Hemophagocytic Syndrome: A Case Report

Hemofagositik Sendrom: Olgu Sunumu

Hemophagocytic Syndrom

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Özet

Hemofagositik sendrom sistemik inflamatuvar bozukluklara eşlik eden T-lenfosit ve makrofajların aşırı aktivasyon ve proliferasyonu sonucu oluşan masif hipersitokinemi seyreden ciddi bir tablodur. Bu olgu sunumunda yüksek ateş ve halsizlikle başvuran hemofagositik sendromlu bir vakanın sunulması amaçlandı. Tedaviye rağmen mortalite yüksek olabilir. Erken tanının önemli olduğu tanıda gecikildiğinde prognozu son derece kötü olan hemofagositik sendromun tanısı mümkün olan en kısa sürede konulmalı, tedavisi ise altta yatan etiyolojiye göre yapılmalıdır

Anahtar Kelimeler

Hemofagositik Sendrom; Acil

Abstract

Hemophagocytic syndrome, a serious clinical condition accompanying systemic inflammatory disorders, is characterized by massive hypercytokinemia as a result of excessive activation and proliferation of T-lymphocytes and macrophages. This article aims to remind clinicians of the hemophagocytic syndrome in the differential diagnosis of patients with fever, pancytopenia, and hepatosplenomegaly. This condition can be highly fatal despite the administration of appropriate therapy. Early diagnosis of hemophagocytic syndrome is of utmost importance, as a delay in diagnosis significantly worsens the prognosis, and treatment should be tailored to the underlying pathology.

Keywords

Hemophagocytic Syndrome; Emergency

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Introduction

Hemophagocytic syndrome (Hemophagocytic Lymphohistiocytosis, HLH) belongs to the macrophage-associated group of the histiocytotic diseases [1,2]. It is characterized by a clinical presentation predominated by fever, hepatosplenomegaly, and cytopenia as a result of the dysfunction of cytotoxic T-lymphocytes and natural killer (NK) cells, activation of macrophages and T-lymphocytes, overproduction of proinflammatory cytokines, and hemophagocytosis. HLH has primary and secondary varieties [1].

In this case report we describe a case of hemophagocytic syndrome that presented with fever and weakness.

Case Report

A 28-year-old woman presented to the emergency department with sore throat, cough, weakness, and fever for the past 2 weeks. She had no history of a chronic disorder. Despite having used several antibiotics for 2 weeks (amoxicillin clavulonic acid 2 gr/day for 5 days; moxifloxacin 400 mg/day for 5 days), her symptoms did not resolve and her fever at times reached 40 °C with concomitant chills. On admission, her general status was well and she was fully conscious; she had a body temperature of 38.6 °C, blood pressure of 90/60 mmHg, pulse rate of 100 bpm, and respiratory rate of 20/min. Head and neck examination revealed pale mucosae as well as painful submental and bilateral axillary lymphadenopathies. Chest examination was characterized by reduced breath sounds in the basal portion of the right lung but no rales or rhonchi were heard in either lung. Cardiovascular system examination was free of any additional sound or murmur. Abdominal examination was positive for pain and tenderness but there was no rebound tenderness or guarding in any quadrant. The liver and spleen were percussed to a depth of 3 cm.Lower extremity examination revealed bilateral pitting edema. Neurological, rheumatological, urogenital, and dermatological examinations were all normal. Abnormal laboratory results are listed in Table 1.

Arterial blood gas analysis, coagulation parameters, renal functions, serum electrolytes (except for sodium), albumin, viral markers, and urinalysis were all normal. Abdominal ultrasonography showed hepatosplenomegaly and multiple lymph nodes at the level of the hepatic hilus, the largest of which was 2 cm. As the patient had persistent fever during her emergency department stay, she was admitted to the department of infectious diseases for further workup. She developed high-grade fever (40° C), tachypnea, hypotension, tachycardia, and diffuse abdominal pain. She thus underwent a thoracoabdominal computed tomography with contrast enhancement, which showed foci of bronchopneumonia, bilateral pleural effusions with right-sided predominance, and multiple enlarged mediastinal lymph nodes; there were also periportal edema, dense fluid around the gall bladder, massive pelvic fluid, and pathological lymph nodes in the paraaortic and mesenteric areas. The patient was referred to the department of general surgery, which gave a diagnosis of acute abdomen and performed an urgent laparotomy upon detecting tenderness, rebound tenderness, and guarding in all quadrants. No closed organ perforation was observed during open abdominal exploration. There were, however, hepatosplenomegaly, inflammation, contaminated ascite fluid, and multiple lymphadenopathies in the entire mesentery of the small intestine. Ascite fluid examination revealed abundant leukocytes and lymphocytes. Lymph node excision examination showed sinus histiocytosis. Histiocytes contained brown PAS (+) fungal spores. Immunohistochemical study histiocytes were CD68(+), CD20 (-), CD3 (-), S100 focal(+), and CD1A(-). Bone marrow aspiration biopsy revealed abundant phagocytic cells containing phagocytosed erythrocytes (Figure 1).

Table 1. The course of laboratory results

	Follow-up	The period of hemophagocytic syndrome
Leukocyte count (/mm3):	8200	3400
Hemoglobin(g/dl)	12.1	6
Thrombocyte count (/mm3)	101000	12000
ALT (U/L)	98.1	270
AST (U/L)	104.5	393
Total biluribin(mg/dl):	1.14	26.32
Ferritin(ng/ml)	1316	42742
ALP(u/l)	75	384
LDH (u/l)	145	663
GGT(u/l)	32	445
Total cholesterol(mg/dl)	110	70
Triglyceride:	286	200
HDL:	23	3
LDL:	35	4
Fibrinogen (mg/dl):	133.3	159.9
INR	1.37	1.25
aPTT seconds	40.3	66.7

(AST: Aspartate aminotransferase (0-32),ALT:Alanine aminotransferase (0-33), GGT:Gammaglutamyl transferase (0-36), LDH:Lactate dehydrogenase (135-214), INR:International normalized ratio (0,91-1,09), aPTT: Activated partial thromboplastin time (26,1-40,1), Ferritin: (30-400), Triglyceride: (<200), HDL:(>65), LDL: (80-120))

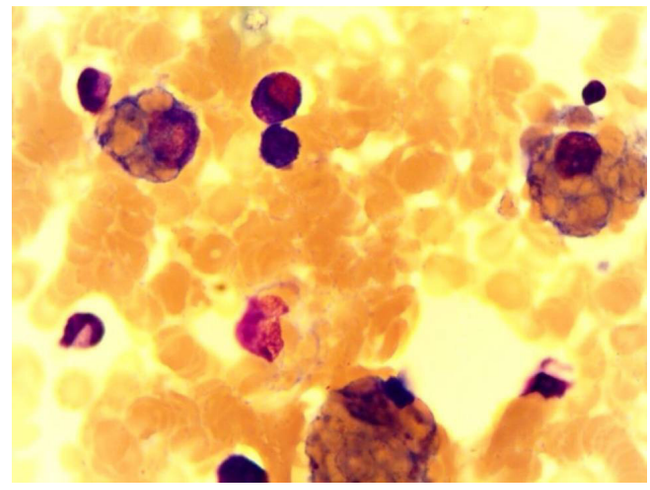


Figure 1. Bone marrow aspiration biopsy showing a phagocytic cell containing many phagocytosed erythrocytes.

Our patient was diagnosed with HLH since she met all of the 8 clinical and laboratory criteria proposed by the hemophagocytic syndrome working group. As part of the HLH-2004 treatment protocol, she was administered dexamethasone, etoposide, and cyclosporin. She was also administered IVIG, plasmapheresis, and mechanical ventilation as a supportive therapy. She was put on dexamethasone 20 mg/day, etoposide 150 mg/m2/day, intravenous immunoglobulin (IVIG) 0.5 gr/kg/day, meropenem

1500 mg/day, and anidulafungin 100 mg/day. She was also administered cryoprecipitate when fibrinogen dropped below 100 mg/dl and thrombocyte apheresis when the thrombocyte count dropped below 50000/mm3.

She subsequently deteriorated and developed disseminated intravascular coagulation (DIC). Upon further deterioration, she was transferred to the intensive care unit. She died 10 days after her hospital admission.

Discussion

HLH is a rare syndrome [1]. Although it may present with various symptoms, clinical signs, and laboratory abnormalities, none of them is specific. Five criteria should be met for the diagnosis of HLH: fever, splenomegaly, bicytopenia or pancytopenia, hypertriglyceridemia and/or hypofibrinogea, and hemophagocytosis. Additionally, elevated serum transaminase, lactate dehydrogenase, bilirubin, and ferritin levels, and hypercholesterolemia may also exist [3]. Similar to cases described by previous reports, our patient had fever, pancytopenia, hepatosplenomegaly, elevated LDH, AST, ALT, and bilirubin levels, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, and reduced HDL, LDL, and sodium levels.

Histologically, hematopoetic cells phagocytosed by macrophages are most commonly shown in bone marrow, lymph nodes, liver, and spleen samples, although every organ can be infiltrated by lymphohistiocytic cells which, despite being cytologically benign, show active phagocytosis [2]. Similarly, bone marrow biopsy of our patient contained phagocytic cells that contained many phagocytosed erythrocytes.

HLH's pathogenesis is still unclear. It is considered that cytokines released from T-lymphocytes against infections, malignancies, and autoimmune factors augment monocyte-macrophage system activity and are thus responsible for the pathogenesis of the disease. This hypothesis is corroborated by high levels of cytokines such as interleukin-2, TNF alpha, and interferon-gamma originating from T-lymphocytes of patients with HLH [4]. Although there are various methods for the treatment of HLH, the HLH-2004 treatment should be preferred. Unless treated, primary HLH is highly fatal, with an average life expectancy of about 2 months. A mortality rate of 50% has been reported for infection-induced HLH [1]. Our patient, too, died.

Infections are the most common cause of HLH. Viral infections in particular, and sometimes bacterial infections, are responsible for the occurrence of this disease. In a prior study Ebstein-Barr virus was the most common causative agent, followed by cytomegalovirus, adenovirus, parvovirus, and varicella zoster virus. In that study, bacterial agents were identified in 11 cases (brucellosis, gram-negative bacterial infections, tuberculosis); fungal agents were found in 2 cases; and Leishmania was responsible for 1 case [5,6]. Malignancies are the second leading cause of HLH. Collagen tissue diseases and certain drugs, mostly antiepileptics, may also rarely cause HLH [7]. A case of unexplained HLH after liver transplantation was reported [5]. Our patient had no family history of any hematological disease or unexplained death, suggesting that HLH was most likely a secondary condition. However, we failed to detect any infectious agent in repeated studies. Bronchoscopic aspiration and pleural fluid samples were negative for bacteriological, mycological, and mycobacteriological proliferation, and the pathological examination also revealed a benign pathology. There was no bacteriological proliferation in blood and sputum samples taken at different points in time.

The primary and secondary goals of HLH treatment are to suppress hyperinflammation and to eliminate the trigger, respectively. Therefore, chemotherapy is recommended against overactivated lymphocytes and macrophages in non-immunosuppressed patients or in those without any identfiable infectious agents [3-5]. Among chemotherapeutics, etoposide and dexamethasone, which are particularly toxic to macrophages, have been reported to be effective [8]. When an infectious agent is identified as the underlying cause, treatment should aim to eliminate it. However, a specific therapy does not exist for the majority of HLH cases. In immunosuppressed patients without any identifiable underlying infectious agent, treatment options include IVIG, colony stimulating factor, plasmapheresis, and bone marrow transplantation. In a prior report, HFS was completely eliminated after the administration of IVIG, colony stimulating factor, and plasmapheresis in a case of HFS that developed under immunosuppressive therapy after liver transplantation [8,9]. In our patient, pulse steroid and IVIG were administered. We also intended to administer other treatment modalities and therapeutic agents for our patient, but unfortunately she died shortly thereafter.

Conclusion

HLH should be considered in the differential diagnosis and appropriate studies should be carried out in cases with resistant fever, pancytopenia, hepatosplenomegaly, hypertriglyceridemia, and hypofibrinogemia. As HLH's prognosis is very dismal unless it is adequately treated in a timely way, its diagnosis should be made as quickly as possible and treatment approaches should be tailored to the underlying pathology.

Competing interests

The authors declare that they have no competing interests.

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