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A Case Report of Lymphohistiocytic Hemophagocytosis Syndrome with Syntaxin11(STX11) Positive Gene and Co-infection with Leishmania

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ABSTRACT

Hemophagocytic lymphohistiocytic syndrome is a rare, significant, and life-threatening disease. We are reporting this case with the hope that it may contribute to saving some patients if treated appropriately.

A 4-year-old boy presented with fever and pancytopenia. He was treated based on the symptoms that matched the criteria of (HLH). Furthermore, the bone marrow biopsy report revealed the presence of Leishman's bodies.

Hemophagocytic lymphohistiocytic syndrome is a rare, important and life-threatening disease that we are reporting this case due to the hope of saving some patients if treated. A 4-year-old boy with fever and pancytopenia, who was treated according to the symptoms matching the criteria of HLH, as well as the bone marrow biopsy report showing Leishman's bodies.

HLH is a life-threatening disease based on cumulative increase and unrestricted excessive activity of T lymphocytes, cytokines and macrophages, which occurs in two primary and secondary forms, which requires the rejection of all risk factors, symptoms similar to the disease, including infections, lymphoproliferative and autoimmune diseases and other causes, and after ruling out other causes, the patient should be treated quickly with the treatment protocol of this disease, which is reported.due to the rarity of this disease and the urgent need for timely diagnosis and treatment; we are trying to report this patient.

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Introduction

Hemophagocytic lymphohistiocytosis is a rare and life-threatening disease that can lead to the patient's death if not diagnosed in time. The prevalence of the disease is notably high from birth to 18 months, but it has also been reported in older ages [1,2,3,4].

In Hemophagocytic lymphohistiocytosis, the uncontrolled cumulative increase of active T lymphocyte cells, activated macrophages, and the intense activity of cytokines play a significant role in the pathogenesis of the disease [1].

The common symptoms of Hemophagocytic lymphohistiocytosis include fever, hepatosplenomegaly, lymphadenopathy, rash, and can mimic the symptoms of hepatitis, encephalitis, and involvement of the CNS and other organs as well [5,10].

The disease occurs in two forms: primary and secondary. The primary form is caused by genetic disorders, and the secondary form is caused by several factors such as viruses (such as Hepatitis B (HB), Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Human Immunodeficiency Virus (HIV), COVID) and bacteria (such as tuberculosis and brucellosis), fungi, autoimmune disorders (such as lupus, rheumatoid arthritis, Sjogren's, sarcoidosis), and also caused by rare factors such as Chadiac Higashi and Duncan syndrome, etc [9,10,1].

Leishmania is an obligate intracellular protozoan that lives inside macrophages [11].

In animal models, Interferon gamma and Interferon alpha play an important role in hemophagocytosis related to infection, and their administration to animal models has caused anemia and hemophagocytosis [11, 15].

Indeed, it can be concluded that infection can be a direct factor in the hemophagocytosis of macrophages.

To confirm the diagnosis, we need all five main criteria, which include: fever, splenomegaly, cytopenia of at least two lines, hypertriglyceridemia or hypofibrinogenemia, and tissue hemophagocytosis. Otherwise, in case of high clinical doubt, the treatment should be confirmed by alternative criteria, including: reduction or inactivity of natural killer cells, ferritin above 500 micrograms/liter, and Cluster of Differentiation 25 (CD25) solution more than 2400 units/ml should be started[1, 6, 16, 2].

Primary lymphohistiocytosis hemophagocytosis is the result of a genetic mutation. Different genetic mutations in familial lymphohistiocytosis hemophagocytosis involvement lead to different clinical features. Today, a number of mutations are known, each of which causes different clinical manifestations. For example, patients with PRF1 mutation are symptomatic during infancy, while the STX11 mutation leads to the disease at an older age. The genes that often change in familial lymphohistiocytosis hemophagocytosis include: UNC13D, Mutations in Perforin (PRF1), Syntaxin11 (STX11), STXBP2(SyntaxinBP2), which respectively cause 2 to 5 family subgroups. The 4th subgroup is caused by a mutation in the STX11 gene, which is located on Chromosome 6q24 and compared to other subtypes, it can appear at an older age [17, 22]. Identification of STX11 deviations and its expression in Kurdish and Turkish children, as well as in the Middle East, is much more than in other regions and races [19, 20, 21].

Considering the importance of early treatment, we decided to report this rare disease. Please let me know if you need further assistance.

Patient introduction

A 4-year-old male patient presented to the hospital, complaining of prolonged fever, weakness, and lethargy, with stable vital signs. He had no significant history of illness or surgery and had been treated with amoxicillin for 7 days due to the prolonged fever. Due to pancytopenia, active bleeding, and respiratory distress, he was transferred to the ICU. In response to these conditions, he was treated with ceftazidime and amikacin. Considering the pancytopenia, a bone marrow aspiration and biopsy were performed.

Due to the continuation of respiratory distress and a chest X-ray indicating consolidation of the right middle lobe and evidence of necrotizing pneumonia, he was treated with respiratory support with oxygen, liposomal amphotericin, meropenem, vancomycin, and methylprednisolone 1mg/kg. Due to epistaxis and severe thrombocytopenia, packed cells, fresh frozen plasma, and cryoprecipitate were transfused several times.

Tests for brucellosis, tuberculosis, hepatitis (HB), Cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human immunodeficiency virus (HIV) were negative. The Lichman antibody and antistreptolysin O (ASO)

titer were also reported as negative. The SARS-CoV-2 PCR test was negative. Normal echocardiography and ultrasound reported evidence of mild splenomegaly. Additionally, peripheral antineutrophil cytoplasmic antibodies (PANCA), antineutrophil cytoplasmic antibodies (ANCA), Rheumatoid factor (RF), Fluorescent Antinuclear Antibody (FANA), and Procalcitonin were normal. Cerebrospinal fluid analysis and culture were normal, and blood and urine cultures were reported negative.

No evidence of malignancy was found in the bone marrow biopsy, but Leishman's body was clearly visible, causing bone marrow hypocellularity. The patient was treated with miltefosine. Due to the lack of clinical improvement, he received two doses of IVIG. Due to the continuation of symptoms, epistaxis, and active melena due to severe thrombocytopenia, fluid and electrolyte resuscitation was administered. As the symptoms matched the lymphohistiocytosis hemophagocytosis criteria and the symptoms did not disappear with the treatment of leishmaniasis, he was treated with the lymphohistiocytosis hemophagocytosis 2004 protocol. Voriconazole was added to the treatment to address lung lesions, which improved the clinical conditions.

During the course of hospitalization, the patient showed improvement in distress, absence of active bleeding, and improvement of laboratory disorders. Consequently, he was transferred to the ward. After 63 days of hospitalization in the center, the patient was in good general condition with stable vital signs and acceptable test results. Genetic test results based on the report for gene detection of STX11 NM_003764: exon2 (familial hemophagocytic lymphohistocytosis 4) were also received. Finally, a bone marrow transplant was performed for him.

Discussion and conclusion

Hemophagocytic lymphohistiocytosis is a rare and life-threatening disease that leads to the patient's death if not diagnosed and treated in a suitable time [8, 9]. This disease has two forms: primary (genetic form) and secondary. The secondary form depends on many factors such as infections, lymphoproliferative diseases, autoimmune conditions, etc. These forms are divided into those that require treatment after proving the five main or secondary criteria in time (after ruling out other causes that produce similar symptoms) [8, 9, 10].

Primary lymphohistiocytosis hemophagocytosis is the result of a genetic mutation. Different genetic mutations in familial lymphohistiocytosis hemophagocytosis involvement lead to different periods of clinical disease. Today, a number of mutations are known, each of which causes different symptoms. For example, patients with a PRF1 mutation are symptomatic during infancy, while the STX11 mutation leads to the onset of the disease at an older age. The genes that often change in familial lymphohistiocytosis hemophagocytosis include UNC13D, PRF1, STX11, and STXBP2, which respectively cause subgroups 2 to 5 of family subgroups. Subtype 4 is caused by a mutation in the STX11 (Syntaxin11) gene, which is located on chromosome 6q24 [16,24]. The identification of STX11 deviations and its expression in Kurdish and Turkish children, and also in the Middle East, is much more than in other regions and races [19,20,21].

In animal models, Interferon gamma and Interferon alpha play an important role in hemophagocytosis related to infection, and their administration to animal models has caused anemia and hemophagocytosis [11,15].

So, it can be concluded that infection can be a direct factor in the hemophagocytosis of macrophages.

In the case of the presented patient, prolonged high fever and involvement of the right lobe of the lung with a high probability of necrotizing pneumonia and severe malaise required the exclusion of important possibilities such as severe pneumonia, sepsis, infective endocarditis, and lymphoproliferative and autoimmune diseases. Serological tests for active infections such as Brucellosis, tuberculosis, EBV, HIV, CMV, HB were negative. All cultures of urine, blood, cerebrospinal fluid were negative. The ASOtiter test was negative, the Sars_COVID PCR test was negative, the immune profile and complements were normal, echocardiography was normal, and investigations were normal in terms of malignancy. Leishman's body was found in the bone marrow biopsy.

Due to the presence of leishmaniasis, the possibility of leishmaniasis and pancytopenia due to the suppression of the bone marrow by infection was suggested, and the patient was treated with miltefosine [1,9,10]. However, on the other hand, active bleeding and severe thrombocytosis of the patient did not support leishmaniasis and the possibility of pancytopenia simply due to infection.

Also, the patient did not meet the criteria for diagnosing lupus or vasculitis, such as microscopic polyangiitis, granulomatosis with polyangiitis, which are the most common causes of macrophage activation syndrome (MAS). Considering the negative RF and the

absence of evidence of rheumatoid arthritis, including joint pain, inflammatory arthritis also did not justify the patient's symptoms [1,3,9].

After ruling out all possibilities, considering the patient's age (4 years), the prevalence of lymphohistiocytosis hemophagocytosis under 18 months, and the presence of Leishman cells in the bone marrow sample [11], the treatment was performed with the suspicion of secondary nature [22]. Due to the lack of clinical improvement, the patient was treated with the treatment protocol of the Histocyte Association in 2004 [2,21], which led to a satisfactory resolution of clinical symptoms and all laboratory abnormalities. Considering the course of improvement of lymphohistiocytosis hemophagocytosis, due to the presence of limited mutations of the primary type at an age older than infancy, such as STX11, and the prevalence of the primary type compared to the secondary and more prevalence and frequency in the Middle East [16,2,18,19,23,24], the patient's genetic test was investigated. The response of the genetic test based on the report indicated gene detection of STX11 NM_003764: exon2 (hemophagocytic lymphohistocytosis familial 4).

Based on the reports, lymphohistiocytosis hemophagocytosis occurs mostly in patients under the age of 18 months [1,5]. Also, the occurrence of primary disease at a young age with traces of infection in the bone marrow can cause confusion in the diagnosis of the primary or secondary form of lymphohistiocytosis hemophagocytosis and avoid the possible final treatment of the primary type (bone marrow transplantation). As a result of the report of this case, it is emphasized to pay attention to different gene mutations in the primary type of lymphohistiocytosis hemophagocytosis and to consider it regardless of age and background infection. Emphasizing the development of this syndrome in the course of common infections and autoimmune diseases and also considering the point that regardless of the evidence, the genetic check of patients suspected of lymphohistiocytosis hemophagocytosis will be a great diagnostic aid. Considering the hope of saving some of the sufferers (although with a high death rate despite treatment), we tried to write this report.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

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Conflict of Interests

The authors have no conflict of interest to declare.

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