DAHİLİ BİLİMLER / *MEDICAL SCIENCES*
Olgu Sunumu / Case Report

Severe Acute Hepatic Failure As an Initial Manifestation of Hemophagocytic Lymphohistiocytosis

Hemofagositik Lenfohistiyoziste Başlangıç Bulgusu Olarak Ciddi Akut Karaciğer Yetmezliği

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Hemophagocytic lymphohistiocytosis (HLH) is a clinicopathologic condition characterized by activation of lymphohistiocytosis, leading to cytokine overproduction. The main clinical futures of HLH are prolonged fever and hepatosplenomegaly. Laboratory findings include pancytopenia, elevated triglycerides, ferritin and low fibrinogen. Hepatic dysfunction is often present but initial presentation as hepatic failure is a rare condition. In this report, we described a selected group of patients with dramatic onset, whose first symptom was hepatic failure. After a while, other symptoms of HLH developed and all children were diagnosed with secondary HLH based on clinical and laboratory criteria. The patients received HLH 94 chemotherapy protocol. They did not go into remission and all patients died due to progressive multiorgan failure. HLH is frequently, rapidly fatal disorder and the main prognostic factor is accurate, early recognition and therapy. For this reason, HLH should be considered in the differential diagnosis of hepatic failure especially if it is concurrent with cytopenias and unexplained prolonged fever.

Key Words : ***Hemophagocytic Lymphohistiocytosis, Hepatic Failur***

Hemofagositik lenfohistiyositozis (HLH) sitokinlerin fazla salınımına yol açan lenfohistiyositozis aktivasyonu ile karakterize klinik bir durumdur. Uzun süreli yüksek ateş ve hepatosplenomegali ana klinik bulgularını oluştururken, pansitopeni, hipertrigliserdemi, hiperferritnemi ve fibrinojen düşüklüğü başlıca laboratuvar bulgularındandır. Hastalığın izleminde karaciğer fonksiyon bozukluğu görülebilmekle birlikte karaciğer yetmezliği ile başlangıç göstermesi oldukça nadirdir. Biz, ilk bulguları karaciğer yetmezliği olan ve zaman içinde diğer HLH bulguları gelişmesiyle sekonder HLH tanısı alan olgularımızı sunmayı amaç edindik. Bütün olgulara HLH 94 kemoterapi protokolü başlandı, ancak remisyon sağlanamaması sonucu gelişen multiorgan yetmezliği ile bütün hastalar kaybedildi. HLH hızlı ve fetal gidişli bir hastalık olup erken tanı ve tedavi çok önemlidir. Bu nedenle etkin başarının sağlanabilmesi için, özellikle ateş ve pansitopeninin eşlik ettiği karaciğer yetmezliği olgularında erken dönemde ayırıcı tanıda akla getirilmelidir.

Anahtar Sözcükler: ***Hemofagositik lenfohistiyositozis, karaciğer yetme***

Hemophagocytic lymphohistiocytosis (HLH) is a rare childhood disorder and it has two variants, namely the familial hemophagocytic lymphohistiocytosis (FHLH) and the secondary HLH. Familial HLH is invariably fatal if not diagnosed at early stage and treated with hematopoietic stem cell transplantation. The findings of mutations in PRF1 (perforin), MUNC 13-4 and syntaxin 11 revealed the genetic causes of FHLH (1). Secondary form has been reported in association with many different conditions such as infections, malignancies, metabolic disorders, and rheumatoid diseases (2).

Hemophagocytic lymphohistiocytosis is characterized by severe hyperinflammation. Impaired function of natural killer (NK) cells, hyperactivation of antigen presenting cells and cytotoxic T cells cause this disorder (1). The infiltration of reticuloendothelial system by these cells leads to progressive organ dysfunction. Patients with HLH have elevated levels of various proinflammatory cytokines generated by uncontrolled activation of histiocytes and T-lymphocytes (2). Therefore many of the symptoms of HLH can be attributed primarily to hypercytokinemia and organ infiltration (1). Cardinal clinical and laboratory features are fever, hepatosplenomegaly, pancytopenia, hypofibrinogenemia,

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and hypertriglyceridemia. The major histologic finding is a non-malignant mixed lymphohistiocytic accumulation in the reticuloendothelial system. The Histiocyte Society has developed a diagnostic guideline that accompanies both clinical and laboratory findings (Table 1) (3).

Children with FHLH may have varying degrees of hepatosplenomegaly and liver dysfunction (4). One of the most important finding that suggests HLH is chronic hepatitis-like finding in the liver biopsy (5). Although hepatic manifestations which include hepatic failure are common in FHLH, there are rare reports of hepatic failure associated with secondary HLH (6). In this report, we present three cases who admitted to Ankara University Medical Faculty Department of Pediatric Hematology with unusual presentation of HLH, hepatic manifestations were the first findings of patients resembling primary hepatic disease. Diagnostic studies of patients are listed in **Table** 2 and Table 3.

Case 1

A previously healthy 15-year-old boy, was admitted to an outside hospital with fever of 38.7°C and abdominal distention six months ago. He was noted to have fever, failure to thrive, pretibial edema, pronounced hepatosplenomegaly, anemia, thrombocytopenia, hyperbilirubinemia, elevated liver function tests, increased triglyceride level. Liver **disease** of **unknown origin** was discussed and the patient was referred to our hospital for further diagnosis and treatment. Of note was that the patient was the **child of nonconsanguineous parents** and his family history was unremarkable.

He admitted to our center and physical examination revealed the following findings: fever of 38.8 oC, malaise, jaundice, diminished breath sounds at the left lung, pretibial edema, abdominal distention, hepatomegaly and splenomegaly 15 cm and 13 cm below the costal margin, respectively. The hemoglobin (Hb) was 6.1 g/dl, white blood cell count (WBC) was 1.3x109/L with decreased neutrophil count (0.2 x109/L), and platelets were 12x109/L. Other laboratory evaluations revealed the following values: fibrinogen 50 mg/dl (normal range, 200-400 mg/dl), triglyceride 525 mg/dl (normal range, 40-200 mg/dl), ALT 222 IU/L (normal range, 10-31 IU/L), AST 449 IU/L (normal range, 10-31 IU/L), GGT 148 IU/L (normal range, 7-32 IU7L), total bilirubin 6.6 mg/dl (normal range, 0.2-1.3 mg/dl), conjugated bilirubin 3.5 mg/dl (normal range, 0.2-1.3 mg/dl), albumine 2g/dl (normal range, 3.5-5.5 g/dl), ferritin 2239 ng/ml (normal range, 12-140 ng/ml). Viral and bacteriological studies were negative. The anemia and thrombocytopenia persisted despite multipl transfusions of packed red blood cell and platelets. In the 2nd week of his admission, hyperbilirubinemia reached to 9.5 mg/dl, with the fraction of conjugated bilirubin 4.5 mg/dl and INR increased to 2.8 and the patient was diagnosed with hepatic failure (7). He **was conscious** and his neurologic examination was normal. Abdominal ultrasonography showed presence of ascites. Liver biopsy of the patient showed chronic active hepatitis with **portal and lobular** inflammation, and parenchymal **impairment** without hemophagocytosis. No autoimmune, hereditary or metabolic causes were detected. Because of the pancytopenia, bone marrow aspiration was performed and it revealed numerous hemophagocytic histiocytes. On cerebrospinal fluid cytologic examination was normal. The patient met the diagnostic criteria of HLH described

Table 1: Diagnostic criteria for hemophagocytic lymphohistiocytosis*

Diagnostic criteria for hemophagocytic lymphohistiocytosis*
The diganosis of HLH can be established if one of either 1 or 2 below is fulfilled
(1) A molecular diagnosis consistent with HLH
(2) Diagnostic criteria for HLH fulfilled (five out of the eight criteria below)
(A) Initial diagnostic criteria (to be evaluated in all patients with HLH)
Fever
Splenomegaly
Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood):
Hemoglobin <90 g/L (in infants <4 weeks: hemoglobin <100 g/L)
Platelets $<100x10^9$/L
Neutrophils $<1.0x10^9$/L
Hypertriglyceridemia and/or hypofibrinogenemia:
Fasting triglycerides > 3.0 mmol/L (i.e., >265 mg/dl)
Fibrinogen < 1.5 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes
No evidence of malignancy
(B) New diagnostic criteria
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin > 500 mg/L
Soluble CD25 (i.e., soluble IL-2 receptor) > 2,400 U/ml

*: Henter JI et al. Pediatr Blood and Cancer 2007

Table 2: Patients' demographic data, clinical characteristics

	Age (y)	Sex	Positive Familial History	Etiology	Fever	Hepatomegaly	Splenomegaly
Case 1	15	M	Absent	Unknown	Present	15 cm	13 cm
Case 2	8.5	F	Absent	Unknown	Present	6 cm	18.5 cm
Case 3	13	F	Absent	Malignancy	Present	4 cm	2 cm

y: year., F: Female; M: Male; Hepatomegaly (under the costal margin), Splenomegaly (under the costal margin),

Table 3. Laboratory findings of the patients.

	Normal values	*ADMISSION*			*LAST RECORDED*		
		CASE 1	CASE 2	CASE 3	CASE 1	CASE 2	CASE 3
WBC (x10^9/μL)	6000-17000	1,3	1,3	13200	1,5	0,6	3,2
ANC (x10^9/μL)	>1500	0,2	0,3	5,2	0,8	0	2,6
Hb (g/dL)	10.5-14	6,1	7.4	7.0	6.6	10.3*	10.0*
Platelet (x10^9/L)	150000-450000	12	46	24	14*	34*	19*
Total bilirubin (mg/dl)	0.3-1.2	6.6	3.53	19.6	24.5	29.0	21.8
Conjugated bilirubin (mg/dl)	0.0-0.2	3.5	1.53	10.2	11.6	12.9	10.8
AST (U/L)	0-37	449	204	194	258	31	33
ALT(U/L)	0-45	222	55	122	142	18	24
Alkaline phosphatase (U/L)	75-390	1191	267	322	530	69	329
GGT (U/L)	0-55	148	32	44	184	53	36
Albumin (g/dl)	3.5-5.2	2.0	2.9	2,6	2,5	3,2	2,6
LDH	0-250	716	545	2132	1380	1013	1390
Triglyceride (mg/dL)	0-150	525	66	201	395	75	ND
Fibrinogen (mg/dl)	203-472	50	68	50	20	351*	17
Ferritin (ng/mL)	30-400	2239	176	4219	15397	434	4119
Protrombin time (sn)	10-14	15.7	29	30.1	30.6	19	21.5
BM hemophagocytosis		Present	Present	Present			
CSF hemophagocytosis		Absent	Absent	ND			

BM: Bone marrow; ND: Not determined; *: Patients received blood products when required

by the Histiocyte Society and his clinical deterioration made us to start the initial part (8 weeks) of the HLH-94 chemotherapy protocol that include etoposide (150 mg/m2/day, **two times in a week** during first two weeks, after than weekly) and dexamethasone (10 mg/m2/ day, 50 % reduced by 2 weeks) (3). Fresh frozen plasma, antibacterial treatment, lactulose and rectal enema were started because of hepatic failure. His symptoms and signs seemed to resolved after completing the **initial part of the therapy** and he was discharged in the 8th week of treatment. On the 10th day of his dischargement, despite continuation of therapy, he admitted to our hospital again with fever. Th**e diagnosis of HLH** recurrence was made after the clinical and laboratory evaluations. Initial therapy of HLH 94 was again started but disease became resistant to **therapy** and progression became clinically apparent. His family decided to take him to home, and we learned that he later died.

Case 2

A previously healthy 8.5 year-old-girl admitted to an outside hospital with fever and abdominal distention eight months ago. She was noted to have fever of 39 ^{0}C, cervical lymphadenopathy, hepatosplenomegaly, anemia, thrombocytopenia, increased coagulation times and elevated liver function tests **revealed hepatic failure**. Liver **disease** of **unknown origin** was discussed and the patient was referred to our hospital for further diagnosis and treatment. There was no consanguinity between her parents and her family history was unremarkable.

She admitted to our center and physical examination on admission revealed the following findings: fever of 39.2 ^{o}C, cervical lymphadenopathy, malaise, jaundice, pretibial edema, abdominal distention, hepatomegaly and splenomegaly 6 cm and 18.5 cm below the costal margin, respectively. The Hb was 7.4 gr/dl, WBC was 1.3x10^9/L with decreased neutrophil count (0.3x10^9/L), and platelets were 46x10^9/L. Other laboratory evaluations revealed the following values; fibrinogen 20 mg/dl (normal range, 200-400 mg/dl), triglyceride 66 mg/dl (normal range, 40-200 mg/dl), ALT 55 IU/L (normal range, 10-31 IU/L), AST 204 IU/L (normal range, 10-31 IU/L), GGT 32 IU/L (normal range, 7-32 IU7L), total bilirubin 3.5 mg/dl (normal range, 0.2-1.3 mg/dl), conjugated bilirubin 1.5 mg/dl (normal range, 0.2-1.3 mg/dl), albumine 2.9 g/dl (normal range, 3.5-5.5 g/dl), ferritin 176 ng/ml (normal range, 12-140 ng/ml). Although liver function tests did not change, total and conjugated **bilirubin continued** to **increase** during the assessment, and reached the level of 24 mg/dl and 10 mg/dl, respectively. A liver biopsy was done and revealed the extent of **hepatic fibrosis, bridging necrosis, inflammation**, and parenchymal **impairment.** Viral and bacteriological studies were negative. No autoimmune, hereditary or metabolic causes were detected. Because of the pancytopenia bone marrow aspirate was performed and hemophagocytic histiocytes were seen. Cerebrospinal fluid cytologic examination was normal. The patient met the diagnostic criteria of HLH and HLH-94 chemotherapy protocol was started on the 7th day of admission (3). Despite treatment her symptoms and signs didn't change except fever. On the 12th day of therapy, fever appeared again, the pancytopenia, bilirubin levels and coagulation tests progressively deteriorated. The rapid onset of altered mental status developed and INR was increased to 2.3. Pulmonary hemorrhage and **minimal pericardial effusion (detected by** echocardiography) **developed. She was** transferred **to intensive care unit**. Fresh frozen plasma, antibacterial treatment, lactulose and rectal enema were started because of hepatic coma. **She** received multipl transfusions of packed red blood cell and platelets, required **mechanical ventilation**, unfortunately, she died

from multiorgan failure on the 19th day of therapy. Her family did not give permission for autopsy.

Case 3

The patient was a 13-year-old girl from Republic of Yemen. She was healthy until the age of 10 when she was diagnosed to have craniopharangioma, no special treatment was started and she was referred to our center for further diagnosis and treatment. There was no consanguinity between her parents and her family history was unremarkable.

Physical examination findings on admission were jaundice, anxiety, signs of respiratuary infection, ascites, hepatomegaly and splenomegaly 4 cm and 2 cm below the costal margin, respectively. The hemoglobin (Hb) was 7.0 gr/dl, white blood cell count (WCC) was 13 x10^9/L with decreased neutrophil count (5x10^9/L), and platelets were 24x10^9/L. Other laboratory evaluations revealed the following values: fibrinogen 50 mg/dl (normal range, 200-400 mg/dl), triglyceride 201 mg/dl (normal range, 40-200 mg/dl), ALT 194 IU/L (normal range, 10-31 IU/L), AST 122 IU/L (normal range, 10-31 IU/L), GGT 44 IU/L (normal range, 7-32 IU7L), total bilirubin 19.6 mg/dl (normal range, 0.2-1.3 mg/dl), conjugated bilirubin 10.2 mg/dl (normal range, 0.2-1.3 mg/dl), albumine 2.6 g/dl (normal range, 3.5-5.5 g/dl), ferritin 4219 ng/ml (normal range, 12-140 ng/ml). The diagnosis of craniopharangioma was confirmed by the computarized tomography. Within the first week of assessment, signs of respiratory infection was observed, her liver enzymes were elevated to 1.000 IU/L with severe hyperbilirubinemia (total bilirubin: 21,8 mg/dl) and after than liver enzymes progressively decreased, bilirubin concentration didn't change. The pancytopenia and deterioration of coagulation parameters persisted despite multiple transfusions of red packed cells, platelets and fresh frozen plasma. Abdominal ultrasonography showed presence of ascites. Liver biopsy could not be obtained because of the risk of severe bleeding. Because of the pancytopenia bone marrow aspirate was performed and hemophagocytic histiocytes were seen. Viral and bacteriological studies were negative. During the second week of admission, her clinical status and laboratory findings deteriorated further. Severe hyperbilirubinemia didn't change, and INR increased to 2.7 and the patient was diagnosed with hepatic failure. She met the diagnostic criteria of HLH and HLH-94 chemotherapy protocol was started on the 10th day of admission (3). Since craniopharangioma, cerebrospinal fluid cytological examination can not be done. Despite chemotherapy administration and intensive care her clinical status and laboratory findings deteriorated further and she developed multiorgan failure (hepatic coma, renal failure, respiratory failure, disseminated intravascular coagulation). There was no clinical or hematological response, and she died from multiorgan failure on the 5th day of treatment. Her family did not give permission for autopsy.

Discussion

We report here three patients with probably secondary HLH that presented as acute hepatic failure. Two of these patients were referred to our center for further diagnosis and the 3rd patient who also had craniopharangioma was diagnosed at outside center. All of the patients met the diagnostic criteria of HLH and although HLH-94 chemotherapy protocol was started, none of the them survived.

It is well known that to distinguish by testing between a familial and secondary form of HLH in each patient is extremely difficult. Although we were not be able to perform familial testing for further diagnosis of FHLH we thought that all the patients had secondary HLH. Because all of them had **non-consanguineous parents and all of them older** than 6 years of age**, and none of them had positive family history of similar clinical manifestations.**

The liver is a hematopoietic organ in the fetus and retains some capacity for hematopoiesis throughout life. Disorders which can lead to generalized macrophage activation and hemophagocytosis can effect liver cells both functionally and histopathologically (4,8). HLH can present initially with acute hepatic failure without any identifiable cause. In these patients, hepatic involvement is primarily related to the substances locally released by the activated macrophages. On the other hand, it may developed secondary to strong immunologic activation, such as severe infection or malignancy (4). de Kerguenec et al. demonstrated that the association of fever, jaundice, and hepatomegaly or splenomegaly is present in 50% of the patients with secondary HLH (8). Liver biopsy is a useful diagnostic procedure in these patients. Nonspecific sinusoidal dilatation, congestion, and hyperplasia of Kupffer cells with hemophagocytic histiocytosis were found in the biopsy specimen in all patients as reported by the study (8). In our patients, liver biopsy could be performed in two patients. Liver biopsy specimen **obtained** from the first **patient** showed chronic active hepatitis with **portal and lobular** inflammation, and parenchymal **impairment** without hemophagocytosis. In the second patient, histopathology determined **hepatic fibrosis, bridging necrosis**, **inflammation**, and parenchymal **impairment. As well as our patients, t**he main **problem is** uncertainty of the **diagnostic histological** differences between HLH and the other causes that lead to hepatic failure because there is no specific marker for secondary HLH. Liver histologic pattern with reactive hemophagocytosis can be seen in association with a lot of different conditions such as infections, malignancies, drug toxicities or metabolic disorders (2). Liver biopsy allows recognition of the underlying disorder in half of the patients diagnosed with HLH (8). On the other hand, negative hemophagocytic pattern does not completely rule out the diagnosis of HLH (1,9). Extensive work-up for an

evaluation of etiologic factors may be time consuming and costly in these patients.

The diagnosis of HLH is sometimes be challenging, because of its multisystemic involvement and heterogenous clinical presentation. The main prognostic factor is accurate, early recognition and therapy. Familial HLH is associated with a high mortality if not transplanted, whereas the prognosis for secondary HLH is reported to variable depending on the early diagnosis and treatment. **The HLH-94 protocol includes** induction with dexamethasone and etoposide, followed by continuous cyclosporine with pulses of dexamethasone and etoposide (10). Suppression of cytokine overproduction by immunosupressive drugs is the principal approach. Treatment should be started as early as possible. Unfortunately, **patients were referred to our center** in the **late** stages and probably they had irreversible and severe hepatic damage. The clinical outcome of the patients was poor, no clinical or hematological response were observed, additionally their clinical conditions progressively deteriorated with the presence of dominant hepatic failure symptoms. As we know that, there are a few reports of hepatic failure associated HLH in the literature and a minority of these patients could have survived (6, 8). Similar to these data, all of our patients died. Although hepatic involvement at the time of secondary HLH diagnosis has a poor prognostic significance, death occurred as a consequence of multiorgan failure as other series (8).

In conclusion, early recognition, diagnosis and treatment of this entity might have an impact on better prognosis. We wish to emphasize that, HLH should be considered in the differential diagnosis of hepatic failure, especially if it is concurrent with cytopenias and unexplained prolonged fever. Also this report demonstrated that besides other conditions (infection associated HLH or HLH with central nervous system involvement), patients initially presenting with hepatic failure with the diagnosis of HLH have poor prognosis.

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