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Case Report

Secondary Haemophagoyctic Lymphohistiocytosis: Diagnostic Challenges

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Abstract

A 60-year-old woman presented with two weeks of cough, fevers, and lethargy and tested positive for coronavirus disease 19 (COVID-19). Her past medical history was significant for extra-nodal natural killer (NK)/T-cell lymphoma, nasal type. Blood tests demonstrated multiorgan dysfunction and hyperferritinaemia. She satisfied HLH-2004 diagnostic criteria and was diagnosed with haemophagocytic lymphohistiocytosis (HLH). The HLH continued to relapse despite recovery from COVID-19 and further investigations for an underlying cause led to a diagnosis of recurrent NK/T cell lymphoma. This case illustrates the importance of recognizing the features of HLH, and of maintaining a broad differential when investigating for secondary aetiologies once the diagnosis of HLH is made.

Keywords: COVID-19; T-cell lymphoma; Hyperferritinaemia; Haemophagocytic Lymphohistiocytosis.

Case Presentation

A 60-year-old woman presented with two weeks of cough, fevers, and lethargy. She was febrile at 38°C and hemodynamically unstable on presentation and was admitted to the intensive care unit. Her past medical history was significant for extra-nodal natural killer (NK)/T-cell lymphoma, nasal type in complete remission post SMILE chemotherapy (dexamethasone, methotrexate, ifosfamide, asparaginase, and etoposide) for the past 8 years.

Initial investigations revealed the patient was coronavirus disease 19 (COVID-19) positive on polymerase chain reaction testing. Blood tests showed significant thrombocytopaenia (27 x 10^9/L), new renal and liver dysfunction (creatinine 202umol/L, aspartate aminotransferase 1888U/L, alanine transaminase 876U/L, a gamma-glutamyl transferase 329U/L, alkaline phosphatase 798U/L), coagulopathy (fibrinogen 0.8g/L, D-dimer > 20mg/L FEU), raised triglycerides (2.8mmol/L) and profound hyperferritinemia of 90300ug/L. The presence of fevers, cytopenias, and hyperferritinaemia raised suspicion for haemophagocytic lymphohistiocytosis (HLH). A bone marrow aspirate and trephine showed evidence of haemophagocytosis (Figure 1) and a soluble CD25 receptor was elevated at 38260pg/ml (reference range <2678pg/ml).

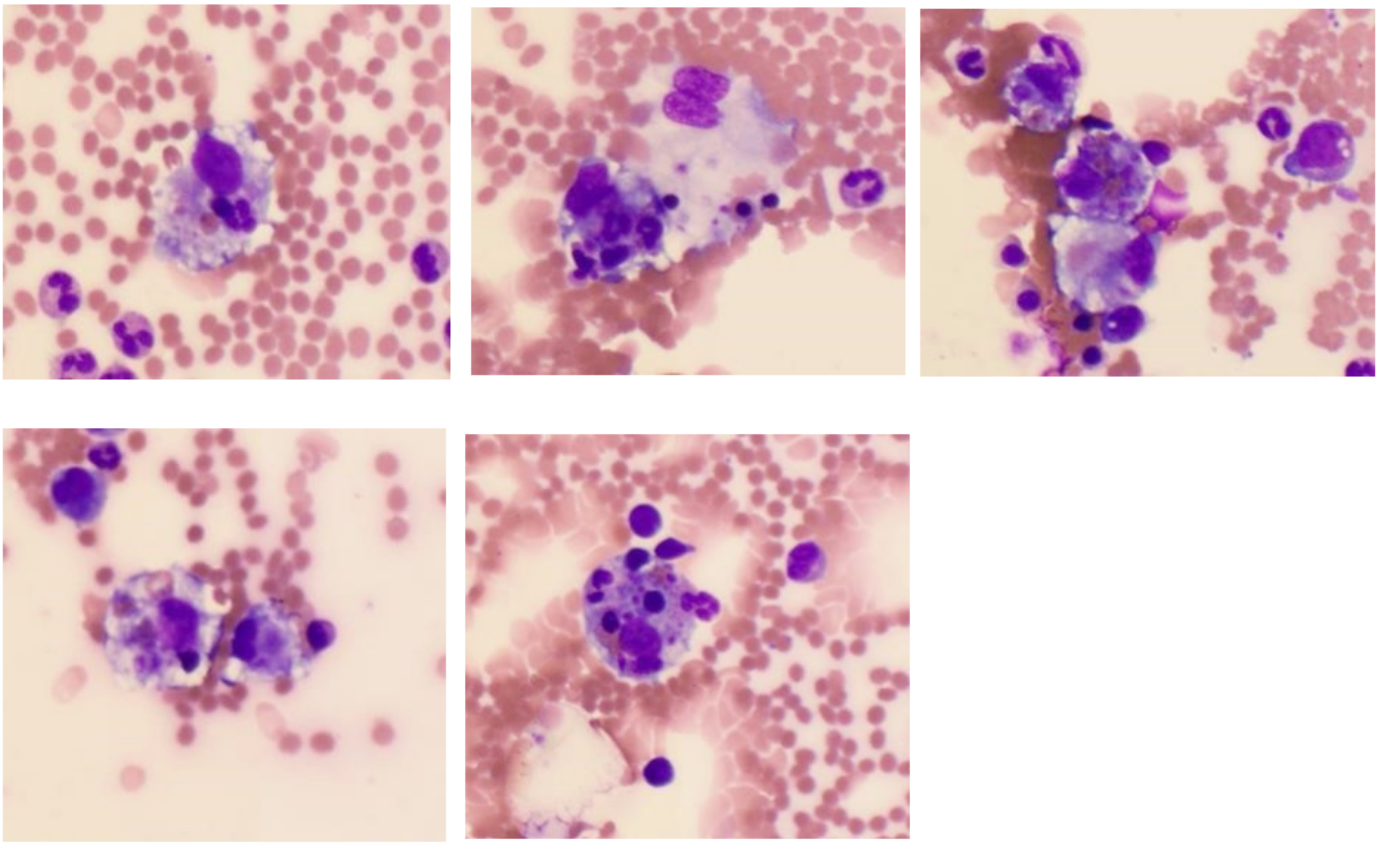

Figure 1: Bone marrow aspirate and trephine shows evidence of haemophagocytosis.

In accordance with HLH-2004 diagnostic criteria (Table 1), the patient was diagnosed with HLH, initially presumed secondary to COVID infection [1]. Due to her clinical state and COVID-19 positivity, restaging for the NK/T-cell lymphoma was not possible. She has commenced on dexamethasone 20mg, reduced dose etoposide (37.5mg/m2), and intravenous immunoglobulin (2g/kg). Despite the resolution of COVID-19 and initial improvement in her clinical state and biochemical results, she suffered repeated relapses when dexamethasone was weaned to 4mg, characterized by recurrent fevers and worsening hyperferritinaemia (Figure 2). An alternative underlying cause for HLH was explored, particularly evidence of lymphoma relapse. Extensive viral serology testing (Table 2) was significant for a high Epstein-Barr viral load of 87029 copies/ml. Positron emission tomography scanning revealed avid nodal disease above and below the diaphragm, raising concerns about the recurrence of lymphoma. Initial targeted core and excisional biopsies showed reactive changes only. Due to high clinical suspicion, a third lymph node core biopsy was performed. The histopathology was positive for relapsed EBV-positive NK/T-cell lymphoma, which was determined to be the driving process behind her HLH. She was subsequently commenced on high-dose chemotherapy for relapsed lymphoma and discharged two months following the initial presentation.

HLH-2004 Criteria: 5 must be fulfilled
Fever (≥ 38.3°C)
Splenomegaly
Peripheral blood cytopenias (affecting ≥ 2 of 3 lineages)
Haemoglobin <90 g/L
Platelets <100 x 10^9/L
Neutrophils <1.0 x 10^9/L
Hypertriglyceridaemia and/or hypofibrinogenaemia
Fasting triglycerides ≥ 3.0 mmol/L
Fibrinogen ≤1.5g/L
Haemophagocytosis in bone Marrow, Spleen or lymph Nodes
Low or absent NK-cell activity
Ferritin ≥ 500 µg/L
Soluble CD25 <2400 U/ml

Table 1: HLH-2004 criteria.

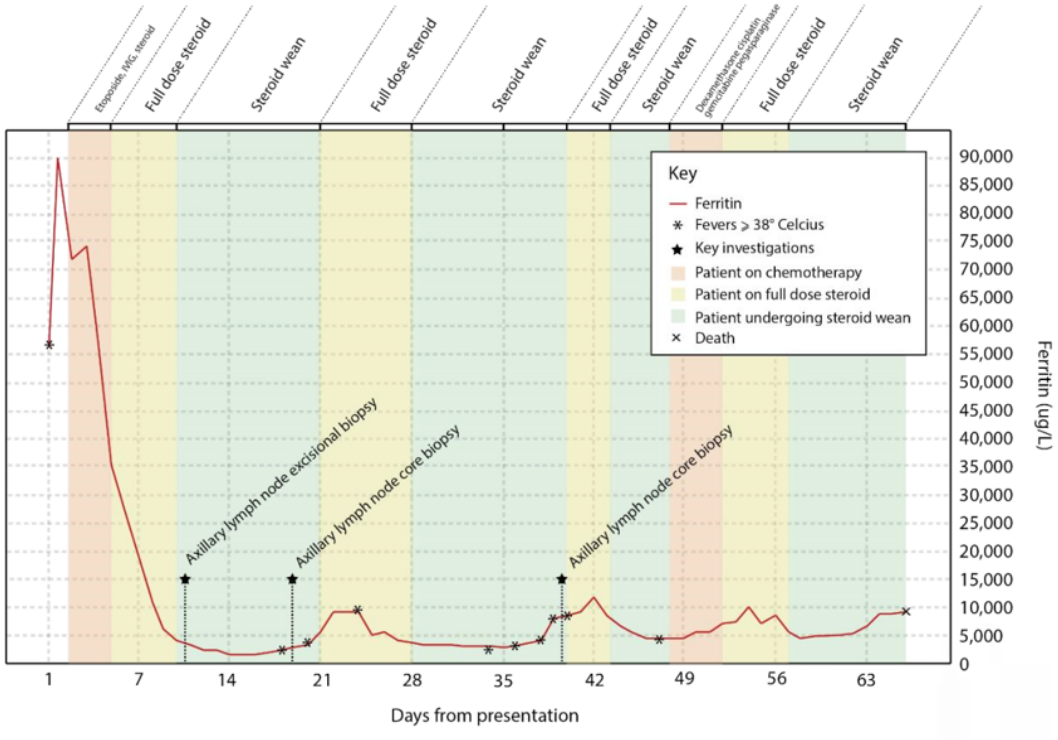

Figure 2: Ferritin levels and fevers as a marker of HLH relapse over time in context of treatment received.

Investigation	Testing
Epstein-Barr virus viral capsid antigen IgM Epstein-Barr virus nucleic acid IgG Epstein-Barr viral load	Not detected Detected 87029 copies/ml
Cytomegalovirus DNA	Detected
Cytomegalovirus viral load	625 IU/ml
Herpes simplex virus type 1 DNA	Not detected
Herpes simplex virus type 2 DNA	Not detected
Varicella zoster virus DNA	Not detected
Enterovirus RNA	Not detected
Hepatitis B surface antigen	Not detected
Hepatitis B core antibody	Not detected
Hepatitis B surface antibody	Detected
Hepatitis C antibody	Not detected

Table 2: Viral serology testing.

Discussion

Haemophagocytic lymphohistiocytosis is a hyperinflammatory syndrome that results from defective NK and cytotoxic T cell function and is clinically characterized by fever, progressive cytopenias, and multiorgan failure [2]. It is considered a cytokine release syndrome and can be broadly divided into primary and secondary subtypes [2]. Primary HLH is due to genetic mutations impairing the cytotoxic function of NK and T cells and typically presents in infancy and childhood [3]. Secondary HLH typically occurs in adolescents and adults and results from a predisposing condition causing immune dysregulation. Secondary triggers of HLH include infection, malignancy, autoimmune disease, and immunodeficiency syndromes [3]. T and NK-cell leukaemias/lymphomas contribute to a majority of cases of HLH in malignancy [4]. In recent years COVID-19 has emerged as a recognized cause of secondary HLH [2]. However, the immune dysregulation caused by COVID-19 itself shares several clinical and biochemical similarities to HLH, making a distinction between some cases of severe COVID-19 and HLH secondary to COVID-19 challenging [2].

The diagnosis of HLH centers around the application of the HLH-2004 criteria [7]. A diagnosis of HLH is made upon identification of recognized genetic mutations or on meeting five out of eight clinical and laboratory criteria. However, diagnosis remains challenging as no single laboratory test or clinical finding is pathognomonic. Furthermore, these guidelines have been derived from the pediatric experience in HLH and lack prospective validation in adult patients. They also likely underrecognize HLH in the critically ill [1].

In this case, the HLH-2004 criteria were applied resulting in a score of 6 out of 8 based on clinical criteria. Primary HLH was thought to be unlikely given her age and presentation. In terms of secondary causes, the patient had both a history of NK/T cell lymphoma and had presented with acute COVID-19. Given relapses of NK cell lymphoma are uncommon eight years following attainment of complete remission, the initial leading differential was COVID-19 causing HLH. However, recurrent relapses of the patient's HLH led to the ultimate underlying diagnosis of relapsed NK cell lymphoma. The elevated EBV viral load reflected the fact that latent EBV infection in tumor cells is linked to the pathogenesis of nasal NK cell lymphoma.

This case illustrates the importance of recognizing the features of HLH, and of maintaining a broad differential when investigating for secondary aetiologies once the diagnosis of HLH is made. Flexibility to revisit the diagnosis is also key, especially when treatment does not yield the expected results. Ongoing close monitoring of inflammatory markers is crucial to assess response to therapy, as elevations in sCD25 or ferritin often precede clinical relapse [6]. However, results from sCD25 testing are often not obtained quickly and therefore sCD25 monitoring is impractical if there is clinical concern over relapse. Whilst it is uncommon for patients with aggressive lymphomas to relapse five years after achieving remission, this case exemplifies that this is still a possibility [5]. We assert that this case is an excellent example of maintaining an open-minded view when attempting to delineate an aetiology in secondary HLH, which can be driven by infectious, malignant, or autoimmune insults.

Outcome

- Haemophagocytic lymphohistiocytosis is a hyperinflammatory syndrome involving immune dysregulation and can be triggered by primary or secondary causes, the latter of which include infections, malignancies and autoimmune conditions
- Diagnosing HLH can be challenging and is assisted by the use of the HLH-2004 diagnostic criteria
- Close monitoring of inflammatory markers to assess for relapse of HLH is critical
- Relapses in secondary HLH despite resolution of a presumed initial trigger should prompt further investigation for an alternative cause.

References

1. Knaak C, Nyvlt P, Schuster FS, Spies C, Heeren P, et al. (2020) Hemophagocytic lymphohistiocytosis in critically ill patients: Diagnostic reliability of HLH-2004 criteria and HScore. Crit Care 24(1):244.

2. Fadlallah MM, Salman SM, Fadlallah MM, Rahal H (2023) Hemophagocytic Syndrome and COVID-19: A Comprehensive Review. Cureus 15(3): e36140.

3. Hayden A, Park S, Giustini D, Lee AYY, Chen LYC (2016) Hemophagocytic syndromes (HPSs) including hemophagocytic lymphohistiocytosis (HLH) in adults: A systematic scoping review. Blood Reviews. Churchill Livingstone 30: 411-20.

4. Devitt K, Cerny J, Switzer B, Ramanathan M, Nath R, et al. (2014) Hemophagocytic lymphohistiocytosis secondary to T-cell/histiocyte-rich large B-cell lymphoma. Leuk Res Rep 3(2):42-5.

5. Kawaura R, Ohnishi M, Hori T (2022) Recurrence 14 Years After Initial Treatment of Extranodal NK/T Cell Lymphoma, Nasal Type. Cureus. 14(4): e24177.