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Case Report / Olgu sunumu

A Clinical Labyrinth: Diagnosis of Hemophagocytic Lymphohistyocytosis

Klinik Bir Labirent: Hemofagositik Lenfohistiyositoz Tanısı

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare, non-malignant immune regulation disorder characterized by hemophagocytosis. The HLH 2004 study listed the widely accepted diagnostic model, which requires the presence of 5 out of 8 criteria (Fever; splenomegaly; cytopenia; hypertriglyceridemia or hypofibrinogenemia; hemophagocytosis, ferritin >500 mcg/L; Low/absent NK-cell activity; soluble CD25 elevation). The current management guidelines based on HLH-94 studies involve immunosuppression with weekly chemotherapy (etoposide) and glucocorticoids (dexamethasone), and intrathecal methotrexate is administered in patients with CNS involvement.CASE:A 4-month-old male patient with no known disease was admitted to our institution with a fever complaint. The physical examination and ultrasound (USG) revealed an enlarged spleen: WBC 2600, Hg 7.3, ANS 390, platelet count 26.000, ferritin 8.300, triglyceride 767, AST 48, ALT 21, total bilirubin 1.6, Na 133, and fibrinogen 70. Genetic tests were processed and intravenous immunoglobulin (IVIG) treatment was initiated with 10 mg/m2/day of Dexamethasone. The findings flared up again in the following period, and a complete treatment regimen was administered according to the HLH 2004 protocol (IVIG + Dexamethasone + Cyclosporine + Etoposide). HLH should be considered in patients with prolonged fever, cytopenia hepatosplenomegaly, and hemophagocytosis, which should be investigated by performing bone marrow aspiration first.

Keywords: Hemophagocytic lymphohistiocytosis (HLH), hematopoietic stem cell transplantation (HSCT), hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis

Öz

Hemofagositik lenfohistiyositoz (HLH), hemofagositoz ile karakterize nadir, malign olmayan bir bağışıklık regülasyon bozukluğudur. HLH 2004 çalışması, 8 kriterden 5'inin (ateş; splenomegali; sitopeni; hipertrigliseridemi veya hipofibrinojenemi; hemofagositoz, ferritin> 500 mcg/L; düşük/L; düşük/yok NK-hücre aktivitesi; CD25 Yüksekliği). HLH-94 çalışmalarına dayanan mevcut yönetim kılavuzları, haftalık kemoterapi (etoposid) ve glukokortikoidler (deksametazon) ile immünosupresyonu içerir ve CNS tutulumu olan hastalarda intratekal metotreksat uygulanır. Bilinen hastalığı olmayan 4 aylık bir erkek hasta, kurumumuza ateş şikayeti ile kabul edildi. Fizik muayene ve ultrason (USG) genişlemiş bir dalak ortaya çıkardı: WBC 2600, HG 7.3, ANS 390, trombosit sayısı 26.000, AST 48, ALT 21, TOPLAM BİLirubin 1.6, Na 133 ve fibrinojen 70. Testler işlendi ve 10 mg/m2/gün deksametazon ile intravenöz immünoglobulin (IVIG) tedavisi başlatıldı. Bulgular bir sonraki dönemde tekrar alevlendi ve HLH 2004 protokolüne (IVIG + Deksametazon + siklosporin + etoposid) göre tam bir tedavi rejimi uygulandı. Önce kemik iliği aspirasyonu yapılarak araştırılması gereken uzun süreli ateş, sitopeni hepatosplenomegali ve hemofagositozu olan hastalarda HLH düşünülmelidir.

Anahtar Kelimeler: Hemofagositik lenfohistiyositoz (HLH), hematopoietik kök hücre nakli (HSCT), hipertrigliseridemi, hipofibrinojenemi, hemofagositoz

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) if not treated is a rare, fatal phenomenon. It is a nonmalignant immune regulation disorder characterized by hemophagocytosis. There is uncontrolled activation of T lymphocytes and macrophages and overproduction of inflammatory cytokines (such as interferon-gamma, interleukin-1, interleukin-6, and tumor necrosis factor). Although there are two types, primary (familial) and secondary HLH, the clinical findings are the same. Fever, hepatosplenomegaly, pancytopenia, and lymphadenopathy are the most common findings.[1] Familial HLH is inherited as an

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autosomal recessive trait usually seen in infancy. Secondary HLH is known to be caused by pathogens. This condition is called infection-associated hemophagocytic syndrome. Secondary HLH is more likely to occur as a result of viral infections.Secondary HLH is more likely to occur as a result of viral infections. For this reason, it was defined as "virus-associated hemophagocytic syndrome."When it was observed that bacterial, fungal, or protozoal infections also caused HLH, it was named "infection-associated hemophagocytic syndrome." Macrophage activation syndrome, which develops due to collagen tissue diseases such as systemic lupus erythematosus and rheumatoid arthritis, is included in secondary HLH. Some immune deficiencies and malignancies also cause HLH.[1,2] The statement that 'HLH should definitely be considered in patients with prolonged fever under chemotherapy.

The HLH 2004 study listed the widely accepted diagnostic model, which requires the presence of 5 out of 8 criteria (Fever; splenomegaly; cytopenia; hypertriglyceridemia or hypofibrinogenemia; hemophagocytosis, ferritin >500 mcg/L; Low/absent NK-cell activity; soluble CD25 elevation). The current management guidelines based on HLH-94 studies involve immunosuppression with weekly chemotherapy (etoposide) and glucocorticoids (dexamethasone), and intrathecal methotrexate is administered in patients with CNS involvement.[3]

CASE

A 4-month-old male patient with no known disease was admitted to our institution with a fever complaint. The patient's fever had started seven days earlier. Physical examination revealed hepatosplenomegaly. There was no family history of malignancy. He was hospitalized due to persistent fever and was taken to the Pediatric Intensive Care the next day due to worsening of his general condition during follow-ups.

The physical examination and ultrasound (USG) revealed an enlarged spleen; WBC 2600, Hg 7.3, ANS 390, platelet count 26.000, ferritin 8.300, triglyceride 767, AST 48, ALT 21, total bilirubin 1.6, Na 133 and fibrinogen 70.

No atypia was seen in the peripheral smear. The patient underwent bone marrow aspiration (BMA). In the evaluation of bone marrow smears, it had a slightly hypocellular appearance. Granulocytic series elements were reduced, but each element was observed at every stage. There was no finding of malignant infiltration, and blasts were not seen. Widespread hemophagocytosis was detected, and megakaryocytes were reduced. Modified HLH 2009 diagnostic criteria were met, but HLH syndrome and disease could not be differentiated.

Previous immunological tests were normal, and genetic tests were processed. In the meantime, intravenous immunoglobulin (IVIG) treatment was initiated with 10 mg/m2/day of Dexamethasone. There was a significant improvement in all findings on the 7th day of dexamethasone; ferritin was 2.200, and it was planned to continue the treatment by decreasing it on the 15th day.

However, the findings flared up again in the following period, and a complete treatment regimen was administered according to the HLH 2004 protocol (IVIG + Dexamethasone + Cyclosporine + Etoposide). Amlodipine was started as the patient developed hypertension. After the patient's clinical condition was stabilized, the diagnosis was evaluated as HLH due to cerebral atrophy and white matter hyperintensity in the brain MRI. At the end of induction, a control brain MRI was planned to be performed under the HLH 2004 protocol, starting in the 3rd week of complete treatment and four doses of intrathecal therapy. UNC13D mutation was homozygous during follow-up from the Primary HLH gene mutation panel. HSCT (hematopoietic stem cell transplantation) was planned for the patient.

DISCUSSION

HLH can mimic several common conditions that cause fever, pancytopenia, hepatic abnormalities, or neurological findings. Many diseases, such as macrophage activation syndrome (MAS), infection/sepsis, liver disease/liver failure, multiple organ failure (MOF), encephalitis, and Autoimmune lymphoproliferative syndrome (ALPS), should be considered in the differential diagnosis. Cytopenia, elevated ferritin levels, and liver function abnormalities are particularly useful in distinguishing HLH from these conditions. Since our patient met the diagnostic criteria, we initiated preliminary treatment in this case. Upon the deterioration of the patient's clinical status, the therapy was converted to a complete regimen, and a rapid response was achieved in the laboratory tests and symptoms. Although the distinction between HLH disease and syndrome can only be performed through genetic tests, the genetic tests usually take a certain period to obtain. The response to treatment during this process guides the clinician.[3,4]

The most typical findings of HLH are fever, hepatosplenomegaly, and cytopenia. A fever of over 38.5°C usually lasts more than seven days. Ecchymosis and pallor secondary to pancytopenia may be observed. Jaundice is present in some cases. The nonspecific rash is detected in 65% of patients with HLH. Neurological symptoms such as convulsion, ataxia, hemiplegia, mental status disorders, and irritability have been reported. Weakness, anorexia, and weight loss may also be observed.[5] The presence of persistent fever for seven days, hepatosplenomegaly, and pancytopenia in our patient was considered indicative of HLH in the differential diagnosis.

There are diagnostic criteria determined by the "Histiocyte Society." HLH is diagnosed if 5 of the eight criteria are present: fever, splenomegaly, cytopenia, hypertriglyceridemia and hypofibrinogenemia, hemophagocytosis in the bone

marrow, spleen or lymph nodes without malignancy, decreased or absent NK cell activity, increased ferritin level and high soluble CD25 level. Although phagocytosis of erythrocytes is mainly seen, leukocytes and platelets are also phagocytosed. Activated macrophages can affect many organs; hence, the spleen, liver, lymph nodes, bone marrow, and central nervous system are commonly affected. In patients with HLH, cytopenia, high triglyceride, low fibrinogen, high ferritin, as well as high lactic dehydrogenase, high transaminase, bilirubin, hyponatremia, low protein, and low albumin may be detected. Moderate pleocytosis may be seen in the examination of cerebrospinal fluid. Prolonged partial thromboplastin time (PTT) and increased fibrin degradation products may be detected. Despite these diagnostic criteria, it may not be possible to distinguish familial or secondary HLH clinically and histologically. Family history and consanguinity between mother and father are helpful in the diagnosis.[6] Familial HLH is mainly seen in the first two years, while secondary HLH can be seen at any age. Not every detected hemophagocytosis is HLH. Hemophagocytosis can be seen in patients who have received blood transfusions or in sepsis. In addition, histiocytosis should be distinguished from X-linked lymphoproliferative syndrome, Chediak Higashi Syndrome, Gricelli Syndrome, lisinuric protein intolerance, DiGeorge syndrome, and Omenn syndrome.[7]

Many studies report that UNC13D mutation is associated with a high central nervous system (CNS) involvement rate. Although many members of the Munc protein family have specific functions in the CNS, Munc13-4 is not expressed in the CNS, so CNS involvement is higher in these patients and is still a matter of research.[8] In the patient discussed in this case report, the UNC13D mutation was homozygous, and CNS involvement was detected on brain MRI.

Familial HLH is fatal if left untreated, and the average life expectancy is approximately two months. The "Histiocyte Society" developed the HLH-94 protocol in 1994 and has been widely used worldwide. This protocol was modified in 2004 by adding intrathecal methotrexate and steroids in some selected cases. This treatment; dexamethasone (10 mg/kg/day for two weeks, 5 mg/kg/day for two weeks, 2.5 mg/kg/day for two weeks, 1.25 mg/kg/day for two weeks then 10 mg/kg/day for three days every two weeks), etoposide (150 mg/m2 iv, first two weeks; twice a week, six weeks; once a week, then once a week), cyclosporine (6 mg/kg/day divided into two doses and blood level will be 200 microg/L) and intrathecal methotrexate and prednisolone (when progressive neurological symptoms and abnormal CSF findings are detected), continues for 52 weeks.[6] Transplantation is recommended when a suitable donor is found for bone marrow transplantation. Even if the underlying disease cannot be demonstrated, the seriousness of the patient's condition is an indication for starting HLH-specific treatment. According to the HLH-2004 treatment guideline, the patient is evaluated after eight weeks of chemotherapy. If the diagnosis of familial or genetic HLH is confirmed, HLH treatment should be initiated and continued until hematopoietic stem cell transplantation (HSCT). If HLH cannot be demonstrated but the disease is persistent at the end of eight weeks of treatment, this treatment should be continued until HSCT is performed. If HLH cannot be demonstrated but resolution is achieved at the end of eight weeks of treatment, the treatment is terminated. However, if reactivation occurs in this group, chemotherapy should be continued until HSCT is performed, as in the other two groups. As understood from the diagnosis and treatment guidelines, morbidity and mortality are very high in both primary HLH and secondary HLH, and HSCT may be required in most patients.[6-8] The patient discussed in this case report was successfully treated with HSCT.

The most extensive single-center case series in the literature on HSCT was the 48 patients published by Chardin et al. In this study, it was found that donor compatibility, age at diagnosis, and the time from diagnosis to HSCT did not affect survival in patients undergoing HSCT, and the only factor influencing survival was disease control at the time of HSCT. Although CNS involvement was not found to affect survival, it was reported that the prognosis after HSCT tended to be worse in patients with neurological findings or neuroradiological imaging findings.[9] Similar results were reported in the study conducted by Yoon et al., emphasizing that the most important factor affecting survival was disease activity at the time of transplantation.[10]

CONCLUSION

As a result, HLH should be considered in patients with prolonged fever, cytopenia hepatosplenomegaly, and hemophagocytosis, which should be investigated by performing bone marrow aspiration first. The diagnosis of HLH can be missed and is often evaluated as sepsis. Mortality is very high in primary HLH patients who have not undergone HSCT. Therefore, mutation studies should be performed without delay.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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