Case Report

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Infection-associated hemophagocytic lymphohistiocytosis: a case report

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Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a rare hyperinflammatory disorder characterized by fever, cytopenia, splenomegaly, and hemophagocytosis. Without prompt treatment, HLH can rapidly progress to life-threatening multiorgan failure. The authors present a case of occult HLH with severe bicytopenia and organ dysfunction requiring intensive care.

Case presentation: A 20-year-old male presented with fever, cough, and constitutional symptoms. He developed hypoxia, elevated transaminases, and bicytopenia. Despite transfusions, platelet counts remained critically low. With high suspicion for HLH, head computed tomography and bone marrow biopsy was although panned but couldn't be performed due to resource less settings. And with suspicion for HLH treatment with high-dose dexamethasone was initiated as counts improved.

Clinical course: The patient required mechanical ventilation for pulmonary infiltrates. He exhibited seizure activity and epistaxis related to coagulopathy. On hospital day 9, he was successfully extubated as counts normalized. He was discharged from the intensive care unit once stable.

Conclusion: This case illustrates a delayed diagnosis of HLH masquerading as a fever of unknown origin. HLH should be urgently considered in patients with unexplained cytopenia, organ dysfunction, and systemic inflammation. Early treatment with immunotherapy can be lifesaving, whereas delays may precipitate irreversible end-organ damage.

Keywords: case report, hemophagocytic lymphohistiocytosis, HLH, immunotherapy, organ failure, pancytopenia

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening hyperinflammatory syndrome characterized by severe hypercytokinemia and uncontrolled activation of lymphocytes and macrophages[1]. There are primary (genetic) and secondary (acquired) forms of the disease. Secondary HLH can occur after infection, malignancy, rheumatologic disease, or other triggers[2].

The hallmark feature of HLH is hemophagocytosis, or the pathological phagocytosis of blood cells and their precursors by activated, morphologically benign macrophages[3]. This occurs throughout the reticuloendothelial system including the bone marrow, spleen, and lymph nodes. Patients clinically present with nonspecific symptoms including fever, hepatosplenomegaly, cytopenia, coagulopathy, and neurological symptoms. Diagnosis is made based on clinical and laboratory criteria from the Histiocyte Society HLH-2004 guidelines[4].

Prompt diagnosis and treatment of HLH is imperative given mortality rates up to 60% in pediatric cases and approaching 100% in untreated adults[1]. Standard HLH therapy consists of immunosuppression and etoposide-based chemotherapy[3,5]. For refractory disease, hematopoietic stem cell transplant may be considered. Supportive care and treatment of underlying triggers are also important. With therapy, survival in pediatric cases now exceeds 90%[5].

HIGHLIGHTS

- Rare condition: HLH is a life-threatening hyperinflammatory syndrome with high mortality rates.
- Diagnostic challenges: Resource limitations prevented some diagnostic procedures, relying on clinical suspicion.
- Rapid progression: Patient quickly deteriorated, requiring ICU care and mechanical ventilation.
- Treatment response: High-dose dexamethasone therapy led to clinical improvement.
- Adult HLH challenges: Higher mortality in adults compared to pediatric cases, emphasizing need for research.

Case details

A 20-year-old unmarried male of Buddhist faith and employed as a part-time chef, resident of Lalitpur, presented to the emergency department with a chief complaint of fever for the past 5–6 days.

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The fever was acute in onset, initially intermittent but later continuous, with a maximum temperature of 103° Fahrenheit, and associated with chills but no rigors. He also reported a cough that started gradually, was progressive in nature, productive with mucoid sputum about 1/2 teaspoon in volume, non-foul smelling, and not associated with chest pain, breathing difficulty, diurnal variation, or positional variation.

In addition to the fever and cough, the patient endorsed constitutional symptoms such as malaise, muscle aches, and joint pain, along with decreased appetite. He did not have any other relevant positive medical history but notably reported recent travel for one day and poor lodging conditions on the night prior to the onset of symptoms. No relevant past history, family and genetic history.

On examination, the patient appeared ill-looking or toxic and was icteric. Cardiovascular, respiratory, and neurological examination were otherwise unremarkable. On abdominal exam, he was found to have right upper quadrant and left upper quadrant tenderness along with splenomegaly on palpation.

In the emergency department, the patient received symptomatic management. A baseline lab workup was ordered along with an abdominal ultrasound. Results showed bicytopenia with severe thrombocytopenia of 34 000 per cubic mm, leukopenia with neutrophil predominance, abnormal liver function tests with total bilirubin of 3 mg/dl, direct bilirubin of 0.9 mg/dl, decreased total protein of 4.4 g/dl, decreased albumin of 2.6 g/dl, and elevated AST and ALT in approximately equal proportions. Abdominal ultrasound revealed grade 1 fatty liver enlargement, splenomegaly, and was otherwise unremarkable.

As lab results were still pending, the patient was admitted to the ICU for a fever of unknown origin with liver dysfunction and bicytopenia. By the day of ICU admission, he had developed hypoxia with oxygen saturations dropping to 83% requiring supplemental oxygen by face mask. Blood counts now showed worsening leukopenia of 2900 per cubic mm and thrombocytopenia of 15 000 per cubic mm. The antibiotic regimen was escalated and platelet transfusions were given.

Over the next several days in the ICU, the patient had persistently critically low platelet counts requiring multiple transfusions. He developed tachycardia and had an episode of epistaxis and seizure on day 4 requiring intubation. Head computed tomography (CT) was planned which showed normal findings. Mechanical ventilation was continued for pulmonary infiltrates now evident on imaging. Hemophagocytic lymphohistiocytosis was clinically suspected prompting high-dose steroid therapy. With immunomodulation, counts started improving. He was successfully extubated on day 9 and transferred out of the ICU once stable.

Follow-up and outcomes

The patient's clinical status was closely monitored, showing improvement in cytopenia, organ dysfunction, and successful extubation after initiating high-dose dexamethasone treatment. Adverse events included respiratory failure requiring mechanical ventilation, seizures, and bleeding complications, which were managed accordingly as per the standard of care.

Discussion

This case highlights a prototypical presentation of secondary HLH triggered by suspected infection in a previously healthy young adult male. The patient exhibited the classic constellation of HLH signs including prolonged fevers, bicytopenia, splenomegaly, elevated ferritin. Infectious pathogens, especially viruses, represent the most frequent precipitant of acquired HLH in adults, with Epstein-Barr virus being the predominant culprit[1]. Although an inciting microbe was not identified in this patient, his clinical picture was compatible with infection-induced HLH.

The diagnostic delay and rapid deterioration seen in this case are tragically commonplace in HLH and with the patient being treated in the center is in rural setting Despite advances in recognition of HLH, the median interval from symptom onset to diagnosis remains ~4 weeks as the disease often initially mimics more benign viral syndromes[6]. By the time full-blown HLH manifests, mortality risk is exceedingly high, underscoring the imperative need for prompt identification and intervention. The recently validated HScore provides a useful tool for risk-stratifying patients with suspected HLH[6]. Immediate initiation of HLH-2004 protocol with high-dose dexamethasone and etoposide has been shown to dramatically improve outcomes even before confirmatory results are available[7].

Neurologic manifestations develop in 20–73% of HLH patients and portend worse prognosis[8,9]. This patient exhibited seizure activity likely stemming from HLH-associated encephalitis. In any HLH case with neurological signs, cerebrospinal fluid analysis should be strongly considered given the potential for central nervous system involvement. MRI findings are variable in HLH but may demonstrate classic changes like bilateral thalamic lesions[10]. Unfortunately, no imaging could be obtained in this resource-limited setting.

Several other noteworthy points are illustrated in this case. The need for ICU-level care and mechanical ventilation reflects the speed at which HLH can progress to life-threatening multiorgan failure. Thrombocytopenia and coagulation defects often complicate HLH, as seen by this patient's epistaxis, further increasing morbidity[1]. Finally, the response to immunomodulation steroids aligns with the expected treatment response, albeit delayed due to late diagnosis.

Regarding diagnosis, fulfilling five out of eight criteria according to the HLH-2004 guidelines remains the standard for definitively establishing HLH[4]. However, waiting for official confirmation often leads to unacceptable delays given the rapid progression of the disease. A threshold ferritin level above 10 000 μg/l carries high sensitivity and specificity for HLH and should prompt immediate initiation of treatment in the proper clinical context[11]. More recently, the HScore has been validated as a useful predictive tool for calculating an HLH probability score based on clinical and laboratory variables[6]. Applying these modern statistical approaches earlier in the diagnostic process may enable lifesaving therapy in occult HLH cases.

The cardinal role of HSCT as the only established curative therapy for genetic and refractory forms of HLH[12]. HSCT can induce long-term remission if applied in a timely manner before end-organ damage accrues. Overall survival now approaches 50-75% in pediatric HLH patients undergoing HSCT, especially with better donor matching and conditioning regimens[13]. Early consultation with a transplant center is imperative when hereditary HLH is suspected or patients fail to improve on standard HLH protocols.

Finally, this case reveals the continued challenges in managing adult-onset HLH. Pediatric HLH survival has markedly improved to over 90% in recent years, while mortality in adults remains 60–75%[1]. The rarity of the disease in adults coupled with low awareness and delayed diagnosis largely explain this discrepancy. Enrollment in clinical trials, genetic testing when

applicable, and centralized care models could help mirror the therapeutic gains witnessed in pediatric HLH. Further research is urgently needed to determine optimal treatment strategies and improve the historically poor prognosis in adult patients with this life-threatening syndrome.

Patient perspective

The patient initially presented with symptoms resembling a viral illness, but his condition rapidly worsened with concerning blood abnormalities, liver issues, and breathing difficulties. Although frightening, the patient's critical illness improved after prompt treatment with high-dose steroids, despite challenges during the intensive care stay. He was ultimately grateful for the medical team's timely recognition and management of his rare, life-threatening condition.

Conclusion

In summary, HLH necessitates prompt recognition and initiation of targeted therapy to arrest the uncontrolled hypercytokinemia and astonishingly high mortality rate. This case reinforces the variable manifestations of HLH and the obligation to maintain a high index of suspicion in the appropriate clinical context. Moving forward, international collaborative efforts for earlier diagnosis and novel therapies such as JAK inhibitors offer promise in improving outcomes for this devastating illness.

Ethical approval

Ethics approval not required for this case report as direct written consent was taken from the patient for the publication. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

K.M. and A.T. were involved in conception of the study, acquisition of data, drafting and reshaping the initial manuscript, and revising the contents. A.C., M.S., S.B.B., P.A. helped in revising the manuscript critically for important intellectual content. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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Data availability statement

I confirm that any datasets generated during and/or analyzed during the current study are available upon reasonable request.

Provenance and peer review

Not applicable.

References

[1] Ramos-Casals M, Brito-Zerón P, López-Guillermo A, *et al*. Adult haemophagocytic syndrome. Lancet (London, England) 2014;383:1503–16.
[2] Canna SW, Behrens EM. Not all hemophagocytes are created equally: appreciating the heterogeneity of the hemophagocytic syndromes. Curr Opin Rheumatol 2012;24:113.
[3] Jordan MB, Allen CE, Weitzman S, *et al*. How I treat hemophagocytic lymphohistiocytosis. Blood 2011;118:4041.
[4] Henter JI, Horne AC, Aricó M, *et al*. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–31.
[5] Marsh RA, Allen CE, Mcclain KL, *et al*. Salvage therapy of refractory hemophagocytic lymphohistiocytosis with alemtuzumab. Pediatr Blood Cancer 2013;60:101–9.
[6] Rivière S, Galicier L, Coppo P, *et al*. Reactive hemophagocytic syndrome in adults: a retrospective analysis of 162 patients. Am J Med 2014;127:1118–25.
[7] Bergsten E, Horne AC, Aricó M, *et al*. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood 2017;130:2728.
[8] Yang S, Zhang L, Jia C, *et al*. Frequency and development of CNS involvement in Chinese children with hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2010;54:408–15.
[9] Kim MM, Yum MS, Choi HW, *et al*. Central nervous system (CNS) involvement is a critical prognostic factor for hemophagocytic lymphohistiocytosis. Korean J Hematol 2012;47:273.
[10] Van Cauter S, Severino M, Ammendola R, *et al*. Bilateral lesions of the basal ganglia and thalami (central grey matter)—pictorial review. Neuroradiology 2020;62:1565.
[11] Allen CE, Yu X, Kozinetz CA, *et al*. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2008;50:1227–35.
[12] Trottestam H, Horne AC, Aricò M, *et al*. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood 2011;118:4577–84.
[13] Marsh RA, Vaughn G, Kim MO, *et al*. Reduced-intensity conditioning significantly improves survival of patients with hemophagocytic lymphohistiocytosis undergoing allogeneic hematopoietic cell transplantation. Blood 2010;116:5824–31.