Fever of Multiple Possible Origins: Acquired Hemophagocytic Lymphohistiocytosis in the Context of Pyelonephritis, Newly Diagnosed Systemic Lupus Erythematosus, and an Ulcer of the Aortic Arch

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Abstract

A 60-year-old man presented with 1 week of fever despite broad-spectrum antibiotics for presumed pyelonephritis based on extended spectrum bacteriuria, recent bladder catheterization, and a negative search for other infections. He developed a maculopapular truncal rash, and pancytopenia with persistent fevers and worsening inflammatory markers despite modifying then stopping antibiotics. The non-specific clinical features at presentation and absence of hemophagocytosis on the initial bone marrow aspirate confounded multiple subspecialists and delayed the final diagnosis of hemophagocytic lymphohistiocytosis (HLH). Once this syndrome was elucidated, he responded well to dexamethasone and etoposide. An underlying diagnosis of systemic lupus erythematosus with aortic vasculitis was made, which in combination with pyelonephritis likely precipitated HLH. We summarize current concepts, pitfalls, and lessons learned in the diagnosis and management of HLH.

Résumé

Un homme de 60 ans se présente à l'hôpital à la suite d'une semaine de fièvre malgré la prise d'antibiotiques à large spectre pour traiter une pyélonéphrite soupçonnée, fondée sur une bactériurie à spectre étendu, un cathétérisme vésical récent et une recherche infructueuse d'autres infections. Il a développé une éruption cutanée maculopapulaire sur le tronc et une pancytopénie accompagnée d'une fièvre persistante et d'une augmentation des marqueurs de l'inflammation malgré la modification, puis l'arrêt des antibiotiques. Les manifestations cliniques non spécifiques à la présentation et l'absence d'hémophagocytose lors de la ponction médullaire initiale ont confondu de multiples surspécialistes et retardé le diagnostic définitif de lymphohistiocytose hémophagocytaire (LHH). Une fois que ce syndrome a été élucidé, le patient a bien répondu au traitement par la dexaméthasone et l'étoposide. Un diagnostic sous-jacent de lupus érythémateux systémique accompagné d'une vascularite de l'aorte a été posé qui, combiné à la pyélonéphrite, a probablement précipité la LHH. Nous résumons les concepts actuels, les pièges et les leçons apprises dans le diagnostic et la prise en charge de la LHH.

Case Report

A 60-year-old man, who immigrated to Canada from Punjab 30 years prior, presented to another hospital with abdominal pain. He was known for a history of hypertension, non-alcoholic steatohepatitis, and obstructive sleep apnea. He was noted to be in urinary retention and was discharged home with an indwelling Foley catheter.

At home, he experienced recurrent fevers over the following week, and presented to a second hospital. Urine cultures grew extended-spectrum beta lactamase-producing E. coli. He was treated for presumed acute pyelonephritis with Piperacillin-Tazobactam and the urinary catheter was removed. Subsequently, an erythematous maculopapular facial and truncal rash appeared along with progressive leukopenia and thrombocytopenia, with mild anemia. Antibiotics were stopped given concern for a drug reaction, and he was transferred to our tertiary care institution for further work-up.

At presentation, he was afebrile and vitally stable. He was noted to have facial edema with a maculopapular rash affecting his face and trunk. There were several oral ulcers. His abdomen was benign, without hepatosplenomegaly. There was no lymphadenopathy. Cardiorespiratory exam was unremarkable.

He was noted to have a leukocyte count of 1.2×10^9 cell/L, neutrophil count of 0.51×10^9 cell/L, platelet count of 43×10^9 cell/L, triglyceride level of 3.44 mmol/L, ferritin level of 2408 g/L, and a fibrinogen level of 2.90 g/L. Blood cultures were sterile. Computed tomography (CT) scans of the chest and abdomen revealed small areas of consolidation in the right upper and middle lobes and a small lung nodule, with slightly enlarged axillary, supraclavicular, mediastinal, and hilar nodes. There were traces of retroperitoneal fluid around the pancreas. The spleen was 13.5 cm. A subsequent positron emission tomography (PET) scan showed no significant fluorodeoxyglucose (FDG) avidity in the lymph nodes and lung nodule. Skin biopsy showed mild, non-specific inflammatory changes, without evidence of drug reaction with eosinophilia and systemic symptoms (DRESS). Lymph node biopsy was non-diagnostic, and bone marrow biopsy was unremarkable. Multiple induced sputa were negative for acid-fast bacilli.

The patient's fevers soon recurred despite starting meropenem. He became increasingly delerious without focal features on neurologic examination, and without meningismus. An MRI of the head was normal. Repeat cultures were still sterile. In light of his worsening condition, a consensus decision between the involved subspecialty services was made to start pulse steroids (solumedrol 100 mg IV q12 h). At this time, the presence of tuberculosis had not been ruled out, so he was started on quadruple therapy with rifampin, INH, pyrazinamide, and ethambutol to prevent TB activation.

Despite an initial improvement with steroids, he again deteriorated, requiring ICU admission and intubation for distributive shock secondary to his severe inflammatory state. At this time, his laboratory parameters had worsened: triglyceride peak of 7.08 mmol/L, ferritin peak of 16,115 g/L. He now met 4/8 clinical criteria for hemophagocytic lymphohistiocytosis (HLH), but had an HScore of 212 (93–96% probability of HLH), so a diagnosis of HLH was favored. Steroids were switched to dexamethasone, and etoposide was started. Quadruple therapy was switched to INH given interaction between etoposide and the other tuberculosis (TB) drugs and a lower suspicion of tuberculosis at that time. A second bone marrow biopsy was performed and showed hemophagocytosis (Figure 1).

Work-up for predisposing conditions was notable for positive anti-nuclear antibodies, anti-double stranded DNA antibodies, and anti-histone antibodies, consistent with underlying systemic lupus erythematosus in the context of his rash and oral ulcers. He was eventually transitioned to steroid-sparing drugs mycophenolic acid and hydroxychloroquine.

The patient's condition improved and he was discharged to a rehabilitation facility. He returned 2 days after discharge following a fall without change in consciousness. A CT angiogram of the chest, done to rule out pulmonary embolism, revealed a

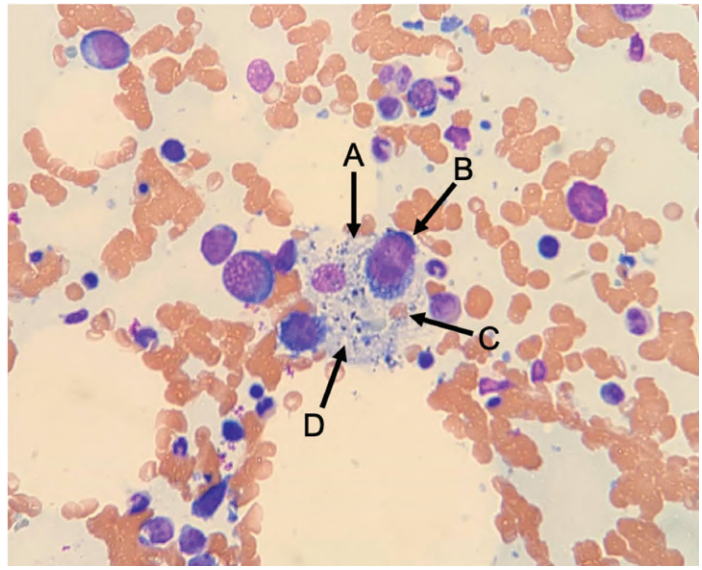

Figure 1. Bone marrow aspirate showing hemophagocytosis. Activated histiocyte engulfing erythrocytes, platelets (A). Early erythroid precursor undergoing phagocytosis (B). Erythrocyte undergoing phagocytosis (C). Platelets undergoing phagocytosis (D).

non-penetrating ulcer of the aortic isthmus which was felt to be secondary to lupus vasculitis. Serial CT scans have shown ulcer stability. The patient is now well and has returned to his previous activities.

Discussion

HLH is a clinical syndrome characterized by an exaggerated systemic inflammatory response secondary to unregulated activation of cytotoxic T lymphocytes and natural killer cells. HLH is classified as primary (aka genetic) HLH, or secondary (aka acquired) HLH.

Primary HLH is predominantly a pediatric disease but has been described in adults. Secondary HLH is usually seen in adults, and may be precipitated by infection, malignancy, or rheumatic disease. In infection-associated HLH, responsible for 50% of secondary HLH,[1] the most commonly identified organisms are viral, particularly EBV, HIV, and CMV.[1,2] Malignancy-associated HLH, 48% of cases,[1] occurs mostly in T-cell lymphomas and leukemias, but may occur with other hematologic or even solid malignancies, and in the context of chemotherapy (especially if the treatment course is complicated by infection).[1,3] HLH associated with rheumatologic conditions is rare but may arise in systemic lupus erythematosus, adult onset Still's disease, systemic onset juvenile idiopathic arthritis and other autoimmune disorders.[1] HLH that is due to rheumatologic conditions is commonly called macrophage activation syndrome (MAS).

HLH is associated with significant patient mortality, ranging from 20 to 88%.[4] Therefore, it is important for clinicians to consider this diagnosis, particularly in patients with evidence of systemic inflammation not responding to other therapy such as broad-spectrum antibiotics or tumor-specific chemotherapy.

Diagnostic criteria for HLH were developed by the Histiocyte Society in the HLH-1994 clinical trial.[5] The criteria were refined for the HLH-2004 clinical trial (Table 1).[6] Five of the eight clinical features are needed for diagnosis of acquired HLH: fever >38.5 C, splenomegaly, cytopenias affecting ≥2 of 3 lineages (hemoglobin <90 g/L, platelets < 100×10^9 cells/L, neutrophils <1.0×10^9 cells/L), hypertriglyceridemia (2.0 mmol/L), and/or hypofibrinogenemia (1.5 g/L), hemophagocytosis, ferritin >500 mcg/L, low/absent NK cell activity, and soluble CD25 elevation. Alternatively, familial HLH may be diagnosed with molecular studies demonstrating mutation in one of seven known HLH-associated genes: *PRF1*, *UNC13D*, *STXBP1*, *RAB27A*, *STX11*, *SH2D1A*, or *XIAP*.

Notably, these diagnostic criteria were established in pediatric patients. In addition, their use is limited by the lack of weighted importance for each criterion, and the difficulty in measuring certain parameters such as NK cell activity and IL-2R levels.

To assist in the diagnosis of HLH in adults, clinicians may use the HScore, an HLH probability calculator.[7] It calculates the probability of HLH based on several weighted clinical parameters, most of which are diagnostic criteria from HLH-2004 (Table 2). The HScore was found to have a sensitivity of 93% and specificity of 86% when the optimal cutoff value of 169 is used.[7] The HScore is more reliable that the HLH-2004 criteria in diagnosing HLH in both pediatric and adult patients.[8] Use of the HScore can also facilitate diagnosis in critically ill patients, in whom the HLH-2004 criteria are less sensitive.[9] Further confusing matters, critically ill patients are more likely to have hemophagocytosis in the absence of HLH.[9] As well, hemophagocytosis is not required for diagnosis of HLH, and is absent in 30–40% of cases.[10,11] Therefore, hemophagocytosis is neither sufficient nor required for diagnosis of HLH.

Treatment protocols are based on the HLH-94 guidelines for treatment of primary HLH in children.[5] According to this protocol, dexamethasone is given daily and tapered every week. Etoposide is given twice weekly, then at gradually increasing intervals. Cyclosporin treatment begins as early as Week 3. Intrathecal methotrexate is given for select patients with neurological symptoms not responsive to steroids, etoposide, and cyclosporin. Earlier administration of cyclosporin was assessed in the HLH-2004 trial, but outcomes were not significantly different.[6] Many pediatric patients will benefit from subsequent allogeneic stem cell transplant.

These protocols were developed for use in children, in whom HLH is almost always primary. There have been no large-scale clinical trials establishing the optimal treatment for adults. Therefore, management recommendations for HLH in adults are provided by the HLH in adults working group of the Histiocyte Society based on consensus expert opinion.[12]

These recommendations suggest that the HLH-94 protocol is highly effective for adults but may result in unnecessary toxicities in older individuals with other comorbidities. Individualized treatment protocols should thus be considered, such as dose reductions and shorter treatment durations. Depending on the underlying precipitant, different treatment protocols are suggested (Table 3).

The treatment differs most substantially for MAS, where high-dose pulse corticosteroids are the mainstay, and cyclosporin, interleukin-1 antagonists and interleukin-6 antagonists may be considered. Dexamethasone and etoposide are reserved for severe or refractory cases.

Table 1. HLH-2004 Diagnostic Criteria

A. Molecular diagnostic criteria for HLH	Mutation in any familial HLH-associated genes: PRF1, UNC13D, STXBP1, RAB27A, STX11, SH2D1A, XIAP
B. Five out of eight clinical criteria for HLH	Fever > 38.5C Splenomegaly Cytopenias affecting ≥ 2 of 3 lineages (hemoglobin < 90 g/L, platelets < 100×10^9 cells/L, neutrophils < 1.0×10^9 cells/L) Hypertriglyceridemia (2.0 mmol/L) AND/OR hypofibrinogenemia (1.5 g/L) Hemophagocytosis Ferritin > 500 mcg/L Low/absent NK cell activity Soluble CD25 elevation

Fulfillment of either A) or B) is required for diagnosis of HLH. Adapted from Henter et al.[6]

Table 2. The HScore

Clinical feature	HScore points	Probability of HLH
Known underlying immunosuppression	No = 0 pts Yes = 18 pts	90 pts = <1% 100 pts = 1% 110 pts = 3% 120 pts = 5% 130 pts = 9% 140 pts = 16% 150 pts = 25% 160 pts = 40% 170 pts = 54% 180 pts = 70% 190 pts = 80% 200 pts = 88% 210 pts = 93% 220 pts = 96% 230 pts = 98% 240 pts = 99% 250 pts = >99%
Temperature (Celsius)	<38.4 = 0 pts 38.4–39.4 = 33 pts >39.4 = 49 pts	
Number of cytopenias	1 lineage = 0 pts 2 lineages = 24 pts 3 lineages = 34 pts	
Ferritin (ng/L)	<2000 = 0 pts 2000–6000 = 35 pts >6000 = 50 pts	
Triglyceride (nmol/L)	<1.5 = 0 pts 1.5–4 = 44 pts >4 = 64 pts	
Fibrinogen (g/L)	>2.5 = 0 pts ≤ 2.5 = 30 pts	
Serum aspartate transaminase (IU/L)	<30 = 0 pts ≥30 = 19 pts	
Hemophagocytosis features on bone marrow aspirate	No = 0 pts Yes = 35 pts	

Weighted scores for clinical features of HLH and the probability of HLH based on total points. Adapted from Fardet et al.[7]

Often, HLH patients will require supportive management in the intensive care unit. This can be necessitated due to multiple organ failures, including vasoplegia,[13,14] acute respiratory distress syndrome,[13,15] neurological symptoms such as coma and seizures,[1,13,16] liver failure,[13] coagulopathies particularly as a result of hypofibrinogenemia,[13,17] and kidney failure.[13,18]

This case highlights the importance of including HLH in the differential diagnosis of patients presenting with fever or cytokine storm particularly if sepsis or malignancy is suspected and the patient is not responding to appropriate therapy. Application of the HLH-2004 clinical criteria and HScore can be useful in diagnosing this uncommon condition. Importantly, the absence of hemophagocytosis should not deter treatment if HLH is suspected, as it is not required for diagnosis. Treatment in adults should be highly individualized and based on the HLH-94 protocol.

Table 3. Summary of Treatment Protocols for Secondary HLH in Adults

		Steroids/IVIG	Etoposide	CNS agents	Stem cell transplant	Other comments
Malignancy-associated HLH	Triggered by malignancy	First-line corticosteroids ± IVIG prior to tumor-specific treatment	May be given prior to tumor-specific treatment or added to tumor-specific treatments such as CHOP	Consider if evidence of CNS involvement	Autologous or allogeneic SCT considered for those eligible for treatment intensification and in young patients with HLH and EBV-driven lymphoma who may have HLH-associated mutations on germline genetic testing	Consider germline genetic testing for HLH mutations in younger patients with HLH and lymphoma, particularly EBV-driven lymphoma
	Associated with chemotherapy	First-line corticosteroids ± IVIG	Avoid use if possible, to allow for bone marrow recovery	–	–	Consider this diagnosis when cytopenias are prolonged, persistent fevers despite antimicrobial therapy, other HLH features Also need to consider recurrent/refractory malignancy as the trigger
Infection-associated HLH	Triggered by EBV	First-line corticosteroids ± IVIG	Use if rapid clinical deterioration or severe disease	–	SCT may be considered for those with increasing or persistently high EBV DNA	May consider rituximab to target EBV replication in B cells
	Triggered by HIV	First-line corticosteroids ± IVIG	May be given for severe disease	–	–	Consider HIV directed therapy
	Triggered by other infections	Generally not required	Generally not required	–	–	Treatment of underlying infection is usually sufficient.
Rheumatic HLH (aka MAS)	–	First-line corticosteroids with high-dose pulse methylprednisolone	Reserved for patients with severe disease or CNS involvement despite steroids, cyclosporin or interleukin antagonists	–	–	MAS treatment differs from other HLH treatment. A highly personalized treatment approach is suggested, with high-dose steroids as the mainstay of treatment. Cyclosporin, interleukin-1 or -6 antagonists (eg. Anakinra and tocilizumab, respectively) can be added in refractory cases

Adapted from La Rosee et al.[12]

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References

1. Ramos-Casals M, et al. Adult haemophagocytic syndrome. Lancet. 2014;383(9927):1503–16. http://dx.doi.org/10.1016/S0140-6736(13)61048-X
2. Rouphael NG, et al. Infections associated with haemophagocytic syndrome. Lancet Infect Dis. 2007;7(12):814–22. http://dx.doi.org/10.1016/S1473-3099(07)70290-6
3. Lehmberg K, et al. Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. Haematologica. 2015;100(8):997–1004.
4. Hayden A, et al. Hemophagocytic syndromes (HPSs) including hemophagocytic lymphohistiocytosis (HLH) in adults: A systematic scoping review. Blood Rev. 2016;30(6):411–20. http://dx.doi.org/10.1016/j.blre.2016.05.001
5. Henter JI, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood. 2002;100(7):2367–73. http://dx.doi.org/10.1182/blood-2002-01-0172
6. Henter JI, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124–31. http://dx.doi.org/10.1002/pbc.21039
7. Fardet L, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014;66(9):2613–20. http://dx.doi.org/10.1002/art.38690
8. Debaugnies F, et al. Performances of the H-score for diagnosis of hemophagocytic lymphohistiocytosis in adult and pediatric patients. Am J Clin Pathol. 2016;145(6):862–70. http://dx.doi.org/10.1093/ajcp/aqw076
9. Meena NK, et al. The performance of diagnostic criteria for hemophagocytic lymphohistiocytosis in critically ill patients. J Intensive Care Med. 2020;35(12):1476–82. http://dx.doi.org/10.1177/0885066619837139
10. Gupta A, et al. The role of the initial bone marrow aspirate in the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2008;51(3):402–4. http://dx.doi.org/10.1002/pbc.21564
11. Riviere S, et al. Reactive hemophagocytic syndrome in adults: A retrospective analysis of 162 patients. Am J Med. 2014;127(11):1118–25. http://dx.doi.org/10.1016/j.amjmed.2014.04.034
12. La Rosee P, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood. 2019;133(23):2465–77. http://dx.doi.org/10.1182/blood.2018894618
13. Lemiale V, et al. Management of hemophagocytic lympho-histiocytosis in critically ill patients. J Intensive Care Med. 2020;35(2):118–27. http://dx.doi.org/10.1177/0885066618810403
14. Buyse S, et al. Critical care management of patients with hemophagocytic lymphohistiocytosis. Intensive Care Med. 2010;36(10):1695–702. http://dx.doi.org/10.1007/s00134-010-1936-z
15. Emmenegger U, et al. Reactive macrophage activation syndrome: A simple screening strategy and its potential in early treatment initiation. Swiss Med Wkly. 2002;132(17–18):230–6.
16. Haddad E, et al. Frequency and severity of central nervous system lesions in hemophagocytic lymphohistiocytosis. Blood. 1997;89(3):794–800. http://dx.doi.org/10.1182/blood.V89.3.794
17. Han AR, et al. Lymphoma-associated hemophagocytic syndrome: Clinical features and treatment outcome. Ann Hematol. 2007;86(7):493–8. http://dx.doi.org/10.1007/s00277-007-0278-6
18. Aulagnon F, et al. Acute kidney injury in adults with hemophagocytic lymphohistiocytosis. Am J Kidney Dis. 2015;65(6):851–9. http://dx.doi.org/10.1053/j.ajkd.2014.10.012