J. Acute Cytomegalovirus (CMV) Infection Associated with Hemophagocytic Lymphohistiocytosis (HLH) in an Immunocompetent Host Meeting All Eight HLH 2004 Diagnostic Criteria. Cureus. 2017;9(3):e1070.
4. Lau A, Youn H, Caricchio R, Brent L. A Case of Cytomegalovirus-Induced Hemophagocytic Lymphohistiocytosis in a Patient with an Underlying Rheumatic Disease. Cureus. 2020;12(5):e8130.
5. Soy M, Atagündüz P, Atagündüz I, Sucak GT. Hemophagocytic lymphohistiocytosis: a review inspired by the COVID-19 pandemic. Rheumatol Int. 2021;41(1):7-18.
6. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014;66(9):2613-20.
7. Janka GE, Lehmberg K. Hemophagocytic lymphohistiocytosis: pathogenesis and treatment. Hematology Am Soc Hematol Educ Program. 2013;2013:605-11.
8. Rolsdorph LÅ, Mosevoll KA, Helgeland L, Reikvam H. Concomitant Hemophagocytic Lymphohistiocytosis and Cytomegalovirus Disease: A Case Based Systemic Review. Front Med (Lausanne). 2022;9:819465.
9. Singh A, Chauhan A, Padole V, Chhabra D, Upneja R. The great masquerader: Hemophagocytic lymphohistiocytosis secondary to cytomegalovirus infection in an immunocompetent young man. J Family Med Prim Care. 2020;9(7):3762-5.
10. Bauchmuller K, Manson JJ, Tattersall R, Brown M, McNamara C, Singer M, et al. Hemophagocytic lymphohistiocytosis in adult critical care. J Intensive Care Soc. 2020;21(3):256-68.
11. Mozaffar M, Shahidi S, Mansourian M, Badri S. Optimal Use of Ganciclovir and Valganciclovir in Transplanted Patients: How Does It Relate to the Outcome? J Transplant. 2018;2018:8414385.
12. Khare N, Jinkala SR, Kanungo S. Performance of HScore in Reactive Hemophagocytic Lymphohistiocytosis. Indian J Hematol Blood Transfus. 2021;37(2):256-63.
13. Yoon JH, Park SS, Jeon YW, Lee SE, Cho BS, Eom KS, et al. Treatment outcomes and prognostic factors in adult patients with secondary hemophagocytic lymphohistiocytosis not associated with malignancy. Haematologica. 2019;104(2):269-76.