Postoperative Hemophagocytic Lymphohistiocytosis in an Adult Patient with High-Grade B-Cell Lymphoma: A Case Report

Mohannad Wazirali, MBBS*

ABSTRACT

Hemophagocytic Lymphohistiocytosis (HLH) is a rare and often fatal clinical syndrome that is frequently underdiagnosed due to a lack of specific clinical features. Malignancy-associated HLH (M-HLH) is a frequently encountered subtype of HLH in adults, with lymphoma being the most common underlying diagnosis; it carries a poor prognosis despite treatment. Surgery is an extremely rare trigger of HLH, which could, in part, be due to a wide range of known postoperative complications leading to underdiagnosis of postoperative HLH. We describe a case of an adult patient who presented with intestinal intussusception secondary to Burkitt or high-grade B-cell lymphoma that required hemicolectomy, followed by rapid postoperative deterioration, leading to the diagnosis of HLH. Postoperative HLH has a nonspecific presentation and shares features of other postoperative complications. However, due to the high risk of mortality if undiagnosed or untreated, considering and testing for HLH in unusual sepsis-like presentations is vital as treatment may improve survival chances.

Keywords: Hemophagocytic Lymphohistiocytosis, Lymphoma, postoperative complication

INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH) is a syndrome of overwhelming immune system activation that leads to hyperinflammation, multiorgan failure, and if untreated, death. With our growing understanding of the presence of genetic defects in some cases and the specific association with certain malignancies, autoimmune conditions, and infections, HLH was classified into two types: primary (hereditary) and secondary (acquired)[1]. Among secondary cases of HLH, surgery has been a rare trigger and was mostly reported in pediatric cases. Here, we describe a rare case of postoperative HLH in an adult patient with high-grade B-cell lymphoma, highlighting the diagnostic and therapeutic challenges.

CASE REPORT

A 36-year-old female presented with a three-week history of right upper quadrant abdominal pain, mild abdominal distention, nausea, fever, night sweats, and a 7-pound weight loss, and non-bloody diarrhea for one day. Her vital signs were unremarkable, and the rest of her physical exam was significant only for diffuse abdominal tenderness and overactive bowel sounds.

Initial workup showed mild leukocytosis, mild anemia, thrombocytopenia, elevated serum creatinine, and mildly elevated aspartate aminotransferase (AST). A peripheral blood smear showed circulating atypical cells suspicious for lymphoma (Figure 1). A computed tomography (CT) scan was performed and revealed hepatosplenomegaly, diffuse retroperitoneal and mesenteric nodularity and mural thickening and dilation of the terminal ileum and the proximal ascending colon with intussusception and possible bowel obstruction (Figure 2). A follow-up CT scan on the next day showed improvement in the bowel dilation, thus no surgical intervention was planned. She was treated conservatively with a plan to complete her workup as an outpatient with a bone marrow biopsy and colonoscopy with biopsies.

Over the next four days, her leukocytosis, serum creatinine, and lactic acid continued to trend upward. This led to the decision to perform an urgent exploratory laparotomy to rule out bowel ischemia, perforation, and for tissue diagnosis of possible malignancy. Intraoperatively, the terminal ileum was found tightly telescoping into the cecum and could not be reduced, but no ischemia or perforation was found. A right hemicolectomy with primary anastomosis and diverting loop ileostomy was performed.

Postoperatively, the patient remained hemodynamically stable for four hours before developing refractory hypotension and requiring norepinephrine. The antibiotic coverage was broadened to broad-spectrum antibiotics and antifungal therapy. Due to worsening acute kidney injury and concern for possible spontaneous tumor lysis syndrome, continuous veno-venous hemofiltration (CVVH) was started. Despite this, she continued to deteriorate rapidly over the span of 12 hours and by the morning she was on five vasopressors (Norepinephrine, Vasopressin, Epinephrine, Phenylephrine, and Angiotensin II). The Hematology team suspected HLH due to elevated serum ferritin (>9000μg/L) and serum triglycerides. They recommended sending confirmatory tests but also to start treatment for possible HLH with high-dose steroid and Anakinra. Later in the afternoon, her peripheral blood flow cytometry results were most consistent with Burkitt or high-grade B-cell lymphoma. Following discussions between the involved teams and the patient's family, the decision was made to start chemotherapy (R-EPOCH: Rituximab, Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin) as it is the only way of possible recovery. Etoposide was started later in the evening. However, a few hours later our patient had asystole and passed away.

DISCUSSION

HLH is a rare disease with a high mortality rate with an incidence of 1 case per 50,000 live births for primary HLH and 4.2-6.2 per million population for secondary forms with 1-year survival rate of 50%[1,2]. It is

* Internal Medicine Department,
Faculty of Medicine. King Abdulaziz University,
Rabigh, Saudi Arabia.
E-mail: mwazirali@kau.edu.sa

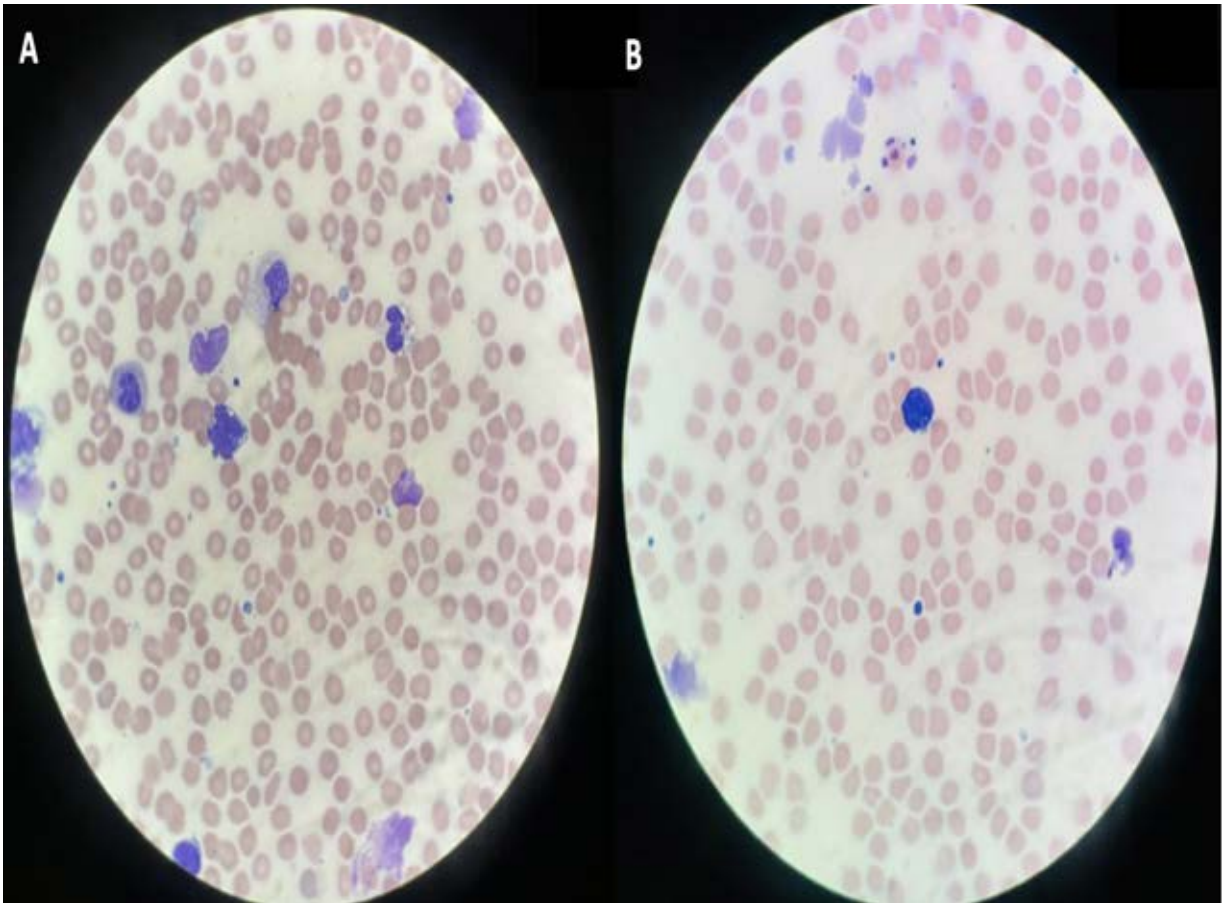

Figure 1. Leukoerythroblastic smear with circulating large atypical cells. The atypical cells have small amount of blue cytoplasm with vacuoles, irregular nuclear contours with variably visible nucleoli. The overall findings are suspicious for circulating lymphoma cells.

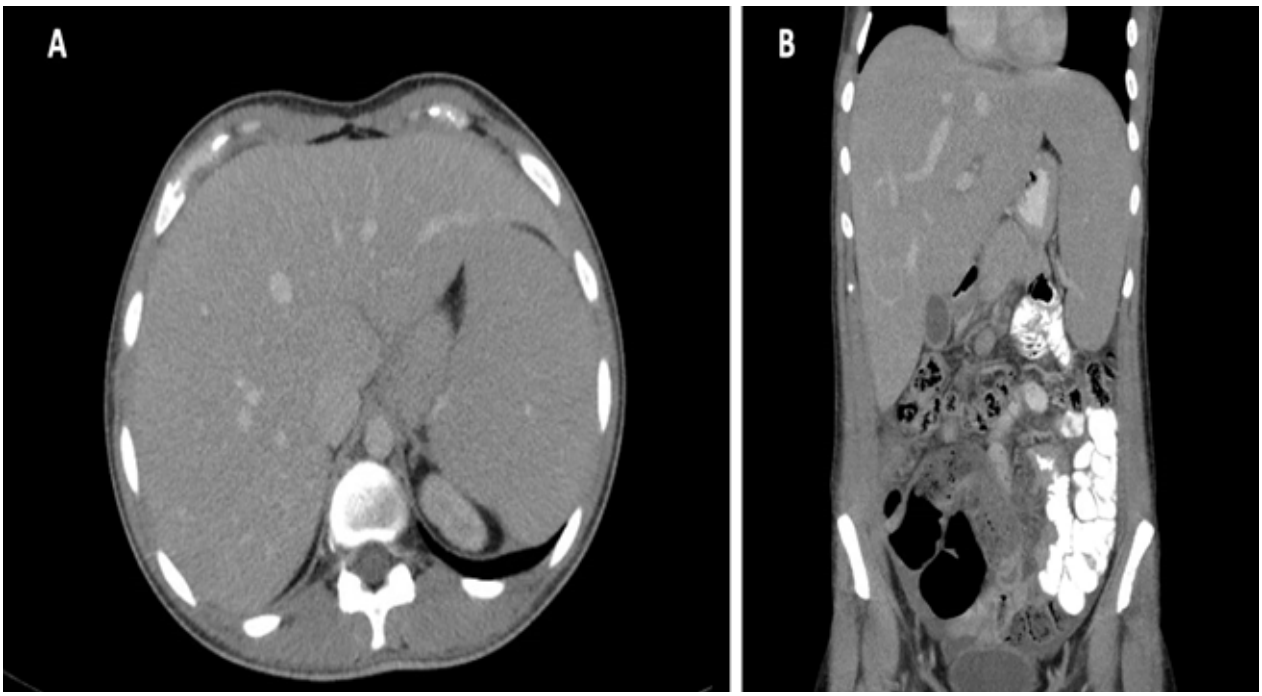

Figure 2: Computed Tomography (CT) scan with intravenous and oral contrast showing hepatosplenomegaly, poorly defined retroperitoneal and mesenteric nodularity, and possible mesenteric infiltration, mural thickening, and dilation of the terminal ileum and thickening of the cecum and proximal ascending colon with intussusception and possible obstruction.

likely a combination of underrecognition and a lack of specific clinical features in most cases that leads to delayed or underdiagnosis.

The pathophysiology of HLH includes a failure of down-regulatory mechanisms of the immune system leading to a feed-forward amplification loop which results in massive activation of cytotoxic T-lymphocytes and macrophages and excessive production of interferon-gamma and other cytokines[3]. However, this pattern of immune system dysregulation is less clear in many cases of secondary HLH which can make the decision to intervene with HLH-specific treatment more complex than in cases of primary HLH. Furthermore, our increased understanding and discovery of genetic mutations -even in what was regarded as secondary HLH- and the ability of certain events, like infections, to trigger HLH in both primary and secondary HLH, and to clarify the choice of initial treatment, the North American Consortium for Histiocytosis (NACHO) introduced a new classification based on the specific etiology of HLH[4]. In this classification, cases that fulfill the diagnostic criteria are described as HLH syndrome. They are then classified as either HLH disease where a distinctive immune dysregulation is the driving abnormality and HLH-specific immunosuppressive treatment is indicated, or HLH disease mimic, which includes other conditions that will fulfill the definition of HLH syndrome but require a different treatment approach.
Malignancy-associated HLH (M-HLH) is a challenging subgroup of HLH cases. It accounts for 15-50% of HLH cases in the adult population, and it has the worst prognosis among the HLH subgroups[5]. M-HLH can present with a new diagnosis of malignancy "new onset" and, in this case, is considered HLH disease mimic as its clinical manifestations are directly driven by the underlying malignancy and antineoplastic treatment should take priority. The other possible presentation occurs during cancer treatment "on therapy" and is related to immunosuppression, immunotherapies, and infections, and it is usually treated with Dexamethasone ± Etoposide[4,6].

Lymphoma is the most common malignancy associated with M-HLH and has the worst prognosis, with an overall median survival of 5.1 months. In this group of patients, treatment with an etoposide-containing regimen (as in EPOCH) has the advantage of targeting the hyperinflammation of the HLH and the lymphoma at the same time[7].

The initial presentation of our patient was consistent with Burkitt or high-grade B cell lymphoma with gastrointestinal involvement, which can rarely be complicated by intestinal obstruction and intussusception[8]. Her lactic acidosis, in the absence of hypoxia or tissue ischemia, was likely due to type-B lactic acidosis which is rare but signifies a poor prognosis due to the aggressive nature and the high burden of the underlying malignancy[9]. However, her postoperative rapid deterioration raised suspicion of another process driving her clinical course. While surgical complications are more common, an evaluation by the surgical team did not suggest such complications based on physical examination and the amount or nature of the drain output. The markedly elevated serum ferritin (>9000μg/L) and elevated triglycerides suggested HLH as a possible diagnosis. The diagnosis of HLH syndrome was made in our patient by fulfillment of five out of eight diagnostic criteria based on HLH-2004 criteria: fever, splenomegaly, cytopenia, hypertriglyceridemia, and hyperferritinemia.

Postoperative HLH is exceedingly rare in adults, with most cases reported in pediatric patients or after liver transplantation[10,11]. Linthorst et al. described a case of HLH in an adult patient following cardiac surgery. However, their patient was diagnosed with possible ventilator-associated pneumonia and was started on antibiotics for an unclear duration followed by prednisone after the diagnosis of HLH, making it less clear whether the HLH was triggered by the surgery or the infectious complication after the operation[12]. Another case was described by Yamada et al. of "hemophagocytic syndrome-like condition" following right hemicolectomy in a patient presented with perforated colon adenocarcinoma and a large retroperitoneal abscess that was treated successfully with steroids. They used this term as their patient did not meet the diagnostic criteria of HLH[13]. It is well described that the extent and the duration of surgeries and the amount of tissue damage associated correlate with the levels of cytokines released and the subsequent activation of neutrophils and macrophages[14]. The ability of the level of serum ferritin in distinguishing HLH from other causes in critically ill patients was evaluated by Lachmann et al. with reported sensitivity and specificity of 92.5% and 91.9%, respectively, for levels exceeding 9000 μg/L[15].

While the initial presentation of our patient could be attributed solely by her lymphoma, her rapid deterioration was not fully explained by it. We believe that the abdominal surgery served as a trigger of HLH in our patient or at least an amplifying event of a less obvious M-HLH from the preoperative period. Despite our relatively early suspicion and aggressive treatment approach, our patient had already developed multiorgan failure, which led to her death.

Our case has several limitations. The diagnosis of HLH was made by using HLH-2004 diagnostic criteria but it was not confirmed with measurement of natural killer cells activity or soluble Interleukin-2 receptors due to the patient's rapid deterioration and death. A planned bone marrow aspirate was not done. However, the criteria commonly used to diagnose HLH were devised for use in a clinical trial; therefore, these criteria are unlikely to capture all HLH cases. Additionally, we were unable to perform a follow-up CT scan postoperatively due to her hemodynamic instability. We relied on our surgical team's clinical assessment to rule out catastrophic postoperative complications. Finally, most of the clinical and laboratory features of HLH lack specificity and can be seen in various other medical conditions including lymphoma. We had to rely on the sudden change in her clinical course and our clinical judgment to diagnose her clinical syndrome as HLH-disease mimic triggered by surgery and rather than attributing it to M-HLH.

CONCLUSION

Postoperative HLH is likely an underdiagnosed and underreported condition due to its nonspecific presentation, mimicking other more common postoperative complications. However, it carries a high risk of mortality and could be treated if recognized early. Medical providers, especially in surgical or intensive care units, should keep a high level of suspicion if unexplained clinical deterioration is observed in the postoperative period, particularly in patients with underlying hematological malignancies. Early measurement of serum ferritin and triglycerides levels, which are widely available and provide rapid results can aid in timely diagnosis.

Authorship Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflicts of Interest: None

Competing Interest: None

Acceptance Date: 11 July 2025

REFERENCE

1. Henter, JI. Hemophagocytic Lymphohistiocytosis. N Engl J Med. 2025; 392(6):584-98.

2. West, J., Stilwell, P., Liu, H. et al. 1-year survival in haemophagocytic lymphohistiocytosis: a nationwide cohort study from England 2003–2018. J Hematol Oncol. 2023;16, 56.
3. Brisse E, Wouters CH, Matthys P. Advances in the pathogenesis of primary and secondary haemophagocytic lymphohistiocytosis: differences and similarities. Br J Haematol. 2016; 174(2):203-17.
4. Jordan MB, Allen CE, Greenberg J, et al. Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: Recommendations from the North American Consortium for Histiocytosis (NACHO). Pediatr Blood Cancer. 2019; 66(11):e27929.
5. Löfstedt A, Jädersten M, Meeths M, et al. Malignancy-associated hemophagocytic lymphohistiocytosis in Sweden: incidence, clinical characteristics, and survival. Blood. 2024;143(3):233-42.
6. Daver N, McClain K, Allen CE, et al. A consensus review on malignancy-associated hemophagocytic lymphohistiocytosis in adults. Cancer. 2017; 123(17):3229-40.
7. Knauft J, Schenk T, Ernst T, et al. Lymphoma-associated hemophagocytic lymphohistiocytosis (LA-HLH): a scoping review unveils clinical and diagnostic patterns of a lymphoma subgroup with poor prognosis. Leukemia. 2024;38(2):235-49.
8. Gupta V, Sangwaiya A, Sharma J, et al. Burkitt′ s lymphoma masquerading as intestinal obstruction: An uncommon entity with variable clinical presentation. Clin Cancer Investig Jl. 2014; 3(5-2014):441-3.
9. Wang C, Lv Z, Zhang Y. Type B lactic acidosis associated with diffuse large B-cell lymphoma and the Warburg effect. J Int Med Res. 2022 Jan;50(1):3000605211067749.
10. Siminas S, Caswell M, Kenny SE. Hemophagocytic lymphohistiocytosis mimicking surgical symptoms and complications: lessons learned from four cases. J Pediatr Surg. 2013;48(7):1514-9.
11. Nakanuma S, Gabata R, Okazaki M, et al. Hemophagocytic Lymphohistiocytosis With Elevated Cytokines Related to Macrophage Activation After Liver Transplantation for Autoimmune Hepatitis: A Case Report. Transplant Proc. 2023;55(8):1946-50.
12. Linthorst L, Aardema H, Tulleken JE. Unexpected hemophagocytic syndrome in a post-cardiac surgery patient. Crit Care. 2011;15(5):440.
13. Yamada, Takayuki et al. A hemophagocytic syndrome-like condition after emergency colectomy for perforated colon cancer: report of a case. Surgery today. 2002;278-81. .
14. Margraf A, Ludwig N, Zarbock A, et al. Systemic Inflammatory Response Syndrome After Surgery: Mechanisms and Protection. Anesth Analg. 2020;131(6):1693-707.
15. Lachmann G, Knaak C, Vorderwülbecke G, et al. Hyperferritinemia in Critically Ill Patients. Crit Care Med. 2020;48(4):459-65.