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Case Report

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Familial hemophagocytic lymphohistiocytosis case in adult age: case report

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is an immune disorder with high mortality due to uncontrolled activation of T lymphocytes and macrophages and excessive proliferation of inflammatory cytokines. A 37-year-old female patient diagnosed with primary HLH is presented here. The patient was hospitalized with complaints of fever, weakness, and joint pain. The patient was pancytopenic, had high ferritin and low fibrinogen. She had hepatosplenomegaly. The bone marrow biopsy pathology result was consistent with hemophagocytosis. The patient's NK cytotoxicity was low. As a result of the genetic whole exon sequencing performed upon the presence of a family history; PRF1/NM-001083116/Ezxone 3, C.560C> G p (Pro187Arg) came as homozygous. HLH 2004 protocol was started with the diagnosis of familial hemophagocytic syndrome. Allogeneic bone marrow transplant was planned for the patient. Pulse steroid was initiated and plasma exchange was performed due to diffuse alveolar hemorrhage in thoracic tomography performed upon the development of dyspnea, tachypnea and tachycardia at the 7th week of the treatment. The patient died at the 8th week of treatment. In adult patients, primary hemophagocytic syndrome should be considered in differential diagnosis, treatment should be initiated after diagnosis and bone marrow transplantation should be performed as soon as possible.

Keywords: Familial hemophagocytic lymphohistiocytosis, hemophagocytic syndrome, hemophagocytic lymphohistiocytosis

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by cytopenia and tissue infiltration due to excessive proliferation of inflammatory cytokines. It is an immune disorder resulting from uncontrolled activation of T lymphocytes and macrophages. Its characteristic clinical features are fever, pancytopenia, hepatosplenomegaly (HSM), and hemophagocytosis in bone marrow, liver, spleen, and lymph tissue. It is of two types as primary and secondary. Familial hemophagocytic lymphohistiocytosis (FHL) is also called primary and shows autosomal recessive inheritance. Secondary HLH is caused by infection, malignancy, collagen tissue diseases, tissue damage, metabolites and immunosuppression.[1]

A 37-year-old female patient who applied to our clinic with the complaints of fever, fatigue, and joint pain and was diagnosed with primary HLH with pancytopenia, HSM, lymphadenopathy (LAP), hyperferritinemia, hypertriglyceridemia, and hypofibronogenemia, is presented here.

CASE

The 37-year-old female patient was admitted to our hospital with complaints of fever, fatigue, and joint pain. Steroid treatment was started with the diagnosis of sarcoidosis by the pulmonology clinic about 1.5 years ago. The patient, who showed a stable course while under steroid treatment, discontinued her steroid treatment byherself about 1.5-2 months ago and applied to our hospital when her fever, weakness, and joint pain persisted. In laboratory tests the results were as follows; hemoglobin: 6.8 g/dl, leucocyte:1.06x10^3/μL, platelet:8x10^3/μL, neutrophil:0.73x10^3/μL, lymphocyte:0.18x10^3/μL, fibrinogen:160.18 mg/dl, AST: 55 U/L, ALT: 118 U/L, lactate dehydrogenase:302 U/L, total bilirubin: 1.72 mg/dl, direct bilirubin: 1.14 mg/dl, albumin:

2.76 g/dl, BUN: 15 mg/dl, serum creatinine: 0.73 mg/dl, CRP: 32.81 mg/L, triglyceride:405 mg/dl, ferritin:2820 mg/dl. She had HSM. The pathology result of the bone marrow aspiration/biopsy performed to determine the etiology of pancytopenia was found as normocellular bone marrow biopsy showing histiocytes with hemophocytic activity and increased lymphoid cells (**Figure 1**). Current findings were "compatible with hemophagocytosis, no concomitant lymphoproliferative disease and EBV infection". As a result of bone marrow flow cytometry, the CD4/CD8 ratio was 72/25 in CD3+ T cells. As a result of flow cytometry studied in terms of immune deficiency, although B cells were within the reference values, loss of CD3 expression was found in T cells. In B cells, the rate of cells capable of transitioning to the memory phase with CD19+IgM+ CD27+ character was <1%. The patient had low natural killer (NK) cytotoxicity (**Figure 2**). In the brain MRI taken for brain involvement, a 20x12 mm signal change in the central part of the pons that did not show pathological contrast enhancement was observed (central pontin myelinosis?). The patient underwent a control lumbar puncture. The result of cerebrospinal fluid pathology was found to be class 1. Genetic analyzes were performed for the whole sequence analysis in the patient with a positive FHL history, in terms of familial hemophagocytic syndrome. Whole exon sequencing resulted in homozygous PRF1/NM-000183116/EXON 3, C.560C>G p(Pro187Arg) (classified as likely pathogenic variant). Since the patient had clinical, laboratory, genetic, bone marrow pathology and family history, familial (primary) hemophagocytic syndrome was considered according to HLH 2009 criteria (**Table**). The patient was started on the HLH 2004 treatment protocol (**Figure 3**). Allogeneic hematopoietic stem cell transplantation (AHSCT) plan was made for the patient after the treatment. Due to tachypnea of shortness of breath at the 7th week of HLH 2004 protocol treatment, consolidation in both lungs and bilateral ground-glass images (vasculitis? alveolar hemorrhage?) were evaluated in the thorax tomography (**Figure 4**). The COVID-19 PCR sample taken from the patient came back negative. A 1 mg/kg/dose prednisolone treatment was started for the patient in terms of diffuse alveolar hemorrhage. In the control thorax tomography of the patient with persistent respiratory distress, the existing lesions showed progression (diffuse alveolar hemorrhage?) (**Figure 5**). As the general condition of the patient worsened and tachypnea and hypoxia deepened, she was followed up in the intensive care unit. A 1 gr methylprednisolone and 1 gr/kg intravenous immunoglobulin (IVIG) treatment was given, plasmapheresis was applied. She was intubated on the 2nd day of her hospitalization in the intensive care unit due to the deepening of respiratory failure. The patient died on the 8th day of her intensive care hospitalization.

DISCUSSION

Being a rare and highly fatal disease, HLH is characterized by phagocytosis of shaped blood elements by macrophages as a result of abnormally increased T lymphocyte and macrophage activation and overproduction of inflammatory cytokines. Primary (familial) HLH demonstrates autosomal recessive inheritance. Despite the fact that the highly fatal

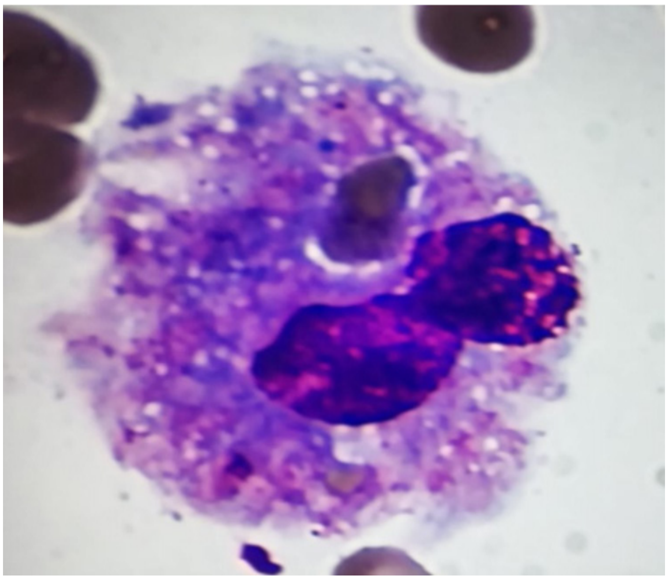

Figure 1. Bone marrow biopsy. Showing histiocytes with hemophocytic activity and increased lymphoid cells

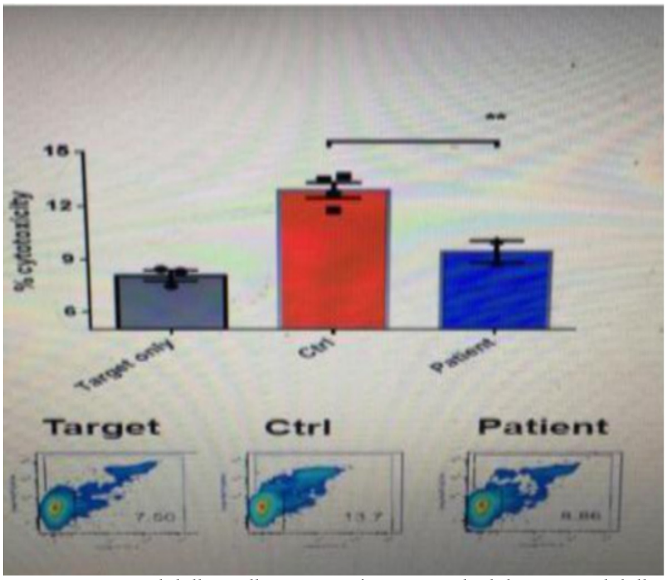

Figure 2. Natural killer cell activity. The patient had low natural killer cytotoxicity

Table. Diagnostic criteria for hemophagocytic histiocytosis (2009)
Molecular diagnosis compatible with hemophagocytic lymphohistiocytosis or x-linked a lenphoproliferative disease
Or at least 3 criteria from the 4 major criteria+at least 1 criterion from the minor criteria below
Major criteria:
1-Fever (over 38.5 °C for 7 days or more) 2-Splenomegaly 3-Bicytopenia(hemoglobin<9 g/dl, neutrophil<1x10^9/L, platelet<100x10^9/L 4-Hepatitis
Minor criteria:
1-Hemophagocytosis 2-Hyperferritinemia (ferritin>500 µg/L) 3-High sIL-2Ralpha 4-Low or undetectable natural killer cell activity 5-Other supporting findings -Hypertriglycerdaemia (fasting TG>265 mg/dl) -Hypofibrinogenemia (fibrinogen level <1.5 g/L -Hyponatremia

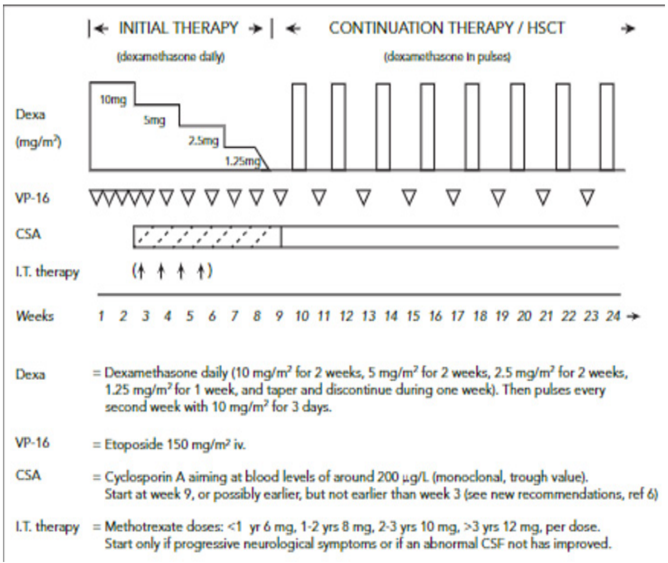

Figure 3. Hemophagocytic lymphohistiocytosis 2004 treatment protocole

Figure 4. Thorax tomography (consolidation in both lungs and bilateral ground-glass images (vasculitis? alveolar hemorrhage?)

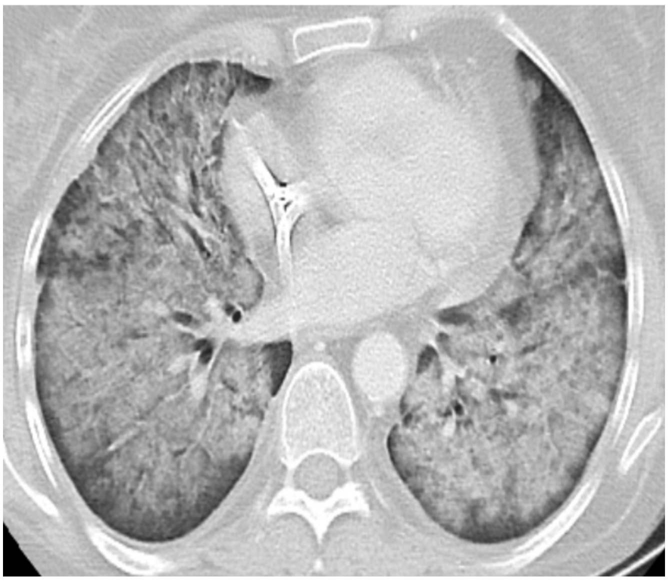

Figure 5. Control thorax tomography (The existing lesions showed progression (diffuse alveolar hemorrhage?)

disease can occur at any age, it most commonly affects infants, but it also occurs in children and adults of all ages. The oldest case was reported to be 65 years old.[1] NK cell and cytotoxic T lymphocyte functions, which are thought to be due to defects in the perforin/granzyme-mediated cytotoxic pathway, decrease in FHL.[2-4] There is usually a positive family history or an identified genetic cause for FHL. There are five different forms of FHL with different genetic mutations identified as chromosome 9q (FHL1), PRF1 (FHL2), UNC13D (MUNC13-4) (FHL3), STX11 (FHL4) and STXBP2 (MUNC18- 2) (FHL5).[5-9] First, Stepp et al.[8] confirmed the relationship between FHL2' and PRF1 in 1999, and it was reported that this mutation in the PRF1 gene causes cytokine storm, which is responsible for the pathogenesis of FHL2. Perforin plays a critical role in the cytolytic process. Impaired cytotoxicity is crucial in the pathophysiology of FHL2. Approximately seventy mutations of PRF1 have been observed in the exon 2 and exon 3 coding region. PRF1 mutation is found in 15-50% of patients with FHL.[10] PRF1 is located on chromosome 10q21-22. PRF1 mutations lead to decreased or lost expression of perforin proteins in cytotoxic T lymphocytes. The most common mutation, c.1122G> A, (which can cause 374 tryptophan codon stagnation) causes nonfunctional PRF proteins to be produced. As a result of perforin gene mutation, the activation of NK cells decreases, and as a result of T cell activation and expansion, excessive cytokine production occurs. Interferon gamma, IL-1, IL-6, TNF alpha and GM-CSF increase, macrophage activation and inflammatory reaction resulting from hemophagocytosis cause clinical findings. This mutation is found at a high rate in patients in Turkiye. In our patient, PRF1 exon 3 c.560C>G p(pro187arg) was found to be homozygous and this mutation has not been observed in any case before.

The diagnostic criteria for hemophagocytosis were determined by the "Histiocyte society" working group in 1994, revised in 2004, and presented again in 2009 (**Figure 3**). Accordingly, for diagnosis, at least three of the major diagnostic criteria (fever, splenomegaly, bicytopenia, hepatitis) and at least one of the minor diagnostic criteria (hemophagocytosis, hyperferritinemia, elevated sIL-2Rα for age, low or undetectable NK activity) are required. Hypertriglyceridemia and hypofibrinogenemia, which were included in the 2004 diagnostic criteria, were accepted as supportive criteria in the 2009 diagnostic criteria.[2,9] FHL is diagnosed in the presence of concomitant gene mutations; however, for the diagnosis of FHL, even in the absence of these mutations, a positive family history is sufficient.[3,9] Our case met the diagnostic criteria for hemophagocytic syndrome with clinical, laboratory, genetic and bone marrow findings. If left untreated, primary HLH is 100% fatal with an average life of two months. If the secondary form is not treated, it is 50% fatal. The HLH-2004 protocol, which consists of dexamethasone, etoposide, cyclosporine, and intrathecal methotrexate, is widely used in treatment.[2,9] The applied treatment protocol is continued for 52 weeks. In our case, the HLH-2004 protocol was started. Erythrocyte, thrombocyte, fresh frozen plasma and fibrinogen support were given. Broad spectrum multiple antibiotics, G-CSF and IVIG were given.

When a suitable donor for bone marrow transplantation is found in patients with FHL, the treatment is terminated.

Neurodevelopmental disorders and mortality are reduced with appropriate early treatment and timely bone marrow transplantation.[9] As for our patient, her sister had 10/10 HLA tissue compatibility. But the patient worsened at the 7th week of treatment and followed up in the intensive care unit with the diagnosis of diffuse pulmonary hemorrhage, died on the 8th day of the treatment.

CONCLUSION

For patients presenting with fever, pancytopenia, HSM, LAP, coagulopathy and a suspected positive family history, Primary Hemophagocytic Syndrome should be considered in the differential diagnosis and tests should be performed for it; and after diagnosis, bone marrow transplantation should be performed as soon as possible.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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