X-Linked Lymphoproliferative Disease Type 2 With Activation of Hemophagocytic Lymphohistiocytosis Secondary to Epstein-Barr Virus Infection

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare yet potentially life-threatening syndrome. It is best described as uncontrolled immune system activation leading to hemophagocytosis. Our case report aims to present a practical approach, discuss the challenges in the diagnosis and management of HLH, and to shed light on the X-linked lymphoproliferative disease type 2 (XLP-2) gene, *STXBP2* gene (as a carrier), and Epstein-Barr virus (EBV) infection in relation to HLH. This is a 2-year-8-month-old Saudi boy, who presented to the emergency department with fever for more than 7 days, not associated with any other major complaints. During the first couple of days of admission, primary results showed hyperferritinemia, low fibrinogen, anemia, high inflammatory markers, high D-dimer, and increasing liver enzymes and triglycerides. The patient fulfilled the diagnostic criteria of HLH on the third day of admission. Further investigations revealed a genetic mutation in XLP-2 gene, *STXBP2* gene (as a carrier) and EBV infection causing HLH. HLH-94 protocol was used for management. The patient had an excellent clinical outcome, unexpectedly, by only using dexamethasone, with complete remission and no recurrence up to date. HLH is not frequently encountered in daily practice. However, it can be fatal. This case report describes a unique case of XLP-2, *STXBP2* carrier with extreme EBV infection and activation of HLH, who was successfully brought into remission by partial application of HLH-94 protocol and careful clinical and laboratory monitoring. The diagnosis and management of HLH can be challenging. However, a reasonable clinical judgment can improve the outcomes.

Keywords: Hemophagocytic lymphohistiocytosis; XLP-2; EBV

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal syndrome. It can be described as uncontrolled activation of cytotoxic T lymphocytes and natural killer (NK) cells. This will result in extensive cytokine release, also known as cytokine storm, leading to macrophage hyperactivation. This hyperactivation will result in hemophagocytosis and immune-mediated injury to many organs [1, 2]. The first case reported in the literature was in 1939 by Scott and Robb-Smith, first described as histiocytic medullary reticulosis [3]. HLH is a rare disease, with an incidence estimated to be 1:800,000 per year in Japan [4]. Another Swedish study estimated the incidence of primary HLH to be 0.12 - 0.15 per 100,000 children per year [5].

HLH can occur as primary, also called genetic HLH. This subtype usually affects children at an early age. However, it can be diagnosed at any age. Another HLH subtype is secondary or sporadic HLH. This subtype usually affects any age and is associated with acquired disorders such as infections, malignancies, rheumatological or immunological disorders. Nevertheless, it is noted that primary disease needs an acquired disorder that acts as a trigger [1, 4, 6, 7].

Clinical presentation of HLH can be wide-ranging. However, the known presentation includes fever, splenomegaly, hepatomegaly, cytopenia, respiratory distress, renal failure, and central nervous system (CNS) toxicity. In addition, liver is commonly involved and is discovered by high aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which may reflect hepatitis or liver failure [1, 8]. HLH-2004 criteria (Fig. 1) are most commonly used to diagnose HLH, which include either 1) establishing a molecular diagnosis of HLH; or 2) fulfilling five out of eight criteria, which include fever, splenomegaly, cytopenias affecting ≥ 2 of 3 lineages, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis demonstrated in the bone marrow or spleen or lymph node, low or absent NK cell activity, ferritin ≥ 500 µg/L, and high soluble CD25 levels (sIL-2 receptor) $\geq 2,400$ U/mL [1, 8]. However, the diagnosis is still challenging due to the non-specific symptoms that can constitute many other differential diagnoses, the uncommonness of the disease, and the nature of the disease, as it is known to be rapidly progressing with rapid evolution in severity, which limits the time for practitioner and necessitate intervention at an early stage of investigations that
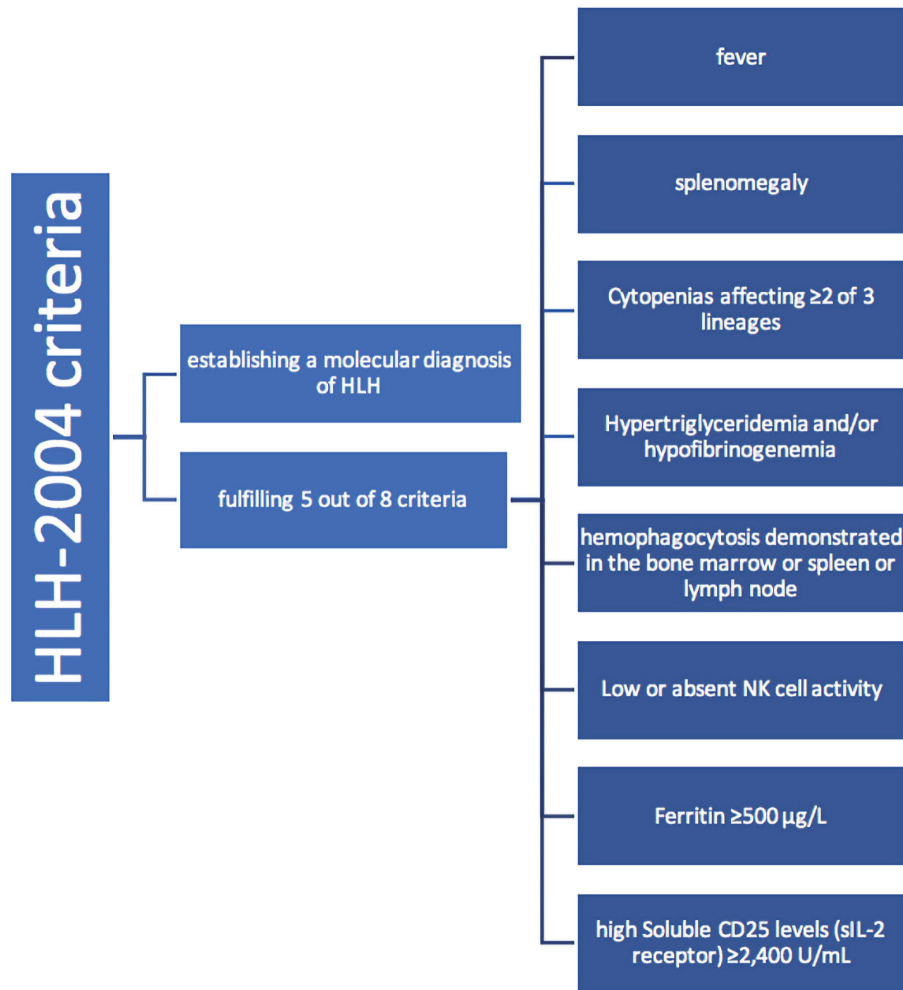
Figure 1. HLH-2004 diagnostic criteria commonly used in HLH diagnosis. HLH: hemophagocytic lymphohistiocytosis; NK: natural killer.

need high clinical sense and reasonable clinical judgment to prioritize investigations over others and decide when it is time to provide therapeutic actions [6]. Our case report aims to discuss the challenges in the diagnosis and management of HLH, and to shed light on X-linked lymphoproliferative disease type 2 (XLP-2) gene, *STXBP2* gene - as a carrier - and Epstein-Barr virus (EBV) infection in relation to HLH.

Case Report

A 2-year-8-month-old Saudi boy, not known to have medical illnesses, presented to the emergency department with a fever for more than 7 days, measured axillary, reaching up to 39 °C. The fever was intermittent, peaked almost every 4 h, and responded to acetaminophen.

His fever was associated with sweating, redness of the eyes, and vomiting with every feed; however, the vomiting was non-bloody, non-bilious and non-projectile. Moreover, the mother reported a history of weight loss of around 1 kg in 1

week and decreased activity and feeding. There was no history of abnormal movements, loss of consciousness, weakness, photophobia, cracked lips, skin rash, jaundice, pallor, joint pain, ear pain or discharge, chest pain, shortness of breath, cough, sore throat, runny nose, abdomen pain, constipation, diarrhea, or urinary symptoms. In addition, there was no history of recent travel, or ingestion of unpasteurized milk. His mother reported a history of previous mild self-limited fever episodes, occurring every 3 - 4 months, lasting for 1 day and then spontaneously resolving. Also, she reported a positive history of contact with several family members with coronavirus disease 2019 (COVID-19) infection around 2 - 3 weeks prior to presentation to the hospital.

He was a product of normal vaginal delivery, full term, with an uneventful and uncomplicated pregnancy and delivery. His vaccines are up to date. His development is appropriate for his age, with unremarkable past medical and surgical history. His parents are non-consanguineous, and he does not have any siblings. However, the mother was pregnant during the time of the patient's presentation.

Table 1. Significant Investigations Conducted Upon Admission

Investigation	Results[a]
Blood cultures	No growth
Complete blood count (CBC)	
WBC ($\times 10^3/\mu L$)	7.8 (6 - 18)
RBC ($\times 10^6/\mu L$)	4.24 (3.5 - 5.2)
Hb (g/dL)	10.1[b] (10.5 - 13.5)
Plt ($\times 10^3/\mu L$)	214 (140 - 450)
R-CRP (mg/dL)	2.38[b] (0.10 - 0.5)
Procalcitonin	4.87[b] (≤ 0.1)
Ferritin (ng/mL)	33,511.20[b] (21.81 - 274.66)
Liver function test (LFT)	
AST (U/L)	401[b] (5 - 34)
ALT (U/L)	141[b] (5- 55)
LDH (U/L)	4,709[b] (125 - 220)
γGTP (U/L)	127[b] (12 - 64)
B12 level (pg/mL)	1,320[b] (187 - 883)
PTT (s)	50.2[b] (25.6 - 42.3)
Fibrinogen level	122[b] (200 - 400)
PT (s)	17.3[b] (13.1 - 17.5)
D-dimer	8.16[b] (≤ 0.5)
Renal function test (RFT), chest X-ray, venous blood gas (VBG), ESR, hemoglobin electrophoresis, G6PD test, triglycerides, INR, electrolytes, amylase, immunoglobulins, echocardiogram (ECHO), electrocardiogram (ECG), urinalysis and culture, other elements of LFT	Unremarkable

[a]Reference ranges listed above correspond to the reference ranges utilized in our hospital's laboratory. [b]Abnormal results. WBC: white blood cell; RBC: red blood cell; Hb: hemoglobin; Plt: platelet; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; γGTP: γ-glutamyl transpeptidase; PT: prothrombin time; PTT: partial thromboplastin time; ESR: erythrocyte sedimentation rate; G6PD: glucose-6-phosphate dehydrogenase; INR: international normalized ratio.

Prior to presentation to our hospital, the patient visited another health facility. Parents were advised for bone marrow aspiration and biopsy due to cytopenias, but they refused and wanted a second opinion.

His physical examination was significant for palpable liver 2 cm below costal margin, and four inguinal lymph nodes were palpable, measuring around 1 cm; the rest of the examination was unremarkable.

Our patient was admitted as a case of fever for further investigation. Upon admission, he underwent investigations (Table 1) and was started on intravenous (IV) fluid, ceftriaxone and acetaminophen when needed. Primary results have shown extreme hyperferritinemia, low fibrinogen, anemia, high inflammatory markers, transaminitis and high D-dimer. Thus, multiple differential diagnoses, such as HLH, macrophage activation syndrome (MAS), multisystem inflammatory syndrome in children (MIS-C), Kawasaki and others, were suggested and needed to be ruled out.

During the first couple of days of admission, the patient still used to have multiple spikes of fever. However, he was stable hemodynamic wise. Follow-up of his investigations showed worsening of liver enzymes, with AST: 727, ALT: 208, lactate dehydrogenase (LDH): 4,970 and γ-glutamyl transpeptidase (γGTP): 285. The lipid profile showed a new increase in triglycerides at level of 386. Complete blood count (CBC) was dropping to the lower border with white blood cell (WBC): 6.4, red blood cell (RBC): 3.42, hemoglobin (Hb): 8.1 and platelet (Plt): 145. The erythrocyte sedimentation rate (ESR) rose to 32. Based on the lateral results, he was started on intravenous immunoglobulin (IVIG) and methylprednisolone (after obtaining the bone marrow samples), and ceftriaxone was switched to cefepime.

More investigations were conducted (Table 2). EBV early antigen (EA) immunoglobulin (Ig)G, EBV nuclear antigen (NA) IgG, EBV viral capsid antigen (VCA) IgG, EBV IgM, rubella IgG, varicella IgG, cytomegalovirus (CMV)-IgG, herpes simplex virus (HSV)-IgM, HSV-IgG, and COVID-19 IgG were positive. Urine protein was 29.3. Abdomen ultrasound (US) showed moderate hepatomegaly with biliary sludge. Results of bone marrow workup showed normocellular marrow for age with evident hemophagocytosis and no evidence of malignancy.

On the third day of admission, based on the clinical presentation and results above, the patient fulfilled the diagnostic criteria of HLH. Thus, more investigations were required to clarify whether it was primary or secondary, and the triggers

Table 2. Additional Investigations Conducted During the Hospital Admission

Investigation	Results[a]
CMV IgG	Positive[b]
CMV IgM	Negative
EBV EA IgG	Positive[b]
EBV-M IgM	Positive[b]
EBV-NA IgG	Positive[b]
EBV-VCA IgG	Positive[b]
EBV PCR test	Positive (19,500 copies/mL)[b]
Chromosomal analysis	No numerical or structural abnormality detected
Bone marrow biopsy	Normocellular marrow for age with evident hemophagocytosis[b] and no evidence of malignancy
Mycoplasma IgG	Negative
Abdomen US	Moderate hepatomegaly with biliary sludge
Rheumatoid factor	< 7
C4 (mg/dL)	22.3 (13 - 57)
Troponin-1 (ng/mL)	< 0.010
Urine protein (mg/dL)	29.3[b] (1 - 14)
IgM	188[b] (41 - 183)
Rubella IgG	Positive[b]
Rubella IgM	Negative
Varicella IgG	Positive[b]
Varicella IgM	Negative
COVID-19 IgG	Positive[b]
COVID-19 IgM	Negative
COVID-19 PCR	Negative
Hepatitis B and C panel	Negative
HIV panel	Negative
HSV IgG	Positive[b]
HSV IgM	Positive[b]
IL-1 (pg/mL)	10.2[b] (≤ 5.0)
IL-6 (pg/mL)	4.4 (≤ 7.0)

[a]Reference ranges listed above correspond to the reference ranges utilized in our hospital's laboratory. [b]Abnormal results. CMV: cytomegalovirus; EBV: Epstein-Barr virus; Ig: immunoglobulin; VCA: viral capsid antigen; EA: early antigen; NA: nuclear antigen; US: ultrasound; COVID-19: coronavirus disease 2019; HIV: human immunodeficiency virus; HSV: herpes simplex virus; PCR: polymerase chain reaction; IL: interleukin.

(Table 2). In addition, although no CNS symptoms were present, a lumbar puncture was necessary. The lumbar puncture showed unremarkable cerebrospinal fluid (CSF) analysis (glucose, protein, culture, and cytology).

The management plan was to start HLH-94 protocol with dexamethasone, repeat the IVIG after 4 weeks, start Septra (trimethoprim/sulfamethoxazole) and nystatin mouthwash as prophylactic, cyclosporine and etoposide to be added if clinically needed. Moreover, we kept monitoring the clinical conditions and laboratory investigation with serial CBC, liver function test (LFT), fibrinogen, triglyceride, and ferritin levels.

Regarding the virology workup (Table 2), it showed positive rubella IgG, varicella IgG, CMV-IgG, HSV-IgM, HSV-IgG, COVID-19 IgG, and EBV antibodies. Thus, a consultation with the infectious disease team was done. After the discussion and based on EBV polymerase chain reaction (PCR) test, which came to be positive, they concluded that it was an acute EBV infection, and the positive serological testes for other viruses were considered a cross reactivity, and they advised to repeat the serological testes later.

After starting the patient on management protocol, the patient showed marvelous improvement. Clinically, he was afebrile and did not develop any new complaints. In addition, his labs were improving, and he was only maintained on dexamethasone without the need for other immunosuppressive or cytotoxic medications. During his hospital course, the patient did not develop any complications such as sepsis, bleeding, or others, and was uneventful. He was fit for discharge after

Table 3. Trend of CBC, LFT, Triglycerides, Ferritin, and Fibrinogen Levels During Follow-Up Visits

Lab investigations results of each visit[a]	First follow-up visit May 30, 2021	Second June 6, 2021	Third June 17, 2021	Fourth July 14, 2021	Eighth October 12, 2022
LFT					
AST (U/L) (5 - 34)	29	25	42[b]	28	25
ALT (U/L) (5 - 55)	39	50	39	34	12
LDH (U/L) (125 - 220)	440[b]	430[b]	494[b]	429[b]	291[b]
γGTP (U/L) (12 - 64)	47	35	32	26	11
CBC					
WBC (× 10^3/μL) (6 - 18)	14.5	16.8	6.0	8.7	10.6
RBC (× 10^6/μL) (3.5 - 5.2)	4.54	4.62	4.93	4.94	5.11
Hb (g/dL) (10.5 -13.5)	10.6	10.0	10.5	10.1	12.5
Plt (× 10^3/μL) (140 - 450)	474[b]	-	411	529[b]	491[b]
Triglycerides (mg/dL) (30 - 200)	90	224[b]	106	55	-
Ferritin (ng/mL) (21.81 - 274.66)	13.43	4.93	953.28[b]	3.75	44.25
Fibrinogen level (200 - 400)	191	173	623[b]	303	-

[a]Reference ranges listed above correspond to the reference ranges utilized in our hospital's laboratory. [b]Abnormal results. CBC: complete blood count; LFT: liver function test; WBC: white blood cell; RBC: red blood cell; Hb: hemoglobin; Plt: platelet; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; γGTP: γ-glutamyl transpeptidase.

18 days of admission. Upon discharge, the examination was unremarkable. Labs showed CBC, renal function test (RFT), and LFT within the normal range, and ferritin level of 40.09. However, fibrinogen level was still 145, cholesterol level was 274 and triglyceride level was 250. He was discharged on dexamethasone and Bactrim (trimethoprim/sulfamethoxazole) with close follow-up in the clinic and IVIG sessions arranged.

Upon his follow-up visits, his labs were normalized (Table 3), and he continued on dexamethasone. In addition, the results of HLH genetic test panel by next generation sequencing showed a heterozygous mutation in *STXBP2*. So, he is a carrier of one of the familial HLH disease (type 5). However, as a carrier state, it cannot explain the clinical picture. Later, the result of primary immunodeficiency panel by next generation sequencing showed a hemizygous mutation in X-linked inhibitor of apoptosis protein (XIAP) along with another variant, which is consistent with the diagnosis of XLP-2. Thus, after reviewing the results, the mother was counseled regarding the bone marrow transplant (BMT), and he was referred to a transplant center. However, she was reluctant to do it, due to her not feeling convinced about the procedure and outcome, especially that he has no human leukocyte antigens (HLA)-matched related donor.

He had a follow-up for more than a year. Dexamethasone had been tapped off. The total duration of dexamethasone use from diagnosis until the last tapped dose is approximately 40 weeks. Between the follow-up visits, he was relapse-free, with a history of two admissions for gastroenteritis. However, it was not associated with major complications. Moreover, he was referred to the pediatric immunology clinic.

Our case shed light on the complexity of clinical practice. This patient turned out to be an XLP-2, *STXBP2* carrier with extreme EBV infection and activation of HLH, who was successfully brought into remission by partial application of HLH-94 protocol and careful clinical and laboratory monitoring. The need for stem cell transplant (SCT) had been reinforced to the parents and he is still on follow-up with both.

Discussion

HLH, which is described as an excessive activation of the immune system, can be a life-threatening syndrome. Although significant advances were noted in understanding this disease, the diagnosis of HLH is still challenging due to nonspecific clinical presentation, overlapping with other inflammatory differential diagnoses or rapid deterioration of the patients due to multiple organ failure or death [6, 9]. As a result, these challenges resulted in delaying the diagnosis. A study conducted in 2021 showed that the median interval time between the onset of signs and symptoms of HLH and the diagnosis was 12 days, and the interval from the hospital admission until the diagnosis was 2 days [10]. In our case report, the diagnosis was made on the third day of admission, which is similar to the lateral study. This emphasizes the importance of listing HLH at the top of the differential list. Though it is a rare and complex disease, it can be fatal, and consideration of it as a differential will significantly impact the prognosis and outcome.

STXBP2 is one of the genetic mutations causing HLH, and it is part of familial hemophagocytic lymphohistiocytosis (FHL), precisely type 5 (FHL-5) [11]. However, our patient was only a carrier of this gene, with no expectation for it to cause any manifestations. On the other hand, XLP, with XLP-1 and XLP-2 as the most common subtypes, also causes HLH, and was detected in our patient. Regarding clinical presentation, XLP-2 has a clinical presentation and management ap-

proach is similar to the other genetic mutations causing HLH. However, it has a lesser severity and better prognosis [12-14]. Though EBV infection was the most common secondary cause of HLH [2], it is commonly associated with XLP-2 [12]. Despite the previous theories classifying HLH as primary and secondary, it has been noticed that many cases of primary HLH were triggered by secondary causes [6], and many cases of primary HLH are discovered in adulthood, especially by the presence of a secondary trigger [15]. This was also noted in our case, where our patient has both XLP-2 and heterozygous *STXBP2* genetic mutations. However, EBV acted as the trigger for HLH to occur. The involvement of these two genes and having the HLH only to be triggered by EBV was not expected. Thus, changing this perspective may help widen the differential diagnosis spectrum and the clinical judgment. In addition, more studies are needed to further extend our knowledge about this syndrome.

COVID-19 infections have been linked to many diseases, including HLH. It has been hypothesized that COVID-19 infections can trigger the cytokine storm causing HLH [16]. There have been many reported cases of HLH triggered by COVID-19 infections. The characteristics of reported cases were variant; cases were reported in adults and pediatrics patients. HLH onset post COVID-19 occurred from days to months, and COVID-19 infection severity ranged from mild to severe [17-20]. All these findings suggest that COVID-19 can trigger HLH in different scenarios, and more studies are required to further understand the link between COVID-19 and HLH. Our patient had contact with COVID-19-confirmed case 1 week prior to the onset of HLH presentation, thus we cannot rule out the possibility of COVID-19, in addition to the other triggers, to cause HLH in our patient.

Generally, the goals of HLH management should focus on, firstly, stabilizing the patient. These patients can present with multi-organ failure or sepsis, which can be life-threatening. Thus, prompt management and supportive therapy are essential. Secondly, investigate the underlying cause of HLH, whether it is primary or secondary, and if secondary, search for the trigger, whether it is malignancy, infection, immune response or others. Thirdly, immune suppression is the core of HLH management [21]. In 1994, the Histiocyte Society commenced a trial (HLH-94), which was later used as a treatment protocol. The use of this protocol showed a dramatic improvement in survival. HLH-94 protocol includes the use of immunosuppressants (etoposide, corticosteroids, cyclosporin A, and, in specific patients, intrathecal methotrexate), which is essential to prevent further provoking of the immune system. Based on trials, physicians start with steroids, specifically dexamethasone, for better penetration into the CNS, in addition to a cytotoxic anti-cancer drug. The most used therapy includes dexamethasone with etoposide, which has been shown to be profoundly compelling and shows a better prognosis. In addition, the effects could be magnified when using cyclosporine in case of no response. Recently, etoposide replacement with antithymocyte globulin (ATG) has revealed notable improvement. Other drugs for relapsing HLH could be alemtuzumab, rituximab and interferon (IFN)-γ blocking monoclonal antibodies, which are under investigation [22-24]. In addition, gene therapy for the treatment of defective genes in HLH is under development, with the next step to be clinical trials [25].

Regarding our patient, he was managed using the HLH-94 protocol. However, he only required partial management. He has shown a significant improvement using only dexamethasone and supportive management, which was not expected while having two gene mutations and an acute EBV infection. Using this protocol, close monitoring and early identification of the disease helped in achieving a good outcome in our patient. Moreover, having the investigations going parallel with the management is timesaving and improves the outcome as seen in our patient.

SCT is the second step, after immunosuppressant of the HLH-94 protocol. SCT is considered a promising definitive therapy for most primary and secondary cases of HLH, which is regarded as a cure for relapsing cases too [21]. A study conducted in 2002 showed the 3-year probability of survival to be between 51% and 55% and to increase to 62% after SCT [23, 24]. However, recent studies showed there are several factors that decide the success of this cure, such as some genes have resulted in better prognosis than others, specifically: *PRF1*, *UNC13D*, *STXBP2*, *STX11*, *RAB27A*, *LYST* and *SH2D1A*. Secondly, the source of bone marrow is one factor. As studies have shown that matched unrelated donor transplants recorded 70% survival compared with matched sibling transplants. In addition, the response to the initial therapy and achieving the first remission may improve the outcome of SCT [26-28]. However various challenges pose some hazards to this operation. The first one is the state of disease. Committing a SCT while the disease is active increases mortality rate, due to numerous side effects. Another one is the complications, some of which are found before that treatment initiation, like CNS involvement, while others like pneumonia, infections, organ failure, hemorrhages, and graft versus host disease (GVHD) could lead to poor prognosis. Eventually, it is the conditioning regimen. Choosing the correct plan in the correct time ensures that GVHD risk is diminished, with no other complications occurring. The issue is that drugs used produce different effects on others, until several studies indicated that the usage of alemtuzumab, fludarabine and melphalan guarantee better results (75% survival). Thus, proper planning, monitoring and enhancing the patient's conditions might reduce the risk of these complications [26, 27]. The genetic mutation in our patient is not from the genes known with its better prognosis. However, his initial response to the management was satisfactory, which may yield a good outcome. In addition, the fact that no related matched donor was found might open the path for possible transplant in the future with a matched unrelated donor and give the chance to observe the outcome of this new approach.

Raising awareness about the SCT and its role, especially in the community, is needed, as it will help ease all the ambiguity, answer all the questions of the patient's families, and help them in decision-making regarding SCT. A study conducted in 2015 in India showed that awareness of stem cells in general was 25% in Delhi, and 18% in Bareilly [29]. Another recent study conducted in 2022 in Saudi Arabia showed that approximately 57% have significant knowledge about SCT in relation to sickle cell disease, and 42% were willing to donate [30]. As seen in our case, the mother was reluctant about the decision of SCT, and not having enough awareness about it, which was one of the reasons.

Conclusions

Diagnosing HLH can be challenging due to the rarity of the syndrome, the nonspecificity of the signs and symptoms, and the fast deterioration nature of it. In addition to that, many cases of primary HLH are triggered by a secondary cause, which is different from what was commonly known for HLH. As a result, delaying or missing the diagnosis can worsen the prognosis and delay the treatment. Raising awareness of this syndrome among healthcare providers will facilitate running the investigations while simultaneously supporting and managing the patients.

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Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Patient consent was waived due to the lack of identifiable patient information.

Author Contributions

Diagnosing and managing the patient: MA. Original draft preparation: SA and NA. Reviewing, editing and proof-reading the final version of the manuscript: MA, SA, and NA. All authors have read and agreed to the published version of the manuscript.

Data Availability

The data used to support the findings of this study are included within the article.

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