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Late-onset Familial Hemophagocytic Lymphohistiocytosis in a survivor of Hodgkin's Lymphoma

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ABSTRACT

Hemophagocytic Lymphohistiocytosis is an inflammatory condition which results in over activation of the immune system. It could be either sporadic or familial. The familial subtype is linked with various genetic mutations and is commonly a disease of the young. Here we report a case of HLH in an adult, occurring in the background of a successfully treated hematological malignancy. Upon workup, he was also found to have pathogenic STXBP2 mutation, suggesting HLH of familial origin. To date, only few cases of adult-onset familial HLH have been brought to light.

1. Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is a life-threatening systemic inflammatory disorder that is characterized by a surge in the proliferation of activated lymphocytes that results in the triggering of cytokines in an uncontrolled manner, causing phagocytosis of hematopoietic cells, thus giving it another name, hemophagocytic syndrome (HPS). [1] Clinical picture of HLH comprises multi-organ involvement with recurrent fever, hepatosplenomegaly, and lymphadenopathy in the background of cytopenias. [2] HLH can be broadly classified into two major subtypes i.e. a primary subtype and a secondary subtype. Primary or familial HLH is an inherited condition that is driven by highly penetrant autosomal recessive genetic mutations, involving Perforin (PRF1), MUNC 13–4 (UNC13D), MUNC 19–2 (STXBP2), and Syntaxin 11 (STX11) genes. [3] Among these, mutations in the PRF1 gene account for 20–50% of the cases. [4] It is mostly encountered in the pediatric age group in contrast to secondary HLH which is commonly seen in young adults or adolescents. [5] Moreover, secondary or sporadic HLH is an immune-mediated disease, caused primarily by acquired factors, such as chronic inflammatory processes, acute infections, or active malignancies. [3] Here, we present a case of familial HLH diagnosed in an adult patient who is a Hodgkin's Lymphoma (HL) survivor and also the first case identified in his family

2. Case

A twenty-three-year-old gentleman, with no known prior comorbidities, and a European Cooperative Oncology Group (ECOG) Performance Status score of 1, presented to our institution in September 2018 with complaints of a swelling on the left side of his neck since two months, which was non-tender and palpable. On examination, he was found to have palpable, non-tender cervical lymphadenopathy with no other significant findings on systemic examination. He subsequently underwent an excisional biopsy of the cervical lymph node which was consistent with Classic Hodgkin's Lymphoma; mixed cellularity type; staged as III-A as per the Positron Emission Tomography-Computed Tomography (PET-CT) scan. He was treated with the standard protocol of ABVD (Adriamycin, Bleomycin, Vinblastine, and Dacarbazine), yielding a complete metabolic response in July 2019, and then placed on surveillance.

He remained well until a year later; when he developed flu-like symptoms and was found to have palpable cervical lymphadenopathy. An immediate suspicion of relapse was raised, but he recovered well with symptomatic care.

However, within two months, he presented with high-grade fever and jaundice. Investigations revealed various abnormalities; raised total bilirubin at 8.8 mg/dL with an alanine transaminase (ALT) of 147 IU/ml; pancytopenia with hemoglobin (Hb) 7.8 g/dL, an absolute neutrophil count (ANC) of 1290 and a platelet count (PLT) of 13×10^9/L. An ultrasound abdomen revealed hepatosplenomegaly with similar findings

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corroborated on PET-CT. These parameters prompted a deeper look into the etiology and he was found to have cytomegalovirus (CMV) viremia with a viral load of 600 IU/ml (via PCR). The co-existence of CMV viremia with fever and deranged liver function prompted a suspicion of CMV-induced macrophage activation syndrome. Relevant investigations revealed raised lactate dehydrogenase (553 IU/L), triglycerides (564 mg/dL) and ferritin (21,566 ng/ml), and low fibrinogen levels (1.1 g/dL).

A bone marrow biopsy showed a cellular specimen with cellularity of around 75–80%, exhibiting trilineage hematopoiesis, with normoblastic erythropoiesis. There was active myelopoeisis with all stages of maturation and differentiation seen. Prominent histiocytes were noted with adequate megakaryocytes. Blast cells and Plasma cells were less than 5% and 3% respectively. Immunohistochemical stains revealed scattered CD68 positivity in histiocytes and a negative CD 30. No granuloma or replacement/infiltration was identified.

Treatment with ganciclovir and steroids was started, following which symptoms abated, laboratory parameters improved and clearance of CMV was achieved. Steroid tapering was initiated, after a month he came into the emergency room with fever, diarrhea, and jaundice. Laboratory workup revealed pancytopenia i.e. Hb – 8.2 g/dL; ANC – 893; PLT – 55 $\times$ 10^9/L, raised total bilirubin of 2.6 mg/dL with normal transaminases. Steroids were restarted and a diagnosis of Hemophagocytic Lymphohistiocytosis (HLH) was made, with an H-score of 206 points and fulfillment of six of eight diagnostic criteria.

Despite significant subjective improvement with the continuation of steroids, the pancytopenia and hyperbilirubinemia persisted. He was subsequently started on the HLH-2004 protocol, consisting of Cyclosporine (target trough levels 200 ug/L), Etoposide (at 150 mg/m2), and Dexamethasone (started at 10 mg/m2 and tapered gradually) administered in induction and continuation phases, lasting roughly three months.

At the same time, genetic testing was carried out using Invitae Diagnostic Testing which revealed two pathogenic variants in STXBP2, *c.1247–1G>C (Splice acceptor),* consistent with Autosomal Recessive Familial Hemophagocytic Lymphohistiocytosis Type 5 (FHL-5), thus fulfilling the diagnostic criteria of molecular confirmation of HLH as well. Genetic testing of family members revealed his three potential sibling donors to be heterozygous carriers. On achieving a complete remission, he was planned for an allogeneic stem cell transplant (Allo-SCT). Using HLA typing, a full-matched sibling donor was identified among the sisters and chosen as the stem cell donor.

He underwent a successful Allogenic SCT in March 2022. He received a conditioning regimen consisting of ATG, Fludarabine, Thiotepa, and Melphalan followed by peripheral blood stem cell infusion followed by cyclosporine as GVHD prophylaxis. His transplant course was uneventful.

Neutrophil engraftment occurred on Day +19 of the transplant and he was discharged from the transplant unit on Day + 22.

Post-transplant care was continued with regular outpatient visits, initially weekly to two-weekly then monthly. Post-transplant issues were Grade 1 GVHD of the upper gut managed with oral beclomethasone and low-dose steroids, herpes zoster reactivation, and mild derangement in renal function due to drug toxicity.

Soon after Day + 180, cyclosporine tapering was initiated with eventual discontinuation at ten months' post-transplant. At his most recent follow-up visit, he is doing well. He has no evidence of chronic GVHD. All of his laboratory parameters including renal functions, hematological indices, liver functions, serum ferritin, and triglycerides are within normal limits. He has no evidence of HLH or lymphoma recurrence on his most recent disease assessment.

3. Discussion

Hemophagocytic Lymphohistiocytosis (HLH) denotes a lethal clinical spectrum characterized by excessive inflammation, due to increased cytokine secretion by T lymphocytes, resulting in over-activation of macrophages, followed by immune-mediated visceral damage, leading to multiorgan failure. HLH was first documented in the literature by Scott and Robb-Smith in the year 1939. [6]

Familial HLH (F-HLH) is predominantly inherited in an autosomal recessive pattern. Though commonly seen in children, F-HLH can be infrequently seen in adults. [7] In two retrospective studies evaluating 500 and 252 patients of F-HLH, 8.8% and 7.1% of the patients were found to have adult-onset F-HLH respectively. [8–9] We can now identify five subdivisions of F-HLH i.e. types 1–5, associated respectively with (a) an unidentified defect on chromosome 9q21.3–22, F-HLH1, (b) perforin gene (PRF1) mutation on 10q22, F-HLH2, (c) UNC13D gene mutation on 17q25.1, which encodes for the Munc13–4 protein, F-HLH3, (d) syntaxin 11 (STX11) gene mutation on 6q24, F-HLH4 and (e) syntaxin-binding protein-2 (STXBP2) gene mutation, which encodes for syntaxin-binding protein2 or Munc18–2 protein, F-HLH5. Of these, mutation in the Perforin gene (PRF1) is the commonly seen mutation [10] whereas mutations in PRF1, MUNC13–4, and STXBP2 correlate to late-onset F-HLH i.e. familial HLH in adult age. [11] In addition STXBP2 mutation is also associated with a milder disease presentation.

In contrast, sporadic HLH is often accompanied by an identifiable predisposition which could be an infection, an auto-immune disease, or an underlying hematological malignancy. Hodgkin's lymphoma account for the most common malignancy associated with HLH followed by T-cell lymphoma. [12] Rivière et al. in their retrospective analysis of 162 HLH patients demonstrated that HL contributed to 6% of HLH cases. [13] In another exploratory review, approximately 14% of the cases were found to arise in the background of HL. [14] Viral infections are by far the commonest triggers of HLH in children and young adults most commonly EBV and CMV. [15] HLH can also occur in the background of an auto-immune condition such as systemic lupus erythematosus (SLE), adult-onset Still's disease (AOSD), or juvenile idiopathic arthritis (JIA), in which case it is referred as macrophage activation syndrome (MAS). [16]

Given the history of Hodgkin's lymphoma in our patient, our initial suspicion was relapse of the disease when he presented with HLH. This was ruled out by a negative PET CT and bone marrow biopsy. He also was found to have low titer CMV viremia. This then led us to believe that he could have secondary HLH due to viral infection. Testing for familial HLH was prompted when he has recurrence despite completing antiviral therapy with a negative CMV-PCR.

The treatment of F-HLH is complex and involves immunosuppression, induced either with the use of systemic steroids or chemotherapy (with etoposide as the backbone), followed by an allogeneic stem cell transplant (HSCT). HLH-94 was the first international study introduced by the Histiocyte Society that showed a 5-year probability of survival up to 54% +/- 6%. Given early mortality before HSCT and delayed neurological adverse events, the model was revised as HLH-2004, which reduced the pre-HSCT mortality rate from 27% to 19%. [17] In a single-center review involving 48 patients with F-HLH, HSCT demonstrated an overall survival of 58.5% that extended up to 20 years. [18] In a Japanese review, HSCT resulted in survival rates of up to 65% at 10 years. [19]

Remission is the key factor correlating with survival and outcomes. Moreover, the transplant-related mortality is significantly found to be influenced by the conditioning regimen itself, with pre-HSCT reduced intensity conditioning resulting in doubling of 3-year overall survival rate, when compared to myeloablative conditioning. [20–21]. The selection of an optimal stem cell donor and source is crucial for a favorable outcome in patients with HLH. Ideally, an HLA-matched sibling donor is preferred. However, given the inherited nature of the disease, genetic assessment and NK cell activity need to be determined prior to donor selection. Unfortunately, in our case, all of the siblings were heterozygous for the STXBP2 mutation. As an unrelated donor source is unavailable in Pakistan, we went ahead with the heterozygous donor as we were confident that the patient should not develop donor-derived HLH.

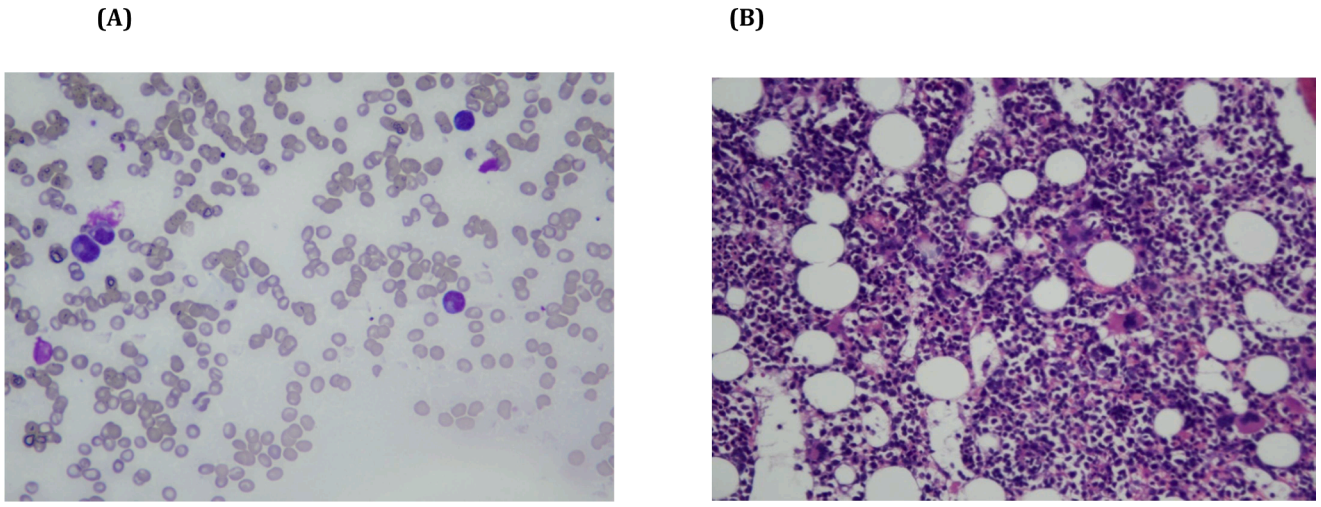

Fig. 1. (A) Bone marrow aspirate showing trilineage hematopoiesis with normocytic erythrocytes and megakaryocytes. (B) Bone marrow trephine showing good cellularity with prominent histiocytes.

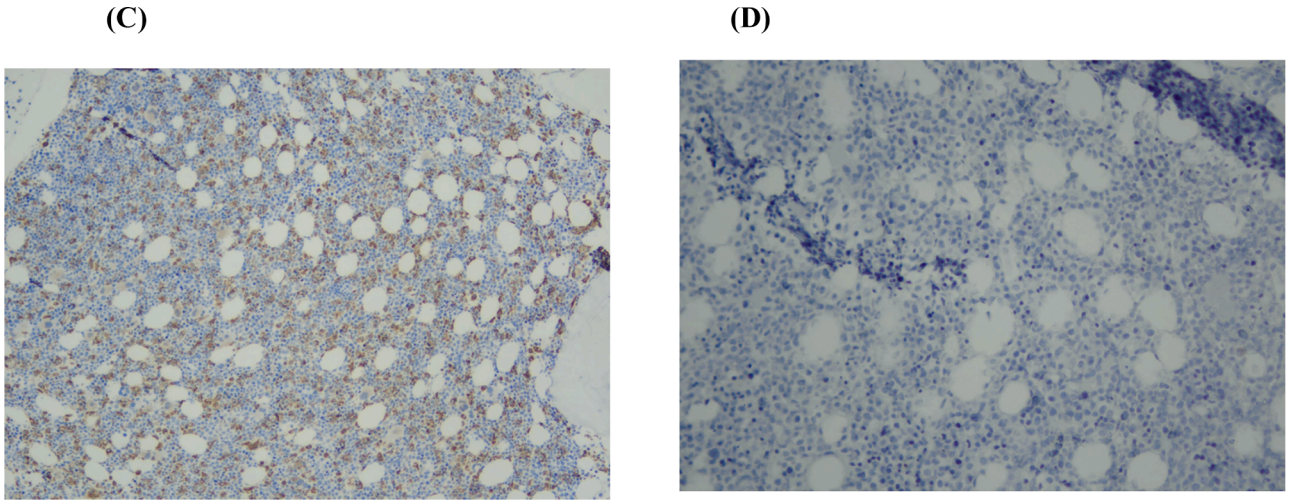

Fig. 2. IHC stain showing (C) CD 68 positivity and (D) CD30 negativity in histiocytes.

There are few case reports that suggest an association between HL and STXBP2 mutation. In all of these reports, the mutation was determined simultaneously with the diagnosis of HL. Therefore, it is unclear whether STXBP2 mutation predisposes to HL. [22] Our case is unique as the patient did not have any evidence of HLH when he was diagnosed with HL and the manifestation of hemophagocytosis occurred a couple of years later (Fig. 1,Fig. 2).

4. Conclusion

HLH has a distinct spectrum of etiologies and presentations. The understanding of the primary etiology leading to the triggering of HLH plays a significant role in the tailoring of systemic treatment. Adults with new onset HLH should be evaluated for genetic mutations. The incorporation of HSCT as a consolidative regimen; significantly increases the clinical outcome of HLH.

Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Authorship

All listed authors meet the ICMJE criteria. We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE.

We confirm that the order of authors listed in the manuscript has been approved by all named authors.

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Declaration of competing interest

No conflict of interest exists.

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