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Pediatric secondary hemophagocytic lymphohistiocytosis: Single-center experience

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ABSTRACT

Objective: Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder in children that are characterized by a persistent fever, splenomegaly with cytopenia, hypertriglyceridemia, and hypofibrinogenemia. HLH can be classified into two major forms: Primary HLH includes familial HLH and several primary immunodeficiencies, which exhibit genetic inheritance and usually occur in infancy. Secondary HLH (sHLH) is associated with infections, autoimmune disorders, or malignancies. It is essential to identify the disorders underlying HLH and provide the disorder appropriate treatment. The main objectives of this study were to identify the etiology of sHLH and prognostic factors.

Material and Methods: We retrospective analyzed clinical and laboratory findings as well as prognostic factors for our pediatric patients diagnosed with sHLH. All statistical tests were performed using the Statistical Package for the Social Sciences (SPSS, Chicago, USA) version 21.0. Ethics committee approval (January 26, 2021) was obtained for the study. Our study was conducted by the principles of the Declaration of Helsinki.

Results: Our patients had Epstein–Barr virus, tuberculosis infection, Hodgkin lymphoma, and desmoplastic small round cell tumor. Six pediatric patients with sHLH were identified. Age ranged from 7 months to 16 years. There were five males and one female patient. Three patients were triggered by infection, two cases were triggered by malignant disease and one patient was suspected of rheumatic disease. All patients fulfilled the criteria fever, cytopenia, and ferritin >500 µg/L. The patients started immunosuppressive therapy according to the HLH-2004 protocol. Only one patient (malignancy-associated HLH) died.

Conclusion: Although HLH is a rare disease, clinicians should be aware of its existence and actively pursue appropriate diagnostic tests in all children suffering from unexplained fever, cytopenias, and/or hepatosplenomegaly, regardless of whether hemophagocytosis is observed or not. It should be remembered that patients diagnosed with hemophagocytosis may have another underlying disease.

Keywords: Hemophagocytosis; pediatric; prolonged fever.

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Çocuk hastalarda sekonder hemofagositik lenfohistiositoz: Tek merkez deneyimi

ÖZET

Amaç: Hemofagositik lenfohistiositoz (HLH) uzamış ateş, splenomegali, hipertrigliseridemi, hiperferritinemi ve hipofibrinojenemi ile karakterize çocukluk çağında nadir görülen bir hastalıktır. Primer ve sekonder HLH olmak üzere iki gruba ayrılır. Primer HLH ailesel hemofagositik lenfohistiositoz, genetik nedenli primer immun yetmezlikler nedeniyle genellikle infantil dönemde görülür. Sekonder HLH enfeksiyonlar, otoimmun hastalıklar ya da maliniteler ile ilişkilidir. HLH tablosuna neden olan hastalığın tespiti ve uygun tedaviye başlanması önemlidir. Çalışmamızın amacı sekonder HLH etyolojisinin saptanması ve prognostik faktörlerin öneminin vurgulanmasıdır.

Gereç ve Yöntemler: Çocukluk çağında sekonder HLH tanısı konulan hastalarımızın klinik, laboratuvar bulguları ve prognostik faktörler retrospektif olarak incelendi. İstatistik testler için SPSS versiyon 21.0 programı kullanıldı. Etik komite onayı (26.1.2021) alındı. Çalışmamız Helsinki Deklerasyon prensiplerine göre yapıldı.

Bulgular: Sekonder HLH tanılı 6 hasta incelendi. Yaşları 7 ay–16 yaş arasındaydı. Hastaların beşi erkek, biri kız çocuğuydu. Hastaların üçünde enfeksiyon, ikisinde malign hastalık tespit edilirken bir hastada romatolojik hastalık şüphesi mevcuttu. Tüm hastalarda ateş, sitopeni, ferritin >500 µg/L bulguları tespit edildi. Hastalara HLH 2004 protokolune göre immunsupresif tedavi başlandı. Malignite ile ilişkili HLH tanısı konulan bir hasta kaybedildi.

Tartışma: Although HLH is a rare disease, clinicians should be aware of its existence and actively pursue appropriate diagnostic tests in all children suffering from unexplained fever, cytopenias, and/or hepatosplenomegaly, regardless of whether hemophagocytosis is observed or not. It should be remembered that patients diagnosed with hemophagocytosis may have another underlying disease.

Anahtar Kelimeler: Hemofagositoz; pediatrik; uzamış ateş.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare disease mainly in children that are characterized by persistent fever and hemophagocytosis by activated macrophages. The pathogenetic mechanisms behind HLH are not completely understood but involve defective granule-mediated cytotoxicity and uncontrolled T-cell activation that is induced by hypercytokinemia. HLH is classified as a primary (familial) and secondary (acquired) disease. Primary HLH, also termed familial HLH (FHL), is an autosomal recessive genetic disorder defined by mutations in the following genes: PRF1 in FHL type 2 (FHL2), UNC13D in FHL type 3 (FHL3), STX11 in FHL type 4 (FHL4), and STXBP2 in FHL type 5 (FHL5). On the other hand, some patients with other congenital immune deficiencies (X-linked lymphoproliferative disorder, Griscelli syndrome, Chediak–Higashi syndrome, and Hermansky–Pudlak syndrome) may develop HLH with major causative genes, namely, SH2D1A/BIRC4, RAB27A, LYST, and ADTB3A (1). Secondary HLH (sHLH) is associated with viral, bacterial fungal, and parasitic infections, autoimmune diseases, and malignant disorders in patients without an identifiable underlying genetic trigger (2). HLH diagnostic guidelines, also known as the HLH 2004 diagnostic criteria, help to guide the diagnosis of primary and sHLH (3). A patient is diagnosed with HLH when the molecular diagnosis is consistent with HLH or at least five of the following eight criteria must be fulfilled: Fever, splenomegaly, cytopenia affecting at least two of three lineages in the peripheral blood, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in the biopsy, low, or absent natural killer (NK) cell activity, hyperferritinemia, and elevated soluble CD25 receptor. These diagnostic guidelines are commonly used in both familial and sHLH (3, 4). Although primary HLH can be controlled by immunochemotherapy, hematopoietic stem cell transplantation (HSCT) is required as a curative therapy (4).

MATERIAL AND METHODS

Patients' data were collected from January 2019 to December 2019 in our hospital. The diagnosis of HLH is based on at least five of the eight criteria identified by the HLH-2004 study including (Table 1) (3). Unfortunately, the tests for soluble CD25 levels and NK cell activity were not available in our hospital. In the study population, the following data were analyzed: Age, sex, detailed physical examination findings, laboratory findings including complete blood count with differential (white blood cell neutrophil and lymphocyte), and platelet count. The diagnosis was made through clinical course and laboratory findings [ferritin, fibrinogen, triglyceride, lactate dehydrogenase (LDH),

Table 1. Revised diagnostic guidelines for HLH (3)

The diagnosis 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 (infant <4 weeks: hemoglobin <100 g/L)
Platetes <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 NK-cell activity (according to local laboratory reference)
Ferritin 500 gm/L
Soluble CD25 (i.e., soluble IL-2 receptor) 2.400 U/ml

HLH: Hemophagocytic lymphohistiocytosis.

Comments:

(1) If hemophagocytic activity is not proven at the time of presentation, further search for hemophagocytic activity is encouraged. If the bone marrow specimen is not conclusive, material may be obtained from other organs. Serial marrow aspirates over time may also be helpful.

(2) The following findings may provide strong supportive evidence for the diagnosis: (a) spinal fluid pleocytosis (mononuclear cells) and/ or elevated spinal fluid protein, (b) histological picture in the liver resembling chronic persistent hepatitis (biopsy).

(3) Other abnormal clinical and laboratory findings consistent with the diagnosis are: cerebromeningeal symptoms, lymph node enlargement, jaundice, edema, skin rash. Hepatic enzyme abnormalities, hypoproteinemia, hyponatremia, VLDL “, HDL #.

viral serology, and polymerase chain reaction (PCR)]. Genetic analysis (UNC13D, STX11, and PRF1) was performed for all the patients. Furthermore, bone marrow aspiration findings, tests for collagen vascular disease, mycoplasma, human immunodeficiency virus, Epstein–Barr virus (EBV), and cytomegalovirus infections were diagnosed with immunoglobulin M (IgM) antibodies or genomic DNA copy number by PCR. Cultures (blood, urine, and cerebrospinal fluid) and imaging findings (abdominal ultrasound and computerized tomography) were recorded. None of the patients showed central nervous system involvement. Treatment modalities were analyzed. Descriptive statistical analyses were performed to determine the demographic data, clinical data, and treatment of the patients. A Chi-square test was used for categorical variables. All statistical tests were performed using the Statistical Package for the Social Sciences (SPSS, Chicago, USA) version 21.0. Ethics committee approval (Date: January 26, 2021, number: B.10.1 TKH.4.34.H. GP.0.01/410) was obtained for the study. Our study was conducted by the principles of the Declaration of Helsinki. Informed consent was obtained from the patients.

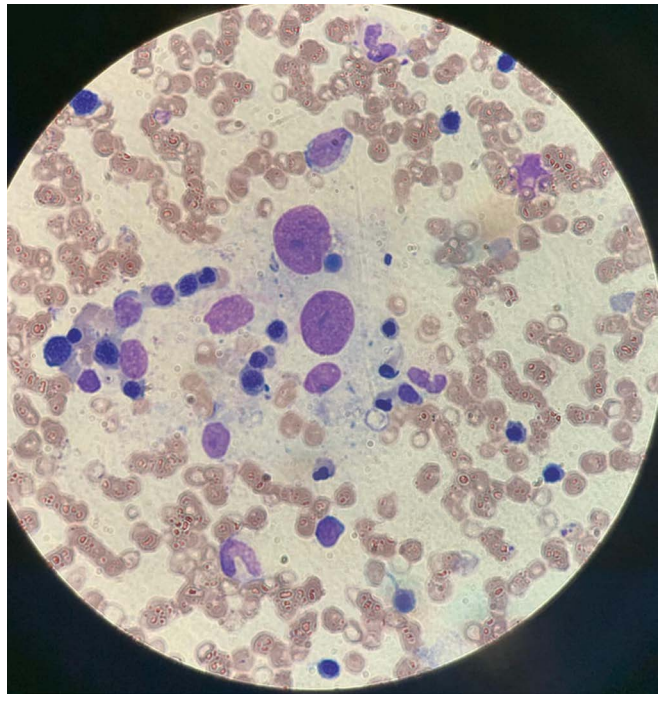

Figure 1. Hemophagocytosis on bone marrow aspiration.

RESULTS

Between January 2019 and December 2019, we followed up with six (five males and one female) patients. Age ranged from 7 months to 16 years. Their characteristics, management, and the outcome are presented in Table 2. The median age at diagnosis of sHLH was 10 years (range: 7 months–18 years). In total, two patients were <24 months of age sHLH. All the patients had fever and hepatomegaly initial symptoms other clinical findings of the patients were different at admission.

Patient 1

An 11-year-old male had pneumonia and pleural effusion. His clinical symptoms did not improve with nonspecific therapy, and he was started antituberculosis treatment. He was noted to have bicytopenia, and a bone marrow aspiration was performed, which revealed signs of hemophagocytosis (Fig. 1) A hemophagocytic syndrome secondary to tuberculosis infection (TB) was diagnosed.

Patient 2

A 10-year-old male patient with fever and weakness. There were palpable cervical and submandibular lymph nodes and hepatomegaly and splenomegaly. Bone marrow aspiration was performed, which revealed signs of hemophagocytosis. As his fever did not subside, it started HLH 2004 protocol. A cervical lymph node and bone marrow biopsy were taken, which was

Table 2. Clinical features of the patients

	Age Gender	HSM	Cytopenia (mg/dl)	Triglycerid (mg/dl)	Fibrinogen (ng/ml)	Ferritin (U/L)	LDH (HP)	BMA (Heterozygot)	Mutation	Etiology	Treatment	Prognosis
1	11 y/Male	+	+	164	159	11735	2936	+	PRF1	Tuberculosis	Dexa+Tbc	Improved
2	10 y/Male	+	+	231	726	5008	450	+	UNC13D	Hodgkin L.	HLH+HL	Improved
3	18m/Male	+	+	287	294	157	283	+	no	EBV	HLH+HSCT	Improved
4	16y/Female	+	+	400	227	27027	1262	+	UNC13D	Unknown	HLH	İmproved
5	7m/Male	+	+	311	356	841	13036	+	no	DSRCT	HLH	Death
6	10y/Male	+	+	182	247	10454	1228	+	no	EBV	HLH*	Improved

BMA: Bone marrow aspiration; HP: Hemophagocytosis; DRSCT: Desmoplastic round cell tumor; Dexa: Only dexamethasone treatment; HLH: HLH 2004 initial +maintenance; HLH*: HLH 2004 only initial phase.

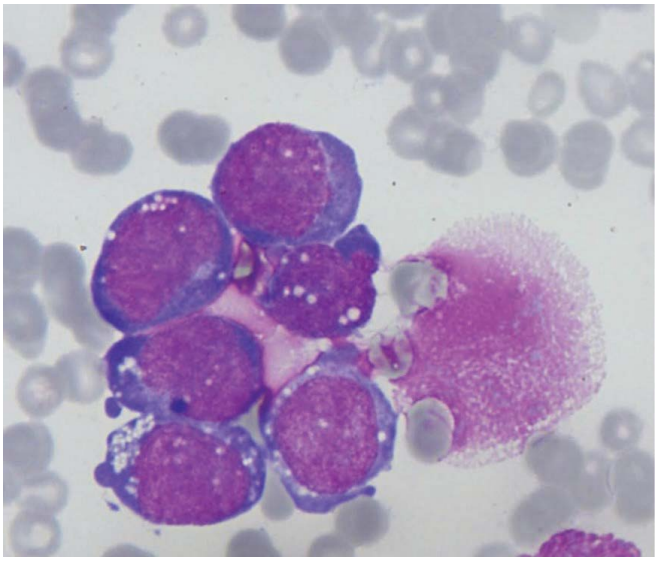

Figure 2. Highly cellular smears with small round cells in small clusters, high NC ratio, irregular nuclear membranes, inconspicuous nucleoli, granular chromatin and blue cytoplasm with vacuolated on bone marrow aspirate (giemsa).

consistent with Hodgkin lymphoma (HL) (Stage IVB). An HLH secondary to HL was diagnosed.

Patient 3

An 18-month-old male patient with fever and liver failure. He was planned to have liver transplantation because of liver failure at another hospital. There were hepatomegaly, splenomegaly, and abdominal ascites. The EBV IgG, IgM, and EBV DNA were positive. Inherited metabolic diseases and immunodeficiency disorders analysis were negative. Bone marrow aspiration and liver biopsy were performed, which revealed signs of hemophagocytosis. A secondary EBV infection was diagnosed.

Patient 4

A 16-year-old female patient with fever and general body pain. On physical examination, she had hepatomegaly and splenomegaly. Viral and bacterial serological tests were all negative. Rheumatologic markers were negative. Double T negativity with flow cytometry was not detected for the autoimmune lymphoproliferative syndrome. Next-generation sequencing analysis for immune dysregulation syndrome and autoimmune disorders was negative. A cervical lymph node biopsy was taken, which showed reactive changes with no specific causes. Bone marrow aspiration and biopsy were performed, which revealed signs of hemophagocytosis. As his clinical condition did not improve with antibiotic treatment, the HLH 2004 protocol (with etoposide) was started. Subsequently, during her follow-up, her fever subsided, rash, tachypnea eliminated, and appetite returned to normal. A hemophagocytic syndrome cause was not detected.

Patient 5

A 7-month-old male patient with fever and liver failure. On physical examination, he had hepatomegaly and splenomegaly. Other physical examination findings were normal. Viral and bacterial serological tests were all negative. Inherited metabolic disease and Pearson syndrome genetic analysis were normal. Abdominal ultrasonography was shown hepatosplenomegaly and multiple nodular lesions in the liver. Bone marrow aspiration was performed showing acute lymphoblastic leukemia (ALL) L3-like lymphocytes with vacuoles and signs of hemophagocytosis but flow cytometric analysis was normal (Fig. 2). Fluorodeoxyglucose-positron emission tomography was normal. He started HLH 2004 protocol. Liver biopsy revealed a desmoplastic small round cell tumor (DRSCT) (Fig. 3, 4). He died after one cure chemotherapy.

Patient 6

A 10-year-old male patient with fever, weakness, and cervical lymphadenopathy. On physical examination, there were bilateral cervical lymphadenopathy, hepatomegaly, splenomegaly. Viral and bacterial serological tests were all negative. The EBV IgG, IgM positive, and EBV DNA were positive. Immunodeficiency disorder tests were negative. Bone marrow aspiration was performed, which revealed signs of hemophagocytosis. A secondary EBV infection was diagnosed.

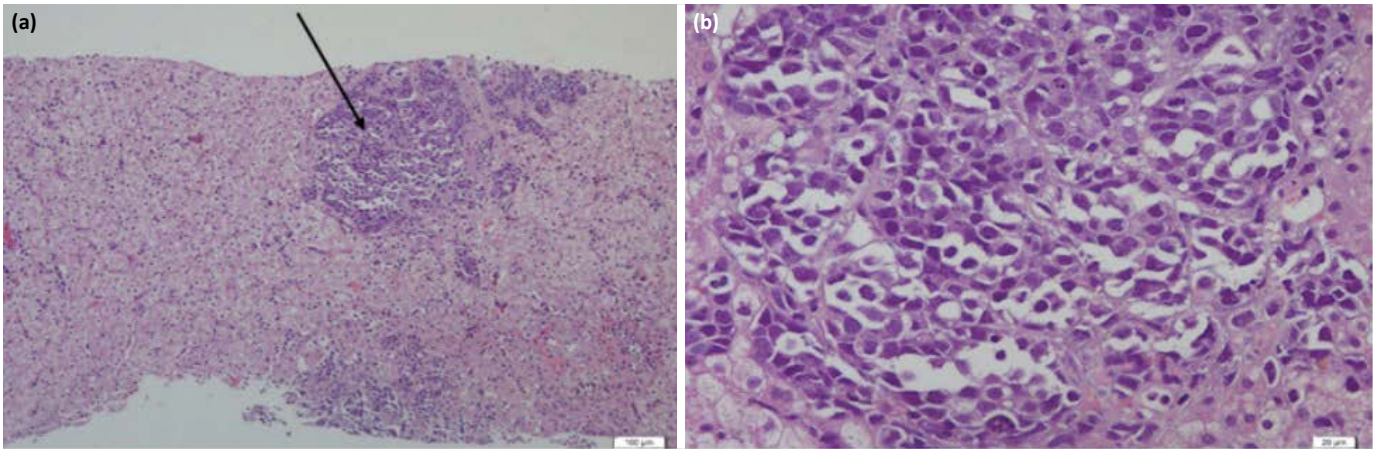

Figure 3. (a) Nests of small round blue cells of variable size and shape within portal area of liver(arrow). **(b)** Tumor cells have round, with finely chromatin, one or two small nucleoli, scant cytoplasm.

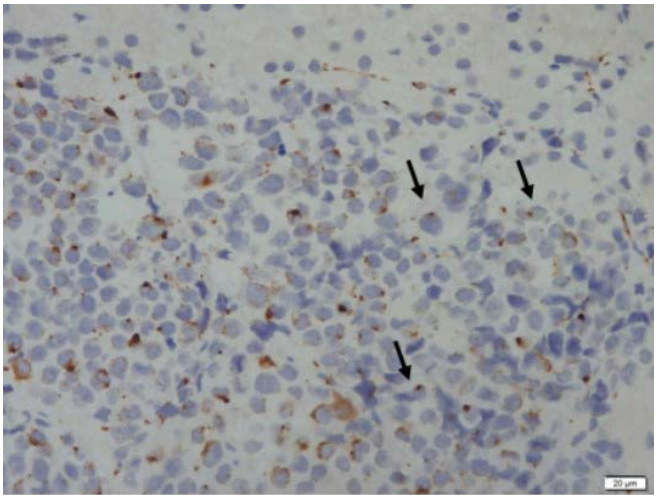

Figure 4. Desmin staining on tumor: dot-like pattern (arrow).

Our patients laboratory findings were median Hb concentration at admission was 7.2 g/dL (range: 4.2–10.6 g/dL). All the patients had normal leukocyte and neutrophil counts, platelet count was low in four patients. Ferritin level was normal in two patients but very high in the other four patients, median ferritin: 10,454 mg/dL (range:157–200,700 mg/dL). The median fibrinogen level was 726 (range: 159–841 mg/dL) one of the patients had a low. The median LDH level was 1262 U/L (range: 395–12,228). Bilirubin level was high in three patients. All patients had findings of hemophagocytosis in the bone marrow. Mutation analysis was performed on all patients, and heterogeneous mutations (one patient's PRF1 and two patients' UNC13D) were detected in three patients.

HLH 2004 treatment protocol was given to all patients suggesting hemophagocytosis. Treatment modifications were performed in three patients. The patient diagnosed with TB sHLH was given only dexamethasone and IVIG. Two patients associated with malignancy were given chemotherapy according to the diagnosis. HSCT was performed in one patient at the end of the HLH protocol.

DISCUSSION

HLH is a potentially life-threatening condition due to uncontrolled inflammatory activation. Many conditions can lead to the clinical picture of HLH, including malignancies (leukemia, lymphoma, and other solid tumors), infections (viral, bacterial, or parasitic), and rheumatoid disorders (3). A variable and non-specific symptomatology can delay the diagnosis and hence requires a high index of suspicion in both primary and sHLH. The patients in our study applied to hospitals with different clinical pictures. The common diagnostic feature of our patients is that they have a prolonged fever of unknown origin (FUO). Several genetic defects in primary HLH have been recently identified, which include PRF1, UNC13D, STX11, and STXBP2. In our study, PRF1, UNC13D, and STX11 mutations were examined in all patients. The heterozygous mutation was detected in three patients. The clinical significance of these mutations is unknown but the presence of mutations may make it easier to see hyperinflammation in these patients.

Therapy of HLH consists of combinations of proapoptotic chemotherapy and immunosuppressive drugs targeting the hyperactivated T cells and histiocytes (5). Most of the HLH patients have severe systemic symptoms at diagnosis, and timely appropriate treatment for HLH is needed before genetic testing to distinguish primary from sHLH. Early use of γ-globulin and/or corticosteroid is sometimes useful to control the activity of HLH, with transient effect (4). However, an aggressive therapeutic approach is warranted in most cases, including immunochemotherapy and HSCT. In our study, when HLH was detected in all patients, dexamethasone was started. Etoposide and cyclosporin A with dexamethasone were started in all patients except the patient with the diagnosis of TB.

HLH is a severe complication of TB infection and has a high mortality. For patients with FUO, HLH-related clinical manifestations sometimes present before the final diagnosis of TB (6). Most previously reported studies to suggest that clinicians consider a diagnosis of HLH when they encounter patients with TB who

have reduced levels of blood cells, hepatosplenomegaly, and coagulation abnormalities (7). In our study, one patient (patient 1) had a TB infection and HLH symptoms were seen despite the treatment of TB. After adding a steroid to treatment, the patient's clinical findings improved.

Malignancy associated HLH (MA-HLH) is mainly reported in adult patients with lymphoma. Around 24 cases of HLH associated with B or precursor T acute leukemia are reported in pediatric patients (8). The rarity of occurrence of HLH and its varied presentation makes the diagnosis of MA-HLH difficult. Pediatric cases have been reported with varied types of malignancy. The largest multicenter study on MA-HLH was published in Turkey (9). It reports HLH associated with ALL, AML, HL, non-HL, rhabdomyosarcoma, neuroblastoma, and Langerhans cell histiocytosis. Once the diagnosis is made, the hyperinflammatory condition needs to be controlled with steroid or complete HLH 2004 protocol. In our study, one patient had HL (patient 2), one patient had DRSCT (patient 5). In MA-HLH our patient, we give a full HLH induction protocol. HL treatment was switched on in our patient who was diagnosed with HL. The delay in diagnosis of this life threatening disorder may be fatal. One of our patients died. This patient had a very rare tumor in his childhood and his diagnosis was made very difficult.

Viral infections, especially EBV, may trigger primary as well as sHLH. Patients with severe sHLH due to EBV infections can be treated with this protocol (10). In a nationwide survey, the most frequent subtype in Japan is EBV-HLH (approximately 40% of all patients with HLH) followed by other infection- or lymphoma-associated HLH (11) The incidence of EBV-HLH is relatively high in Asian countries, indicating the underlying genetic background in the pathogenesis of EBV-HLH. Phenotypically, EBV-HLH is a heterogeneous disorder with various symptoms, ranging from mild to severe, and with a variable clinical course, ranging from self-limiting to severe/aggressive or fatal. Therefore, prompt and appropriate treatment should be established according to prognostic factors. We have two EBV-HLH patients. One of them (patient 6) improved with the first 8 weeks of HLH protocol treatment but one patient (patient 3) did not sufficiently respond to the initial treatment (persistent disease) and HSCT was performed. In Japan, 57 patients (43 with FHL and 14 with EBV-HLH) underwent HSCT between 1995 and 2005 (12). Unrelated donor cord blood transplantation was employed in half of these cases and RIC regimen was used in 26%. The overall survival rate was 65.0% for FHL and 85.7% for EBV-HLH. The prognosis was better for EBV-HLH than for FHL after HSCT because of the high incidence of early treatment-related deaths in FHL. HSCT was performed in one patient with EBV DNA positivity. A myeloablative conditioning regimen was given for this patient. Bone marrow from the match sibling donor was used as a stem cell source.

Macrophage activation syndrome (MAS), a serious complication of systemic rheumatoid arthritis and other childhood systemic inflammatory disorders, is thought to be caused by excessive activation and proliferation of T lymphocytes and macrophages. The recognition that MAS belongs to the secondary or reactive hemophagocytic syndromes has led to a proposal to rename it according to the contemporary classification of histiocytic disorders (13). In our patient who developed MAS clinical findings (patient 4), a diagnosis of the rheumatological disease could not be made. The patient's HLH treatment was discontinued and is being followed up for signs of rheumatological disease.

CONCLUSIONS

HLH is a very important dilemma in childhood. The underlying genetic causes, infections, malignancy, metabolic, and rheumatologic disorders should be investigated. Given the high mortality rate in this group of patients who did not display specific clinical manifestations, careful consideration by clinicians is necessary to achieve early diagnosis, and early intervention may help improve the prognosis.

Ethics Committee Approval: The Ümraniye Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 26.01.2021, number: B.10.1.TKH.4.34.H.GP.0.01/382).

Informed Consent: Written informed consent was obtained from the families of the patients who participated in this study.

Conflict of Interest: No conflict of interest was declared by the authors.

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Authorship Contributions: Concept – FÇK; Design – FT; Supervision – BŞK; Fundings – ÜMY, BS; Materials – EIZ; Data collection and/or processing – SE; Analysis and/or interpretation – SÇK; Literature review – SÇK; Writing – SÇK, FK; Critical review – SÇK.

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Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastaların ailelerinden alınmıştır.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazarlık Katkıları: Fikir – FÇK; Tasarım – FT; Denetmele – BŞK; Kaynaklar – ÜMY, BS; Malzemeler – EIZ; Veri Toplanması ve/veya İşlemesi – SE; Analiz ve/veya Yorum – SÇK; Literatür Taraması – SÇK; Yazıyı Yazan – SÇK, FK; Eleştirel İnceleme – SÇK.

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