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An Overlap Presentation of Immune Reconstitution Inflammatory Syndrome and Hemophagocytic Lymphohistiocytosis in a Patient with Advanced HIV

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Case Report

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Abstract

Background

Hemophagocytic lymphohistiocytosis (HLH) is a fatal hyperinflammatory syndrome frequently triggered by infections in immunocompromised hosts. In HIV patients, upon initiation of antiretroviral therapy (ART), tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) can overlap and present with fever, cytopenias, and hepatosplenomegaly.

Case Presentation:

A 44-year-old male, a known case of HIV with poor ART adherence, presented with four weeks of cough, fever, and weight loss. He had completed treatment for disseminated TB three years prior. Cervical lymph node biopsy GeneXpert was positive for rifampicin-sensitive *Mycobacterium tuberculosis*. PET-CT showed pulmonary, nodal, marrow, and splenic involvement. He was restarted on anti-tubercular therapy (ATT) and ART. After initial improvement, he deteriorated with persistent fever, worsening respiratory symptoms, severe pancytopenia, hepatosplenomegaly, hyperferritinemia, and hypertriglyceridemia. Bone marrow studies showed florid hemophagocytosis and non-caseating granulomas. He met six of eight HLH-2004 criteria and had an HScore of 237 (98%-99%), establishing a diagnosis of secondary HLH overlapping with paradoxical TB-IRIS. He was managed with an Etoposide-Dexamethasone combination alongside ATT and ART.

Conclusion

This case highlights the importance of maintaining a high index of suspicion when managing HIV patients in TB-endemic regions for HLH-IRIS overlap. Early suspicion, application of the HLH criteria/HScore, bone marrow evaluation, and initiation of timely treatment are necessary for improving patient survival.

Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is an aberrant hyperinflammatory, hyperferritinemic immune response syndrome driven by T-cells and associated with a potentially fatal cytokine storm [1, 2]. It can be categorised as primary and secondary HLH.

Secondary HLH is an acquired immune dysfunction that occurs mainly in response to infections, autoimmune disorders, and malignancies [3]. HLH poses significant morbidity and mortality due to a combination of delayed diagnosis and delayed initiation of treatment.

Individuals with HIV on antiretroviral therapy are at risk of developing TB-associated immune reconstitution inflammatory syndrome (TB-IRIS), an inflammatory complication due to rapid restoration of immune response following ART, leading to an exaggerated inflammatory response to *Mycobacterium tuberculosis* antigens [4]. HLH and TB-IRIS share overlapping manifestations such as fever, cytopenias, organomegaly, and systemic inflammation. Therefore, distinguishing them is often difficult and a high index of suspicion is frequently needed. The overlapping presentation of TB-IRIS and HLH is peculiar, making this case noteworthy for clinicians in order to recognise and manage such presentations. This report presents a rare case of overlapping TB-IRIS and secondary HLH successfully managed with steroids and etoposide therapy.

Case Presentation

This patient is a 44-year-old male farmer who is a known case of HIV-1 for the past nine years and is non-compliant with medication. He presented with complaints of four weeks of cough, fever, and weight loss of seven kilograms over the past one month. He had similar complaints three years prior and was diagnosed with disseminated tuberculosis (TB) sensitive to rifampicin, for which he was started on an HRZE regimen, which he completed. His vitals on admission were as follows: Temperature 104°F, HR 130 bpm, BP 130/90 mmHg, RR 26 cpm, and oxygen saturation 92% on room air. He was admitted to the Department of General Medicine for further evaluation. His initial workup is summarised in Table 1.

Table 1
– Initial workup of the patient on admission.

Parameter	Value	Reference Range
AST	250 IU/L	10–40 IU/L
ALT	129 IU/L	7–56 IU/L
CRP	130 mg/L	< 5 mg/L
Haemoglobin (Hb)	8.7 g/dL	12–16 g/dL
Platelets	215 ×10³/µL	150–450 ×10³/µL
Total Leukocyte Count (TLC)	4.39 ×10³/µL	4–11 ×10³/µL
Creatinine	1.34 mg/dL	0.6–1.2 mg/dL
CD8	860 cells/µL	150–1000 cells/µL
CD4	70 cells/µL	500–1500 cells/µL

A bronchoalveolar lavage GeneXpert was negative for TB; however, an ultrasound-guided cervical lymph node aspiration GeneXpert was positive for *Mycobacterium tuberculosis* with rifampicin sensitivity. PET-CT was suggestive of disseminated tuberculosis with pulmonary, lymph node, bone marrow, and spleen involvement. The patient was started on HRZE followed by the TLD regimen (Tenofovir–Lamivudine–

Dolutegravir). The patient initially showed some signs of clinical improvement over one week. However, his condition began to deteriorate with persistent fever spikes and worsening cough. His laboratory parameters are shown in Table 2.

Table 2
– Pancytopenia with elevated ESR, CRP, ferritin, and triglycerides.

Parameter	Value	Normal Range
ESR	93 mm/hr	0–20 mm/hr
C-reactive protein (CRP)	130 mg/L	< 5 mg/L
Procalcitonin	19 ng/mL	< 0.05 ng/mL
Serum lactate	3.3 mmol/L	0.5–2.2 mmol/L
Serum creatinine	2.0 mg/dL	0.6–1.2 mg/dL
Total serum bilirubin (TSB)	0.3 mg/dL	0.2–1.2 mg/dL
Alkaline phosphatase (ALP)	148 IU/L	40–120 IU/L
Gamma-glutamyl transferase (GGT)	266 IU/L	9–48 IU/L
Aspartate aminotransferase (AST)	52 IU/L	5–40 IU/L
Alanine aminotransferase (ALT)	65 IU/L	7–56 IU/L
Serum albumin	2.5 g/dL	3.5–5.0 g/dL
Serum globulin	5.3 g/dL	2.0–3.5 g/dL
Ferritin	1650 ng/mL	30–400 ng/mL
Triglycerides	340 mg/dL	< 150 mg/dL

His blood counts demonstrated pancytopenia: haemoglobin 7.3 g/dL, white blood cell count 4,250 cells/µL, and platelets 7,000 cells/µL. Blood and urine cultures showed no growth. Serum cryptococcal antigen was negative.

Ultrasound of the abdomen showed hepatosplenomegaly with splenic microabscesses. HRCT chest showed patchy consolidation in the right lower lobe.

The progressive pancytopenia in a patient with HIV, in the presence of raised ferritin, triglycerides, and hepatosplenomegaly, prompted bone marrow aspiration and biopsy. Marrow aspiration revealed plasma cell predominance with florid hemophagocytes, engulfed platelets, and nucleated erythrocytes. Marrow biopsy showed a normocellular marrow with well-defined epithelioid cells, non-caseating granulomas, and Langhans giant cells. Reticulin stain showed grade II fibrosis (0 to III). Acid-fast staining did not reveal any acid-fast bacilli.

The patient presented with six of the eight HLH-2004 diagnostic criteria: an elevated ferritin of 1,650 ng/mL, triglycerides of 340 mg/dL, pancytopenia, high fevers, hepatosplenomegaly on ultrasound, and evidence of hemophagocytosis on bone marrow aspiration. The patient had an HScore of 237, predicting a 98–99% probability of HLH, and we arrived at a final diagnosis of secondary hemophagocytic lymphohistiocytosis with paradoxical TB-immune reconstitution inflammatory syndrome (IRIS).

The patient was started on etoposide and dexamethasone for HLH and IRIS, and the infections were treated with the TLD regimen and anti-tubercular therapy consisting of rifampicin, moxifloxacin, isoniazid, and ethambutol. Etoposide was administered on days 1, 4, 8, and 15, followed by a weekly dose for a total duration of eight weeks. The patient's clinical status improved significantly, and his blood counts showed improvement within two weeks: haemoglobin 8.4 g/dL, white blood cell count 3,080 cells/µL, and platelets 142,000 cells/µL. He was subsequently discharged and continued follow-up with medical oncology. Informed consent was obtained from this patient for this study.

Discussion

Secondary HLH is a serious haematologic condition elicited by immune hyperactivation in response to different triggers, including autoimmune and autoinflammatory diseases, persistent infections, and malignancies [5]. Based on the available literature on TB-associated HLH, consisting of 115 cases, the overall mortality rate was higher in patients with TB-associated HLH compared to other infection-induced HLH [6, 7, 8]. A high proportion of TB-triggered HLH cases have extrapulmonary TB, mainly involving the bone marrow. In our case, *M. tuberculosis* was detected from the GeneXpert sample, and bone marrow showed changes suggestive of TB. However, no bacilli could be isolated from the marrow, as the patient had already been receiving anti-tubercular therapy.

TB-IRIS is a paradoxical worsening or recurrence of pre-existing tuberculous lesions, or development of new lesions, in patients on effective antituberculosis treatment. There are two forms of IRIS: paradoxical and unmasking. Paradoxical IRIS is defined as recurrent, new, or worsening symptoms in a previously treated case [9]. In our case, the patient had disseminated tuberculosis three years prior and had completed the full course of ATT. Following initiation of ART, he experienced progressive deterioration, which was consistent with a classification of paradoxical TB-IRIS.

Current available literature recognises that severe TB-IRIS has an overlapping phenotype with HLH, owing to their shared pathogenesis involving IFN-γ and unopposed T-cell activation, causing severe inflammatory disease. Patients with a dual diagnosis of IRIS-HLH had a more severe clinical course requiring more steroids and a longer duration of immunosuppression, with many requiring additional therapies beyond steroids due to refractory symptoms or steroid intolerance [10, 11].

Our patient fulfilled six of the eight Henter *et al.* validated HLH-2004 diagnostic criteria [12]:

1. Fever ≥ 38.5°C

2. Splenomegaly
3. Cytopenias affecting at least two of three peripheral blood lineages: haemoglobin < 9 g/dL, platelets < 100 × 10^3/mL, neutrophils < 1 × 10^3/mL
4. Hypertriglyceridaemia (fasting > 265 mg/dL) and/or hypofibrinogenaemia (< 150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
6. Ferritin > 500 ng/mL

NK-cell activity and IL-2 receptor levels were not measured due to limited resources. However, bone marrow findings of florid hemophagocytosis, plasma cell predominance, non-caseating granulomas, Langhans giant cells, and grade II reticulin fibrosis — despite a negative AFB stain — combined with an HScore of 237, further solidified the clinical probability of HLH [13].

Based on available literature, there is limited information on the mortality of HLH-IRIS specifically; however, a systematic review of 116 cases reports a 45% mortality rate in patients with TB-associated HLH, underscoring the importance of prompt recognition and initiation of ATT and immunomodulatory therapies to improve patient outcomes [7]. In our case, the patient was initially worked up for sepsis, which was excluded. Paradoxical IRIS was considered and confirmed based on the patient's clinical timeline and paradoxical worsening following ART initiation, and steroids were commenced immediately. Given the pancytopenia and markedly elevated ferritin, we maintained a low threshold for bone marrow histopathological evaluation. The patient was started on etoposide (150 mg/m^2 on days 1, 4, 8, and 15, then weekly for eight weeks) combined with dexamethasone, which effectively controlled HLH features. Rapid improvement in fever, cytopenias, and clinical status was observed within two weeks. Concurrent ATT and ART were continued to address the underlying TB and HIV [14].

Conclusion

This case highlights the importance of considering HLH in patients with advanced HIV presenting with persistent fever and cytopenias after ART initiation. Early recognition and initiation of combined immunosuppressive and antimicrobial therapy can significantly improve outcomes.

Abbreviations

HLH
Hemophagocytic lymphohistiocytosis
TB
Tuberculosis
HIV
Human Immunodeficiency Virus
IRIS
Immune Reconstitution Inflammatory Syndrome
ART

Antiretroviral therapy
ATT
Antitubercular therapy
TLD
Tenofovir–Lamivudine–Dolutegravir.

Declarations

Ethics approval and consent to participate: Ethics approval was not required for this study, as this is a single-patient case report and did not involve and experimental intervention or research on human subjects. Informed consent was obtained from the patient for the publication of this case report and any accompanying images and data, in accordance with the Declaration of Helsinki.

Consent for publication: Informed consent obtained from the patient.

Competing interests: The authors declare that they have no competing interests.

Authors' contributions: All authors contributed to the management of the patient, data collection, drafting, and revision of this manuscript, and approved the final version for submission.

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