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Case report

Hemophagocytic lymphohistiocytosis secondary to visceral leishmaniasis: A case report of a rare complication of visceral leishmaniasis

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially life-threatening clinical syndrome characterized by hyperactivation of inflammatory mediators and harmful end-organ damage. Visceral leishmaniasis (VL)-induced HLH is a rare disease with significant diagnostic and management implications. Herein, we present a case of secondary HLH as a complication of visceral leishmaniasis in a two-year-old toddler. A 2-year-old male toddler was admitted for evaluation of a prolonged 4-week fever. Accompanying the fever, he developed progressive abdominal swelling, intermittent bilateral nasal bleeding, and repeated chest-focus infections of similar duration. The patient was acutely sick, with chronic signs of malnutrition (mid-upper arm circumference of 10.5 cm), fever (39 °C), tachypnea (70 breaths/min), tachycardia (132 beats/min), pallor, and hepatosplenomegaly. Initial investigation revealed leukopenia (2240/μl), anemia (7.3 g/dl), and severe thrombocytopenia (26,000/μl). With consideration of febrile neutropenia, the patient was started on cefepime with further revision to vancomycin and meropenem based on the culture result. After 10 days of persistent fever and poor clinical condition, an immunochromatographic rapid test with the rK39 antigen was conducted, and the patient was found to be positive for *Leishmania* spp. Intravenous liposomal amphotericin B (AmBisome) was initiated. On the 6th day of treatment, the patient's clinical and laboratory profiles severely deteriorated, and further laboratory investigation showed elevated triglyceride (524 mg/dl) and ferritin levels (1500 ng/mL). VL-induced secondary HLH was confirmed, and intravenous dexamethasone was initiated. Subsequently, his clinical and laboratory findings significantly improved, and he was discharged with PO dexamethasone. Our case highlights the intricate nature of VL-induced HLH and the need for high index of suspicion and timely management.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a clinical condition brought on by the over-activation of lymphocytes and macrophages, leading to the secretion and release of high levels of proinflammatory cytokines [1,2]. Visceral leishmaniasis (VL) is a systemic parasitic infection caused by *Leishmania* spp. and spread by sand flies. It manifests in different clinical forms, such as cutaneous, mucocutaneous, and visceral. VL-induced HLH poses a unique diagnostic challenge and often carries life-threatening complications if left untreated [3,4]. HLH is diagnosed according to the HLH-2004 Diagnostic Criteria, which includes a molecular diagnosis consistent with HLH or 5 of the 8 clinical and laboratory findings [5]. The primary treatment modality in primary HLH constitutes the use of immunosuppressive drugs. In case of VL-associated HLH, the principal mode of treatment is via liposomal amphotericin (LA), although the use of immunomodulating agents may be considered in unresponsive cases.[5–8].

Case report

We report a case of a 2-year-old male toddler who presented with a prolonged fever for 4 weeks. He was generally healthy 4 weeks ago, at which time he started to develop a high-grade persistent fever, accompanied by progressive abdominal swelling, intermittent bilateral nasal bleeding, cough, and malaise. Upon presentation, the patient was acutely sick, with chronic signs of malnutrition (middle-upper arm circumference of 10.5 cm), fever (39 °C), tachypnea (70 breaths/min), and tachycardia (132 beats/min). There was conjunctival and palmar

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pallor. The chest was clear, and no murmur or gallop was auscultated. There was no lymph node enlargement. The spleen was palpable at 9 cm along its line of growth, and the total liver span measured 14 cm along the midclavicular line. There was grade II bilateral pitting edema. Neurological examinations were normal, and the patient achieved age-appropriate developmental milestones. There was no history of consanguineous marriage within the family. The patient's initial investigation revealed: WBC 2240/μl with an absolute neutrophil count (ANC) of 356/μl, hemoglobin 7.3 g/dl, platelet 26,000 μl, creatinine 0.3 mg/dl, urea 17 mg/dl, Na+ 130 mEq/l, K+ 2.9 mEq/l, Cl- 90 mEq/l, AST 105 IU/l, ALT 46 IU/l, ALP 585 IU/l, ESR 20 mm/hr, and CRP 15 mg/dl. Complete infection work-ups (hepatitis B, hepatitis C, HIV, mycobacterium Gene Xpert, malaria Rapid Diagnostic Test, and blood film) were negative. Initial bone marrow aspirations showed no evidence of hematologic malignancy or infection. The abdominal ultrasound was unremarkable except for the massive hepatosplenomegaly. The chest X-ray was non-revealing.

With the impression of febrile neutropenia, blood, urine, and stool cultures were sent, and the patient was started on cefepime (50 mg/kg/dose, TID). He was also transfused with red blood cells and platelets. The patient was monitored using clinical and laboratory parameters but showed no obvious improvement. On the 4th day of treatment, based on the blood culture result, the antibiotic was changed to meropenem (40 mg/kg/dose, TID) and vancomycin (90 mg/day). Subsequent blood workup on the 4th day showed: WBC 2450/μl with absolute neutrophil count (ANC) of 390/μl, hemoglobin of 7.1 g/dl, platelet 19,000 μl, creatinine of 0.3 mg/dl, urea of 13 mg/dl, Na+ of 137 mEq/l, K+ of 4.6 mEq/l, Cl- of 109 mEq/l, AST of 313 IU/l, ALT of 84 IU/l, and ALP of 813 IU/l. After 10 days of supportive care and antibiotic administration, further investigation was proposed because the patient's clinical condition did not improve. Considering the patient's epidemiologic profile, an immunochromatographic rapid test with the rK39 antigen was conducted, and the patient was found to be positive for *Leishmania* spp. The antibiotics were stopped, and intravenous liposomal amphotericin B (AmBisome, 5 mg/kg/day) was initiated. After 6 days of treatment with liposomal amphotericin B, the patient's clinical condition started to deteriorate (body temperature rose to 39.3 °C and spleen size progressed to 15 cm), and his blood work showed: WBC 1009/μl with an absolute neutrophil count (ANC) of 70/μl, hemoglobin 7 g/dl, platelet 15,000 μl, triglyceride 524 mg/dl, ferritin 1500 ng/mL, and LDH 808 IU/l. Total bilirubin 18.7, direct bilirubin 9.9, albumin 2.2 g/dl, fibrinogen 2.3 g/l, Prothrombin time: 21.8 s; partial thromboplastin time: 43.4 s; international normalized ratio: 1.9.

VL-induced secondary HLH was confirmed after five out of eight criteria for HLH (fever, splenomegaly, cytopenias involving three lineages, hyperferritinemia, and hypertriglyceridemia) were fulfilled [5]. Measuring low natural killer (NK) cell activity and soluble CD25 [interleukin (IL)−2 receptor] was not possible due to resource limitations. Repeated bone marrow aspiration and bone marrow biopsy were performed, but the results were normal. The patient was started on intravenous dexamethasone at a dose of 10 mg/m2/day (etoposide was delayed due to impaired liver function status). After 4 days of dexamethasone therapy, the patient's clinical condition dramatically improved, the spleen regressed, and blood workup showed: WBC 9170/μl with absolute neutrophil count (ANC) of 4460/μl, hemoglobin 10.3 g/dl, platelet 218,000 μl, creatinine 0.2 mg/dl, urea 26 mg/dl, Na+ 140 mEq/l, K+ 4.2 mEq/l, Cl- 111 mEq/l, AST 91 IU/l, ALT 54 IU/l, and ALP 174 IU/l. The patient was discharged after 21 days of hospital stay with PO dexamethasone and regular follow-up.

Discussion

Hemophagocytic lymphocytosis (HLH) is a clinical syndrome that results from excessive release of inflammatory mediators and often poses a significant risk of mortality if not promptly treated [9]. Classically, HLH has been categorized into primary and secondary. The first year of life is considered the peak age for F-HLH and usually harbors 70–80 % of familial HLH cases. It has also been linked to uncommon genetic conditions, such as Chediak Higashi and Griscelli syndrome [10]. It has been proposed that secondary HLH could be the product of inherited genetic susceptibilities and extrinsic factors, such as infection, neoplasm, or autoimmunity [11]. Whole genome sequencing is the preferred method of genetic analysis for understanding acquired HLH [9]. Genetic testing was not performed in our patient due to resource limitations.

Various clinical conditions have been associated with secondary HLH, including, but not limited to, infection, malignancy, metabolic disturbances, rheumatologic diseases such as juvenile arthritis or systemic lupus erythematous, post allogeneic hematopoietic stem cell transplantation (HSCT), and drug hypersensitivity. It is associated with a range of infectious culprits like viruses, bacteria, fungi, and parasites, such as leishmaniasis. The leading causes of infectious secondary HLH are viruses, and Epstein-Barr virus (EBV) is the most frequent HLH-associated virus [9]. The production and release of proinflammatory cytokines are overwhelmed in secondary HLH [12]. The basic mechanism underlying this hypercytokinemia is poorly understood, but the excessive production of proinflammatory agents is linked to continual toll-like receptor activation by autoimmune or infectious triggers [9].

HLH is a clinical entity characterized by signs of systematic illnesses and various signs and symptoms. Typical signs and symptoms of HLH comprise fever, organ enlargement, neurological issues, and various end-organ damages [13]. Hemophagocytosis, which is the result of phagocytosis by activated macrophages, is a distinctive histopathological feature. Although a typical feature, it is not required for diagnosis because it is present only in 25–100 % of cases [14]. Our patient's bone marrow study was also non-diagnostic twice.

Cytopenias are the most frequent laboratory findings, with thrombocytopenia (78 %) being the most common finding, followed by anemia(67 %) and neutropenia(42 %) [15]. Although none are pathognomic, a broad spectrum of laboratory findings have been reported, including hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, elevated levels of the sIL2r**α** chain (sCD25), reduced natural killer cell function measured by chromium release assay, soluble CD 163, and an abnormal liver function test [16].

HLH is now diagnosed according to the HLH-2004 Diagnostic Criteria [5], which includes a molecular diagnosis consistent with HLH or 5 of the 8 criteria listed below.

1. Fever $\geq$ 38.3ºC.
2. Splenomegaly.
3. Cytopenia (affecting at least two of the three lineages in the peripheral blood).

Hemoglobin $<$ 9 g/dL (infants $<$4 weeks: hemoglobin $<$10 g/dL).
Platelets $<$ 100 $\times$ 10^3/lL.
Neutrophils $<$ 1000/lL.

4. Hypertriglyceridemia ($\geq$265 mg/dL) and/or.
Hypofibrinogenemia ($<$150 mg/dL).
5. Hemophagocytosis in bone marrow, spleen, and lymph.
nodes or liver.
6. Low or absent NK cell activity.
7. Ferritin $\geq$ 500 ng/mL.
8. sCD 25 (sIL2R **α**) $\geq$ 2400 U/mL.

Our patient had a fever, splenomegaly, cytopenia (involving 3 cell lines), hypertriglyceridemia, hyperferritinemia, coagulation abnormalities, and liver function abnormalities, keeping up with the clinical presentation and diagnostic criteria of HLH.[5].

Another important tool that helps in diagnosing HLH is the HScore, which assesses nine different criteria: the presence of immunosuppression, maximal temperature, organomegaly, higher triglyceride level, higher ferritin levels, aspartate aminotransferase/serum glutamic oxaloacetic transaminase levels, lower fibrinogen levels, number of cytopenias, and hemophagocytosis in bone marrow aspirate. A score above 169 was found to be predictive of HLH with, 93 % sensitivity and 86 %

specificity. It was also shown that HScore performed better in the pediatric age group with 100 % sensitivity and 86 % specificity. Our patient's calculated HScore was 218. [17].

Owing to HLH's life-threatening nature, timely and aggressive initiation of therapy is often warranted. Currently, the most widely used management approach is based on the Histiocyte Society HLH-1994 and HLH-2004 studies and primarily involves the use of etoposide and dexamethasone. In cases of relapsed or refractory HLH, various salvage therapies, including chemotherapeutic agents such as cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)-like regimens with etoposide, anti-CD52 antibody alemtuzumab, anti-IFN-∂ antibody emapalumab, and cytokine adsorption using filter columns or plasma exchange have been suggested [9]. In a study by Mottaghipisheh et al., VL-induced HLH was successfully treated with liposomal amphotericin without the need for etoposide or cyclosporine. Dexamethasone was used only in a minority of patients who presented with severe disease. The response was remarkable, with no death or recurrence in the 40-month follow-up period, further emphasizing the efficacy of treating the underlying cause without resorting to etoposide-based chemotherapy. [18].

The underlying consensus for treating HLH is that therapeutic actions should be tailored to the most likely predisposing cause [19]. VL-induced HLH should initially be treated with liposomal amphotericin, followed by immunomodulating agents in cases of no response. [5–8].

Conclusion

VL-induced secondary HLH is an extremely rare disease with significant diagnostic and management challenges. It is frequently underdiagnosed due to its overlapping clinicopathological presentations. Given its rarity and potentially life-threatening nature, a high level of suspicion and timely initiation of treatment are imperative.

CRediT authorship contribution statement

Telila K.Belisa: Writing – original draft, Resources, Data curation, Conceptualization. **Asteway M. Haile:** Writing – original draft, Resources. **Getinet B. Mesfin:** Writing – review & editing, Writing – original draft. **Biruk T. Mengistie:** Visualization, Software, Data curation. **Chernet T. Mengistie:** Writing – review & editing, Data curation. **Bezawit M. Haile:** Supervision.

Ethical approval

The study was approved by the relevant body.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Consent

Written informed consent was obtained from the mother of the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Statements

1) Written informed consent was obtained from the mother of the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

2) All authors attest that they meet the current ICMJE criteria for Authorship.

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