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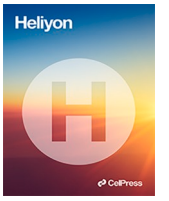

Case report

Disseminated tuberculosis in rare association with hemophagocytic lymphocytosis - A case report from central India

Disha Gautam [a], Malti Dadheech [a], Vaibhav Ingle [b], Erukkambattu Jayashankar [c], Shashank Purwar [a], Anand Kumar Maurya [a,*]

[a] Department of Microbiology, All India Institute of Medical Sciences, Bhopal, India
[b] Department of General Medicine, All India Institute of Medical Sciences, Bhopal, India
[c] Department of Pathology, All India Institute of Medical Sciences, Bhopal, India

A B S T R A C T

Hemophagocytic Lymphohistiocytosis (HLH) is an uncommon, diverse and rare genetic hyper-inflammatory syndrome. HLH associated with tuberculosis (TB-HLH) has been described as a clinical and diagnostic quandary. The co-existence leads to significantly higher morbidity and mortality. Our case highlights the presence of disseminated tuberculosis and worsening of the case due to underlying hemophagocytic syndrome leading to rapid deterioration of patient prognosis. Prompt diagnosis and treatment remains help to improve patient management.

1. Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is a diverse and rare genetic hyper-inflammatory syndrome. It is a life-threatening immune syndrome associated with a significantly higher rate of mortality and morbidity [1]. The pathogenesis of HLH is very complex and not well understood. The secondary hyper-activation of $CD8^+$ T lymphocytes and macrophages in the lack of regulatory Natural Killer (NK) cells results in extensive cytokine production that elicits end-organ damage [2,3]. The HLH syndrome has a proposed classification by NACHO (North American Consortium for Histiocytosis). It consists of all conditions meeting the diagnostic criteria of HLH. This syndrome includes conditions termed as “HLH disease” and “HLH disease mimics”. "HLH disease" refers to conditions that would benefit from HLH-directed immunosuppressive therapies, while "HLH disease mimics" refer to conditions that would not benefit or would require entirely different treatments. There are several distinguishable subgroups of HLH disease: including HLH seen following immune-activating therapy (also known as cytokine release syndrome), HLH linked to malignancy, HLH in association with rheumatologic diseases (also known as macrophage activation syndrome), HLH related to the immunological compromise and HLH not related to any other particular conditions. It is crucial to recognize these subgroups since doing so may change the course of treatment and improve prognosis. But some categories might overlap or have very hazy borders and contain examples of both HLH disease and HLH disease mimics. The usage of such category-specific words is preferable to the historical labels "primary" and "secondary," as the former terms are unclear due to the role of infection in causing numerous distinct types of HLH, growing knowledge of genetic complexity, and a variety of uses [4]. The diagnosis of HLH is achieved by fulfilling one of the HLH 2004 criteria: A) Family history of HLH or diagnosis by molecular test (mutations of UNC13D, PRF 1, STX11, BIRC4, STXBP2, Rab27A, or SH2D1A genes) or B) Any five out of the following eight criteria: splenomegaly, fever $\geq$38.5 °C, cytopenia with absolute neutrophil

Abbreviations: AFB, Acid-Fast Bacilli; ATT, Anti-Tubercular Treatment; HLH, Hemophagocytic Lymphohistiocytosis; MTB, *Mycobacterium tuberculosis*; NK Cells, Natural Killer Cells; RIF, Rifampicin; TB-HLH, Tuberculosis-Hemophagocytic Lymphohistiocytosis.

* Corresponding author.
E-mail address: anand.microbiology@aiimsbhopal.edu.in (A.K. Maurya).

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count <1.0 × 10^9/L, platelets count <100 × 10^9/L, hemoglobin <100 g/L, hypofibrinogenemia i. e; fibrinogen <150 mg/dL) and/or hypertriglyceridemia i. e; fasting triglycerides >265mg/dL), hemophagocytosis in the lymph nodes or spleen or bone marrow or liver, absence of activity of the NK cell, ferritin >500 ng/mL and increased soluble CD25 (≥2400 U/mL) that measures 2 standard deviations above age-adjusted laboratory-specific norms [5].

Tuberculosis (TB) is a chronic disease with significant morbidity and mortality. For centuries it continued to remains as a common health issue in Southeast Asia and other underdeveloped countries. *Mycobacterium tuberculosis* (MTB) is the causative organism of this deadly disease and it has a diverse range of clinical manifestations and complications. The association of HLH with TB is rare and its diagnosis is often missed which causes delay in the conclusive treatment therapy leading to elevated mortality and morbidity.

This case presents a brief literature regarding the disseminated TB infection associated with HLH with regard to the immunopathology, clinic pathological characteristics, and therapeutic outcomes.

2. History

A 65-year old male from Madhya Pradesh, India came to the emergency department of our institute with persistent high-grade fever, nausea, vomiting and generalized weakness for the last 10 days. He was a known case of hypertension and benign prostate hyperplasia and was on regular medication since the last 6 months and 2 years respectively. Prior to the arrival at our institute, he had been reported at another hospital for a month old history of intermittent high-grade fever, vomiting, loss of weight and night-sweats. On further examination, he was noted to be conscious, well-built and oriented but lethargic, febrile temperature of 101 °F with significant mild hepatosplenomegaly and conjunctival pallor. On radiological evaluation, it showed hepatosplenomegaly with fatty liver, mild urinary bladder wall thickening and mild cystitis. Patient's laboratory evaluation on second day showed mean corpuscular volume (MCV): 78 fL (76–93fL)], absolute neutrophil count (ANC): 2.17 × 10^3/μL], microcytic hypochromic anemia [hemoglobin: 9.4 g/dL (11–15 g/dL) leukocytopenia [leukocyte count: 2.94 × 10^3/μL (ref.; 4–11 × 10^3/μL), total platelet count: 90 × 10^3/μL (150–450 × 10^3/μL) suggesting bicytopenia, raised liver transaminases (>3 times the upper limit of normal) and total bilirubin: 0.85 mg/dL (direct 0.26 mg/dL and indirect 0.59 mg/dL). Serum triglyceride and plasma fibrinogen levels were within the normal reference limit. Serology tests such as hepatitis B and C viruses, HIV, malaria, dengue and scrub typhus as well as culture of urine, sputum and blood samples were negative. On eighth day, due to manifestations such as continuous fever, increasing cytopenias, fatigue, and organomegaly, bone marrow and trephine biopsies were performed. The bone marrow and trephine biopsy showed erythroid hyperplasia with megaloblastic erythropoiesis with evidence of erythroid and lymphophagocytosis (Figs. 1–4). The Biochemical evaluation showed raised lactate dehydrogenase (1552.30 IU/L), hyperferritinemia (>1700ng/mL), hyponatremia (117 mmol/L) and decreased total protein (4.72 g/dL). Direct microscopy of bone marrow biopsy did not show Acid-Fast Bacilli (AFB) but in the TrueNat MTB/RIF Assay; MTB was detected with Rifampicin (RIF) as indeterminate on the same specimen. We could not perform QuantiferonTB for the diagnosis of TB. The CECT thorax and abdomen suggested mild hepatomegaly and prostatomegaly. The PET Scan revealed hepatomegaly with external iliac lymphadenopathy suggesting disseminated tuberculosis. On fifteenth day, because of the fulfillment of the 5 out of 8 diagnostic criteria (fever, hypertriglyceridemia, pancytopenia, hemophagocytosis and hyperferritinemia) for HLH the supportive measures and broad-spectrum intravenous antibiotics were initiated. He was transfused with two units of PRBC (Hb 7.7 g/dL (11–15 g/dL). Furthermore, he was started on modified Anti-Tubercular Treatment (ATT) with ethambutol, levofloxacin and streptomycin in view of disseminated tuberculosis and deranged liver enzymes. He was also prescribed methylprednisolone and Intravenous Immunoglobulin (IVIG) as a part of therapeutic management.

On sixteenth day, the patient developed sudden onset breathlessness with SpO2 -90% on room air and was shifted to the intensive care unit immediately. The laboratory investigation showed hemoglobin: 7.7 g/dL (11–15 g/dL), leukocytopenia - leukocyte count: 0.90 × 10^3/μL (ref.; 4–11 × 10^3/μL), total platelet count: 32 × 10^3/μL (150–450 × 10^3/μL), Urea- 91 mg/dL (06–24 mg/dL), LDH - 8000 U/L (<248 U/L), AST - 1000 U/L (<50 U/L), creatinine −1.39 mg/dL (0.6–1.2 mg/dL) and ALT – 230 U/L (<50 U/L). The patient's general condition worsened and he was intubated in view of status epilepticus and poor Glasgow Coma Scale. He failed to respond to the therapy and resuscitation measures. He was declared dead on Day 20 of the complete hospital stay.

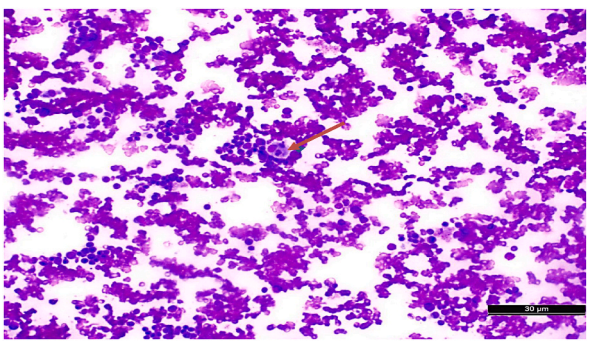

Fig. 1. Bone marrow aspirate, Giemsa stain with evidence of hemophagocytosis (under 40x).

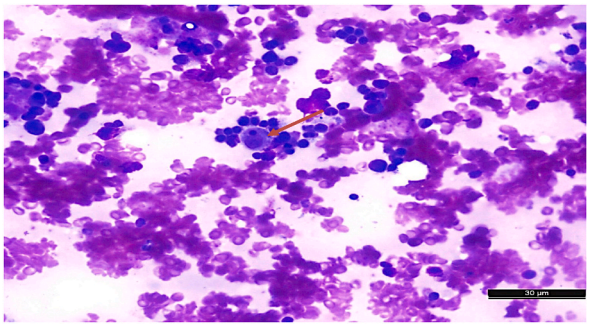

Fig. 2. Bone marrow aspirate, Giemsa stain with evidence of hemophagocytosis (under 40x).

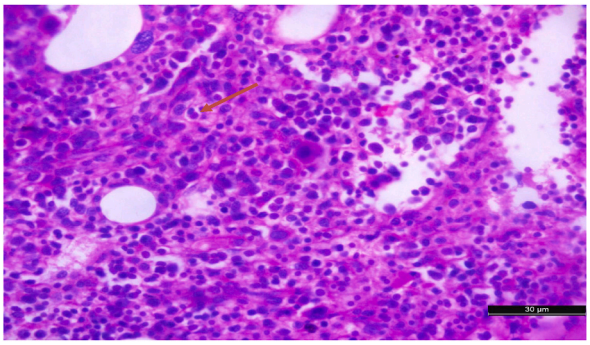

Fig. 3. Bone Marrow Aspirate, Hematoxylin and eosin stain (under 40x).

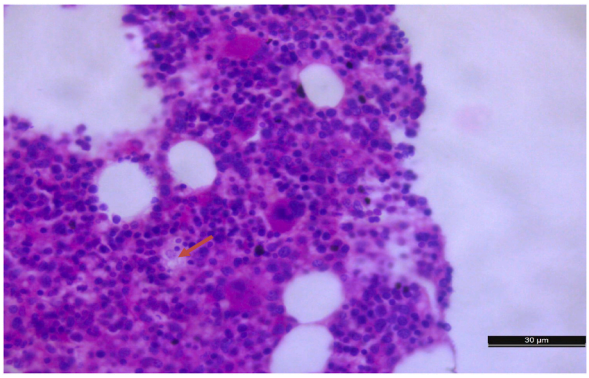

Fig. 4. Bone Marrow Aspirate, Hematoxylin and eosin stain (under 40x).

3. Discussion

HLH can exist as a primary (caused by mutation in the gene i.e. PRE, UNC213D, STXBP2, STX11, and RAB27A) or secondary disorder (activated through the autoimmune diseases, malignant diseases, pregnancy or infection) [6]. Cytokine storm may result from naturally occurring microbial infections. Disseminated infections causing sepsis induce cytokines that may lead to fever, cell death, coagulopathies, and multi-organ dysfunction. The collateral damage caused by the immune response in attempt to clear the pathogen is more deadly than the pathogen itself. Patients with hyperinflammatory responses to microbes often have defects in pathogen detection, effector and regulatory mechanisms, or resolution of inflammation [7].A new concept of infection-induced cytokine storm during covid pandemic has been observed. Critics of COVID-19 cytokine storm syndrome posit that hypercytokinaemia might be necessary for viral clearance and observe that median IL-6 levels are low in COVID-19 compared with other inflammatory conditions. High levels of inflammatory cytokines lead to maladaptive immune response driving COVID-19-related morbidity and mortality [8]. Tuberculosis accounts for 3% of the secondary HLH with mortality as high as 50% [9]. Our patient resides in India which is an endemic country for TB. This case report exhibits the rare association of two so-called “mimickers”. Due to the various clinical manifestations,

tuberculosis is also known as a "great mimicker" and HLH can be mistaken as sepsis [10,11]. The fundamental mechanism of HLH secondary to TB remains to be explained. The symptoms of TB-HLH are non-specific and involve multiple systems. Usually present with fever, fatigue, anorexia and weight loss. Most of the patients (65%) with TB-HLH have co-morbid conditions (our patient too had comorbidity). The most common clinical sign is fever in 100% of the cases and hepatosplenomegaly in 70% of the cases [12]. Our patient presented with non-specific findings such as persistent fever, weakness, worsening cytopenias and organomegaly with an infective source not initially identified. The pattern of fever, pancytopenia, hypertriglyceridemia, hyperferritinemia and hemophagocytosis heightened the clinical suspicion of HLH.

It is very difficult to diagnose TB due to its diversity in clinical manifestations. Extrapulmonary TB is furthermore challenging to diagnose, due to lower sensitivity of smear but molecular methods such as PCR have better outcome of results in poor bacillary load. In our case, the confirmation of TB was done on the bone marrow biopsy by TrueNat MTB/RIF assay, which revealed MTB with RIF as indeterminate. The TrueNat assay was developed for the detection of MTB and RIF resistance by targeting the nrdB single copy target and the rpoB gene. There were no granulomas as foci and AFB stain was negative on bone marrow specimens hence molecular testing was done for confirmation. Promptly the patient was initiated on modified Anti-tubercular Therapy (ATT), methylprednisolone and IVIG. However, the patient did not respond to the above management and succumbed. The major hurdle into a successful outcome for patients with HLH is late diagnosis but in this case, the prompt clinical suspicion led to early detection of the organism microbiologically and early confirmation of HLH by histopathology& biochemical parameters. It led to the early initiation of modified ATT, IVIG & steroids.

Treatment of TB should be immediately started in disseminated TB cases complicated by HLH. Most important the cytokines and chemokines driving the pathological process can be identified, and inhibition of these cytokines can improve outcomes [13]. In our case the importance of combining immunosuppressives and effective antimicrobials was the plan of management. Concerning the use of immunosuppressants in TB-HLH cases, the corticosteroid is the foundation in the HLH 1994 and HLH 2004 treatment protocols. Etoposide being a chemotherapeutic drug selectively inhibit T-cell growth and cytokine production making it standard treatment in patients with adult HLH. Such cytotoxic chemotherapy is very challenging in patients with acute infection such as our case, hence it was not part of management [14]. Intravenous immunoglobulin (IVIG) and plasma exchange are effective in the treatment of severe HLH cases with multiple organ dysfunction syndromes (MODS) [5]. Our patient was given modified ATT (ethambutol, levofloxacin and streptomycin); in addition to IVIG & corticosteroid (based on HLH 2004 protocol). The overall prognosis of TB-HLH is unfavorable, with a mortality rate reaching 49% of all cases [12]. Several factors are associated with a worse prognosis of HLH include male gender, non-resolving fever, malignancy, splenomegaly, coagulopathy, markedly elevated serum ferritin (>1000 ng/mL), hypoalbuminemia, and lacking etoposide in the treatment regimen [15]. Unfortunately, this patient did not show any signs of improvement and succumbed to illness. The fatal outcome in this case highlights the importance of emerging therapies such as JAK inhibitors (ruxolitinib) and interferon-gamma inhibition with monoclonal antibodies like emapalumab [16,17]. Agents such as these ameliorate the hypercytokinemia but are not as toxic as etoposide-based therapy for HLH.

4. Conclusion

TB-HLH is a serious condition often delayed in diagnosis and treatment. This case highlights the importance of considering HLH when the clinicians encounter a case of severe infection showing the features of hyperferritinemia and pancytopenia in bone marrow. A high index of suspicion on unusual presentation prevents delay and potentially-directed therapy on time may dramatically result in a better outcome. Many of the cases disclose that any delay in the definitive therapy leads to the death of the patient. Corticosteroids and IVIG have shown to be effective in the treatment of severe TB-HLH. Early diagnosis and treatment remains mainstay for better survival of the patient. However, more research is needed in this area to decide the optimal management for TB associated HLH cases.

Declarations

Consent

Informed consent of the patient was obtained for the publication of this article.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

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Data availability

Data will be made available on request.

Declaration of competing interest

The authors have no conflict of interest to declare.

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