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Original Article

Comparison of Hemophagocytic Lymphohistiocytosis Diagnostic Criterias in Malignancy-associated Hemophagocytic Lymphohistiocytosis Patients

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ABSTRACT

Background Fulfilling diagnostic criterias of hemophagocytic lymphohistiocytosis (HLH) is challenging due to unavailable laboratory tests. Hence, we aimed to reveal malignancy-associated-HLH (M-HLH) patients in our center, which can not be reached in all tests.

Material and Methods Nine patients with M-HLH were analyzed retrospectively.

Results The median age was 59 years. The distribution of the underlying diseases were like diffuse large B cell lymphoma in 3 patients, acute myeloid leukemia in 2 patients, Hodgkin lymphoma in 2 patients, T cell non-Hodgkin lymphoma in 1 patient and small cell lung cancer in 1 patient. According to HLH-2004 diagnostic criteria except soluble CD25 and natural killer activity tests; one patient had 3/6, six patients had 5/6, two patients had 6/6 criteria while the median H-score was 258 at diagnosis. According to Tamamyan et al's criteria; at the diagnosis all patients had ≥7 (between 7-12) of 18 parameters. Patients fulfilled ≥5 parameters a median 15 days (3-52 days) before the diagnosis and on that time six patients had 3/6 criteria of HLH-2004. 88.8% of the patients died. The median duration of survival was 8.5 days (1-18 days).

Conclusions Unavailability of the tests in some countries and centers as in ours results in complicating to fulfill 5 of 8 criteria and being delayed to diagnose and treatment. We need to develop more specific and accessible criteria, and grading systems for M-HLH diagnose.

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Introduction

Breast hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening disorder which is difficult to diagnose and to manage especially in adults. The pathogenesis of HLH consists of increased activation and stimulation of macrophages, cytotoxic T-lymphocytes and natural killer (NK) cells resulted in cytokine storm and hyperinflammatory syndrome due to a genetic mutation or a trigger mechanism.[1] Increased cytokines such as interferon γ, tumor necrosis factor-α, interleukin (IL)-6, IL-8, IL-10, IL-12, IL-18, and macrophage colony-stimulating factor and infiltration of tissues by overactivated cells induce tissue injury and multiorgan dysfunction and can prompt to death rapidly.[2] Histiocyte Society Steering Committee classified HLH into 3 categories as primary (familial) HLH, macrophage activation syndrome (MAS)-HLH and secondary HLH. If there is a known genetic defect associated with lymphocyte cytotoxicity or a family member who has HLH history is defined as primary (familial) HLH. When there is an auto-immune condition which triggers hyper and uncontrolled inflammation is called MAS-HLH. Ultimately, if HLH is originated from some sort of underlying medical status (infection, malignancy, metabolic diseases, inherited or acquired immunodeficiencies) it is named as secondary HLH.[3] Familial HLH is encountered in children commonly while MAS and secondary HLH are seen in adults generally.[4] In adults, the accurate incidence of HLH is not known due to the fact that mis or underdiagnose in critically ill. In a Japan nation-wide study, HLH rate in adults was 40% of all HLH cases.[5] Malignancy-associated HLH (M-HLH) is common in adults especially in older age (1% of all malignancies and nearly 50% of adult HLH) and mostly originate from lymphoma (80%) especially NK/T cell lymphoma (35%) and lesser in multiple myeloma, acute leukemia, chronic leukemia and solid cancers.[6-8] M-HLH may begin during malignancy treatment or in remission probably due to immunosuppression and/or infection or before treatment even as a presenting symptom of malignancy at diagnosis or relapse.[4,7,9] Therapy-induced HLH is associated with immune activating therapies for malignancies lead to activation of $CD8^+$ T cells and drug induced hypersensitivity syndrome (DIHS).[10]

Clinical findings such as fever (>38.5 °C), cytopenia, splenomegaly, hepatomegaly, liver failure, increased aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin levels, ascites, elevated lactate dehydrogenase (LDH), D-dimer levels (even while international normalized ratio, partial thromboplastin time and fibrinogen levels are normal), encephalopathy, respiratory distress syndrome, renal failure, edema, purpura, bleeding, arthralgia, diarrhea, rash and neurological symptoms (loss of consciousness, convulsions, cranial nerve abnormalities and ataxia) can occur in HLH and these abnormalities can be seen together or progressively within a few days or weeks. These clinical and laboratory findings also help to differential diagnosis and to assess the response to treatment with supporting diagnose.[4,8] The HLH-2004 diagnostic criteria (*Table 1*) of the Histiocyte Society which was developed for children is in use also for adult HLH although there is no validation data for adult patients. According to HLH-2004 diagnostic criteria patients should have ≥5 of 8 criteria for diagnosis.[11] Fardet et al.[12] developed another diagnostic scoring model which is called H-score and was validated in adult and children regarding reactive and immune hemophagocytic syndrome in adults (*Table 2*). Tamamyan et al.[13] announced extended 18 parameters to help early diagnosis in M-HLH in 2016 (*Table 3*). The patients who fulfilled 5 parameters of 18 were considered as high likelihood of M-HLH.[13]

During the treatment the main aim to restrict the hyperinflation besides that to provide the balance between HLH specific and malignancy specific treatment and to success this aim without any guideline. Infection is also a known trigger of HLH in immunocompromised patients. Especially, HLH specific treatment can be devastating in such a group of patients instead of anti-inflammatory approach.[14] First line treatment is generally corticosteroids however dose-adjusted etoposide (50-100 mg/m^2) can be chosen if the multiorgan failure is in the foreground before the malignancy specific treatment according to disease adapted HLH-94 treatment protocol.[7] Etoposide can also be used with CHOP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone as

CHOEP) or CHOP-like (dose-adapted etoposide and CHOP as DA-EPOCH) chemotherapy protocols.[15]

Diagnosis of HLH is increasing in recent years depending on raising awareness with this disorder.[16] Nevertheless, soluble CD25 (soluble IL-2 receptor), NK activity according to HLH-2004 diagnostic criteria are not always accessible and obtained criterias in every country and center. Due to impossibilities and lack of standard suggestion in these circumstances we thought to share our experience of diagnosis and treatment in M-HLH patients in our tertiary university hospital in the last three years.

Material and Methods

This retrospective study was conducted between October 2018-October 2021 at our hospital and approved by the Institutional Ethical Committee (BAEK 2021/448). We determined nine patients who were approved and treated as M-HLH. Patients' all data were collected from electronic medical files. Patients' age, gender, underlying disease, date of diagnosis, status of the underlying disease, last date of chemotherapy, presenting symptoms of HLH, physical examination findings, laboratory tests, microbiological tests, radiological images (such as X-ray, computerized tomography, magnetic resonance), positron emission tomography (PET) images, pathology of biopsies, presence or suspicion of infection, exposure to antibiotics, treatment of HLH and/or specific malignancy, response to treatment, outcomes and survival period of the patients were evaluated. HLH-2004 diagnostic criteria was used for diagnosis.[11] However, the diagnosis of HLH was done based on 6 criteria instead of 8 due to the absence of soluble CD25 (soluble IL-2 receptor) and NK activity laboratory tests in our center. Therefore, if the patient did not fulfill five of six criteria the diagnosis of HLH was supported with other suspicious findings and tests such as hepatomegaly, elevated hepatic transaminase and bilirubin levels, LDH, hypoalbuminemia, coagulopathy and strong consideration of HLH as a clinician. Besides that, H-score was calculated for every patient.[12] We also reassessed the patient group in terms of Tamamyan et al.'s extended criteria.[13] Response to treatment was determined as improving clinical findings and abnormal laboratory tests. Survival period of the patients was defined as the days after diagnosed HLH. According to pathology evaluation and PET findings hemophagocytosis or remission/non-remission status of the malignancy were revealed. We decided to infection status according to microbiology-culture and scanning tests and response to specific antimicrobial treatment. HLH-94 protocol or corticosteroids were used as etoposide 150 mg/m^2 first and second days in the first two weeks and subsequent once weekly and dexamethasone 10 mg/m^2 per day in first week and 5 mg/m^2 per day in the second week, 2.5 mg/m^2 per day in the third week, 1.25 mg/m^2 per day in the fourth week or with only dexamethasone for HLH specific treatment.[17]

Statistical analysis was not applied.

Table 1. HLH-2004 diagnostic criteria.[11]

Fever
Splenomegaly
Cytopenia (≥2 lineages in the peripheral blood)
Hemoglobin <9 g/L or platelets <100,000/mm^3 or neutrophils <1,000/mm^3
Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides ≥3.0 mmol/L (i.e., ≥265 mg/dL) and/or fibrinogen ≤1.5 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes
Low or no natural killer cell activity
Ferritin ≥500 mg/L
sCD25 (i.e., soluble IL-2 receptor) ≥2,400 U/mL

Table 2. H-score system.[12]

Findings	Points
Known underlying immunosuppression	No:0
	Yes:18
Temperature (°C)	<38.4: 0
	38.4–39.4: 33
	>39.4: 49
Organomegaly	No: 0
	Hepatomegaly or splenomegaly: 23
	Hepatomegaly and splenomegaly: 38
Number of cytopenia (hemoglobin 9.2 g/L and/or leukocyte ≤5x10 ^{9} /L and/or platelet ≤110x10 ^{9}/L)	1 lineage: 0
	2 lineages: 24
	3 lineages: 34
Ferritin (mg/L)	<2,000: 0
	2,000-6,000: 35
	>6,000: 50
Triglyceride (mmol/L)	<1.5: 0
	1.5-4: 44
	>4: 64
Fibrinogen (g/L)	>2.5: 0
	≤2.5: 30
Aspartate aminotransferase (U/L)	<30: 0
	≥30: 19
Hemophagocytosis on bone marrow aspirate	no: 0
	yes: 35

Results

In our tertiary hospital which serves generally Marmara region of Turkey on an average 190 patients are diagnosed newly with hematologic malignancy per year. Lymphomas which are the most accused hematologic etiology of HLH represent nearly 40% of this number of patients. In our patient group, the mean age of patients was 54 (24-78 years) and the median age was 59. Six patients (66.6%) were male while three patients (33.4%) were female. The distribution of the underlying diseases in patients was like three patients with diffuse large B cell lymphoma (DLBCL), two patients with acute myeloid leukemia (AML), two patients with classical Hodgkin lymphoma (HL) and the others with small cell lung cancer and T cell non-Hodgkin lymphoma (T-NHL). One of these patients who was counted as AML had diagnosed and treated for DLBCL two and half years before. One of the patient was diagnosed with HLH and DLBCL simultaneously. In only one patient who had T-NHL developed HLH during malignancy specific therapy. Rest of patients had

Table 3. Tamamyan et al.'s extended criteria[13]

Bone marrow/ lymph node/spleen hemophagocytosis per pathology evaluation	Renal failure (≥50% increase in creatinine over baseline)
Fever	Elevation of liver enzymes (≥2.5 times the upper limit of normal)
Splenomegaly (clinically palpable spleen)	Hypofibrinogenemia (fibrinogen ≤150 mg/dL)
Hepatomegaly (clinically palpable liver)	Hyperferritinemia (ferritin ≥500 µg/L)
Anemia (hemoglobin <9.0 g/L)	Coagulopathy (prothrombin time ≥1.5 times the upper limit of normal and/or partial thromboplastin time ≥1.5 times the upper limit of normal, and/or D-dimer ≥10.0 µg/mL)
Thrombocytopenia (platelets <100x10^{9}/L)	Hypoalbuminemia (<3.5 g/dL)
Neutropenia (absolute neutrophil count <1.0x10^{9}/L)	Elevated β2-microglobulin (≥2 mg/L)
Monocytosis (absolute monocyte count >1.0x10^{9}/L)	Elevated lactate dehydrogenase (≥2.5 times the upper limit of normal)
Hypertriglyceridemia (≥265 mg/dL)	Elevated soluble IL-2 receptor

Table 4. Characteristics of malignancy-associated hemophagocytic lymphohistiocytosis patient group.

Age (median-years)	59
Male (%)	66%
Underlying malignancy (number of patients)	Diffuse large B cell lymphoma (3) Acute myeloid leukemia (2) Hodgkin lymphoma (2) T cell non-Hodgkin lymphoma (1) Small cell lung cancer (1)
Clinical and laboratory findings at diagnosis (%) (HLH-2004 diagnostic criteria) [11]	Fever (100%) Splenomegaly (88.8%) Hypertriglyceridemia (88.8%) Hyperferritinemia (88.8%) Anemia (77.7%) Thrombocytopenia (66.6%)
Clinical and laboratory findings at diagnosis (Tamamyan et al.'s extended criteria) [13]	Fever (100%) Splenomegaly (88.8%) Thrombocytopenia (88.8%) Hepatomegaly (77.7%) Anemia (66.6%)
Median H-score at diagnosis [12]	258
Duration of application to hospital to HLH diagnosis (days)	16 (4-53)
Number of criteria at diagnosis (HLH-2004 diagnostic criteria) [11] (number of patients)	3/8 (1) 5/8 (6) 6/8 (2)
Mortality rate (%)	88.8
Median duration of survival (days)	8.5 (1-18)

active malignancy such as relapse, uncompleted therapy or newly diagnosed when diagnosed with HLH. The most common application symptom was fever (6 patients) and followed by dyspnea (4 patients) and weakness equally. Somnolence was the concomitant symptom to fever and weakness in one patient. The mean duration of application to hospital to HLH diagnosis 23.4 days (4-53 days), median time was 16 days. According to HLH-2004 diagnostic criteria in 8 criteria apart from soluble CD25 (soluble IL-2 receptor) and NK activity laboratory tests; one patient had 3/6, six patients had 5/6, two patients had 6/6 criteria when they were approved as HLH at the time of diagnosis. Six patients of nine had hemophagocytosis in bone marrow biopsy. The mean H-score was 256 while median score was 258 at diagnosis. One patient's whom had 3/6 HLH-2004 diagnostic criteria H-score was 219. The patients' whom had 5/6 HLH-2004 diagnostic criteria H-score were between 173 and 317. Two patients' H-score were 213 and 307 with 6/6 HLH-2004 diagnostic criteria. When medical records were reviewed due to Tamamyan et al.'s study[13], we could reach data in all patients mostly except soluble IL-2 receptor level and β2-microglobulin level. According to this extended criteria; at the diagnosis of HLH, all patients had ≥7 (between 7-12) of 18 parameters. When we analyzed the time which patients fulfilled ≥5 parameters it was a mean 17.7 days and median 15 days (3-52 days) before the diagnosis of HLH. On that time six patients had 3/6 criteria of HLH diagnostic criteria while the other patients had 2-4-5/6.

Regarding ferritin which was found one of the most related laboratory finding to HLH due to level, eight of nine patients had elevated ferritin (≥500 μg/mL) level while six of them had ≥1500 μg/mL. Defect of coagulation parameters and bleeding diathesis were not remarkable however

Table 5. Features of malignancy-associated hemophagocytic lymphohistiocytosis patient group.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Age (years)	68	40	30	67	24	54	99	66	78
Gender	Male	Male	Male	Female	Female	Male	Male	Female	Male
Underlying malignancy	T NHL	HL	AML	DLBCL	AML	SCLC	HL	DLBCL	DLBCL
HLH-2004 diagnostic criteria[11]									
Fever	+	+	+	+	+	+	+	+	+
Splenomegaly		+	+	+	+	+	+	+	+
Hemophagocytosis	+	+	+	+	+	+		+	
Hemoglobin <9 g/L					–	+	+	–	+
Neutrophils <1,000/mm³			–				+		
Platelets <100,000/mm³			–		–	+	+	–	+
Hypertriglyceridemia	+	+	+	+		+	+	+	+
Hypofibrinogenemia	+	+							
Ferritin ≥500 ng/L		+	+	+	+	+	+	+	+
sCD25	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Low or no NK cell activity	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
H-score (at the time of diagnosis)[7]	219	317	307	272	268	307	238	213	173
Tamegnon et al.'s extended criteria (at the time of diagnosis)[7]									
Hemophagocytosis	+	+	+	+	+	+		+	
Fever	+	+	+	+	+	+	+	+	+
Splenomegaly		–	–	+	–	+	+	–	+
Hepatomegaly		–	–	+	–	+	+	–	
Anemia (hemoglobin <9.0 g/L)	+				+	+	+	+	+
Thrombocytopenia (platelets <100×10⁹/L)		+	+	+	+	+	+	+	+
Neutropenia (absolute neutrophil count <1.0×10⁹/L)			+				+		
Monocytosis (absolute monocyte count >1.0×10⁹/L)			+	+	+		+	+	
Hypertriglyceridemia	+	–	–	+		+	+	–	+
Renal failure		–				+	+		
Elevation of liver enzymes		+				+	+		
Hypofibrinogenemia	+	+							
Hyperferritinemia		+	+	+	+	+	+	+	+
Coagulopathy	+	+	+		+				
Hypoalbuminemia	+			+	–	+		–	+
Elevated β2-microglobulin								–	
Elevated lactate dehydrogenase		+		+	+			+	+
Elevated soluble IL-2 receptor	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

T NHL: T cell non-Hodgkin lymphoma, HL: Hodgkin lymphoma, AML: acute myeloid leukemia, DLBCL: diffuse large B cell lymphoma, SCLC: small cell lung cancer, LDH: lactate dehydrogenase, N/A: not available

D-dimer levels were ≥10.0 μg/mL whom was performed.

Seven patients were receiving broad-spectrum antibiotics at HLH diagnosis and two of them were also using antifungal treatment. In only one patient's concurrent two blood culture were resulted as "*Acinetobacter baumannii*" on the same day she deceased. Regarding antifungal treatment, it was given as "possible" fungal infection according to host and clinical features with imaging findings without mycological evidence.

Two of the patients could not have treatment while two of seven patients had dexamethasone and five of them had etoposide and dexamethasone protocol as mentioned before. Four of these five patients had also chemotherapy during HLH treatment. Chemotherapies were performed as CHOP protocol, 7+3 protocol (100/200 mg/m^2 /day cytarabine, 7 days and 60 mg/m^2 /day daunorubicin, 3 days), brentuximab or rituximab and bendamustine. Plasmapheresis for 2 days (one volume with fresh frozen plasma) and IVIG (0.5 g/kg) were performed to one patient but he did not respond to these interventions.

Outcomes of nine patients; only one patient recovered from HLH clinic status however he

deceased related to progression of the primary disease. Remained of the patients whether treated or untreated died related to uncontrolled HLH status and multiorgan failure in the intensive care unit. The mean survival time of the treated patients was 12.6 days (7-21 days). Characteristics and features of M-HLH patient group are summarized in Table 4 and Table 5.

Discussion

Infections or malignancies can initiate HLH pathogenesis if they are not managed properly nevertheless infections can seem a trigger of HLH deceptively in patients with underlying autoinflammatory or malignant disorders.[18] Mortality rate is extremely high along with bleeding, infections, loss of consciousness and refractory hypotension due to multiorgan involvement and failure.[4,8] Machazka et al.[6] announced the incidence of M-HLH as 1% in hematological malignancies. Cumulative incidence rate was reported as 2.8% in malignant lymphoma patients while 9% in acute myeloid leukemia patients after remission treatment.[19,20] Hematological malignancies are the most common cause of M-HLH in a rate of 40-70% and up to 93.7% in a review of M-HLH. Distribution of them is like 35-40% T/NK cell lymphoma-leukemia, 30-40% B-cell lymphoma, 5-8% Hodgkin lymphoma, 8% acute myeloid leukemia, 8% myelodysplastic syndrome.[21,22] In our study, the distribution was like DLBCL in 3 patients, AML in two patients, HL in two patients. Median age of our patient group was 59 and it was similar to the other studies.[13,18,22,23] In terms of clinical and laboratory findings, fever (100%), splenomegaly (88.8%), hypertriglyceridemia (88.8%), hyperferritinemia (88.8%), anaemia (77.7%), thrombocytopenia (66.6%) were seen mostly and the least met criteria was neutropenia (11.1%) according to HLH-2004 diagnostic criteria. This was supported by German registry study and a multicenter study from USA regarding fever, splenomegaly, anemia, thrombocytopenia, hyperferritinemia but neutropenia was determined 43% and 76% in these studies, respectively.[18,23] Fever (100%), splenomegaly (88.8%), thrombocytopenia (88.8%), hepatomegaly (77.7%), anemia (66.6%) were determined frequently regarding Tamamyan et al.'s[13] extended criteria. The distribution of the criterias was different from the original study as fever (42%), splenomegaly (35%), thrombocytopenia (48%), anaemia (39%).[13] This diversity could be associated with the underlying disease, ethnicity or small patient group that we examined. Besides that, monocytosis was seen in four patients (44.4%) and two of them were diagnosed with AML while it was 17% (6 patients) in the original study and three of them were AML. Therefore, we think monocytosis could be confusing in terms of HLH probability when the underlying disorder is AML in M-HLH.[13] Hyperferritinemia was not found as a distinctive indicator for adult HLH patients nevertheless it was found as an important marker for diagnostic work-up in Schram et al.'s study.[24] Tamamyan et al.'s[13] and our study correlate in terms of hyperferritinemia which was found nearly 90% in the patient groups. In our patient group, 75% of patients (6 patients) with hyperferritinemia had >1,500 μg/mL ferritin level. The other criteria of extended criteria that are defect of coagulation parameters and bleeding diathesis were not remarkable however D-dimer levels were ≥10.0 μg/mL whom was performed. Any patient could not fulfilled these criteria with only high D-dimer level. In Schram et al.'s study[23], 85% of M-HLH patients represented coagulopathy. This parameter may be separated for assessment HLH because of D-dimer could be find high due to underlying malign disorder not only with bleeding diathesis or disseminated intravascular coagulation.

Fever, bicytopenia with increased risk of bleeding and splenomegaly are triad and suspicious findings for adult HLH and in patient who has these findings it is recommended that to initiate diagnostic examinations regarding HLH rapidly.[4,8] If the clinical status does not respond and even gets worse with accurate antimicrobial therapy, this condition could be approved as a possible signal of HLH. Re-assessment of clinical findings, physical examination and laboratory tests closely are the fundamental for diagnosis.[4] However, treatment is recommended in patients who are suspected strongly for HLH despite cannot provide 5 of 8 HLH-2004 diagnostic criteria and we also initiated treatment in a patient with 3/6 criteria due to significant clinical support.[4] Besides that,

H-score can be used for diagnosis however H-score could not be adequate to determine M-HLH due to population of validation groups. Tamamyan et al.[13] also reported extended diagnostic criteria to this patient group who has poor prognosis for providing earlier intervention. Therefore, they suggest to workup for HLH and to pretend as HLH in patients who has hepatic or renal failure of unknown etiology, sudden-onset multiorgan failure, culture negative sepsis or encephalopathy of unknown etiology.[13]

We think that reaching to all HLH-2004 diagnostic criteria which as mentioned before soluble CD25 (soluble IL-2 receptor) and NK activity laboratory tests is difficult in every country and center as, in our country and in a tertiary hospital. Unavailability of these tests results in complicating to fulfill 5 of 8 criteria and being delayed to diagnose and treatment. Therefore, we aimed to reveal the process of diagnose and outcomes in limited patient group. Hemophagocytosis in bone marrow or lymph node or spleen is another criteria which is difficult to interpret in status of malignancy and inflammation.

The mean duration of HLH diagnosis 23.4 days according to HLH-2004 diagnostic criteria in 6 criteria apart from soluble CD25 (soluble IL-2 receptor) and NK activity laboratory tests. In terms of the differentiation efficiency of HLH patients with H-score, the number of patients are limited to conclude however the score was not correlate with HLH-2004 diagnostic criteria due to co-occurrence of lower HLH 2004 criteria and high-level H-score. According to Tamamyan et al.'s criteria all patients had HLH clinic status probably on average 17 days before the day of HLH diagnosis and on that time most patients had 3 or 2/6 criteria of HLH-2004 diagnostic criteria.[13] We cannot reveal any benefits to determine patients with HLH earlier however we think that to change our approaching to this patient group and to be on alert regarding unfulfilled HLH-2004 diagnostic criteria to do not miss the cases and be late for diagnosis.

Regarding diagnosis and treatment, HLH patients need multidisciplinary approach along with hematology, oncology, pathology, infectious diseases and intensive care. M-HLH is the poorest prognostic HLH subtype. There is still no specific diagnostic tool or treatment or guideline for M-HLH due to lack of prospective, randomized and controlled studies.[25] HLH which occurs during treatment and is with prolonged neutropenia, fever despite of antibiotic treatment benefit from especially corticosteroids due to anti-inflammatory feature and IVIG nevertheless excluding of non-remission malignancy should be done.[4]

Mortality rate was 88.8% in our patient group and the median duration of survival was 8.5 days (1-18 days) in all patients while it was 12.6 days in treated patients. Mortality rate was reported 80% and the median survival time 1.5 months in Tamamyan et al.'s study[13] and mortality rate were 100% and the median survival time was 22 days in another study from Sweden in M-HLH.[26] These mortality rates were not so different from our results however the median survival time is shorter in our patient group probably due to being late for diagnosis.

In the latest study which has the largest M-HLH patient group, sCD25 >3,900 U/mL and ferritin> 1,000 ng/mL were reported as "Optimized HLH Inflammatory" (OHI) index. And this index suggests to provide more accurate pathological state of HLH.[22] However, diagnosing and managing of M-HLH is still challenging especially unavailability of tests which are associated to reveal hyperinflammation.

Conclusions

Mortality rate of HLH in adults especially in M-HLH still high. Adult HLH especially M-HLH are candidates for improvements and some studies are going on regarding treatment currently. Considering HLH in differential diagnosis and awareness of HLH are still essential for diagnosis and treatment. We need to develop more specific and accessible criteria and grading systems for diagnosis and more targeted therapy options for M-HLH.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical Approval

For this study, approval was obtained local ethics committee.

Authors' Contribution

Study Conception: HOK, TAK, UD, SKG, VB, EGU, AMD; Study Design: HOK, TAK, UD, SKG, VB, EGU, AMD; Supervision: HOK, TAK, UD, SKG, VB, EGU, AMD; Literature Review: HOK; Critical Review: HOK; Data Collection and/or Processing: HAK, TAK, UD, SKG, VB; Analysis and/or Data Interpretation: HAK, TAK, UD; Manuscript preparing: HAK, TAK, UD, SKG, VB, EGU, AMD.

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