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Hemophagocytic Lymphohistiocytosis

Ayşe Gonca Kaçar[1], Tiraje Tülin Celkan[2]

[1]Clinic of Pediatric Hematology and Oncology Adıyaman University Training and Research Hospital, Adıyaman, Turkey
[2]Division of Pediatric Hematology-Oncology, İstinye Faculty of Medicine, İstanbul, Turkey

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive life-threatening disease that consists of uncontrolled activated lymphocytes and macrophages that secrete excessive cytokines. Symptoms and laboratory findings of HLH include prolonged fever, cytopenia, hepatosplenomegaly, liver dysfunction, hypertriglyceridemia, hyperferritinemia, increased soluble interleukin-2 receptor, low fibrinogen, and neurological problems. HLH has two forms: primary (familial autosomal recessive) or secondary (related to infections, malignancy, autoimmune and metabolic disorders, transplantations, chimeric antigen receptor T-cell therapies, etc.) form. As underlying conditions in HLH varied, clinical findings are nonspecific and disease diagnosis is challenging. Furthermore, patients diagnosed with primary HLH can have a secondary triggering agent, such as infection. Thus, there is no clear-cut distinction between these two forms. Abnormal immune response and a low number or absence of natural killer cells and cytotoxic T-lymphocytes are hallmarks of HLH. Despite the early and aggressive treatment, HLH is a deadly disease. Urgent immunosuppressive therapy is necessary to control hyperinflammation. Hematopoietic stem cell transplantation is a curative treatment in familial forms. Targeted therapy with emapalumab was also recently reported to be effective.

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive life-threatening disease that involves uncontrolled activated lymphocytes and macrophages that secrete excessive cytokines. HLH includes various clinical situations that affect both children and adults, and its diagnosis and therapy are challenging.[1-8]

Interest in HLH has increased during the pandemic period. More than 4,400 publications on this topic were published. Hemophagocytic syndrome affects all ages. Genetic forms that are known problems in children can be also seen in adults.[9-14]

HLH is caused by the exaggerated response of the immune system.[15] T-cells and macrophages are activated and proliferated massively, leading to marked hypercytokinemia. Abnormal immune response and a low number or absence of natural killer (NK) cells and CD+8 cytotoxic T-lymphocytes (CTL) are the hallmarks of HLH.[1-4,16-21] HLH has high mortality rate when it is untreated, but even with extensive treatment, the result might be fatal.[22,23]

HLH has characteristic clinical and laboratory signs such as prolonged fever, lymphadenomegaly, hepatosplenomegaly, pancytopenia, liver dysfunction, hypertriglyceridemia, hyperferritinemia, high cytokine levels (interleukin [IL-6], interferon-alpha, and tumor necrosis factor [TNF]-α).[1-8,24-28] The phagocytosis of hematopoietic cells by macrophages can be seen in the bone marrow and reticuloendothelial system on histological evaluation.[1-8,29-31]

HLH has a primary (familial autosomal recessive) or a secondary form. HLH frequently develops in cases with underlying genetic alterations. Apart from genetic defects, albinism syndromes, and X-linked lymphoproliferative syndromes, underlying conditions (infections, rheumatic and metabolic disorders, and malignancies) can lead to HLH.[1-8,32-47]

T helper cells are cells that secrete all cytokines that initiate hemaphagocytosis. In most common hematological malignancies, lymphomas, acute leukemia, or multiple myeloma, malignant cells are thought to release cytokines themselves.[35,48]

EPIDEMIOLOGY

No clear data is available on the incidence of HLH. Primary HLH has an incidence rate of 0.12/100,000 in Sweden, 0.342/100,000 in Japan, and 7.5/100,000 in Turkish hospitalized children.[49-51] The ratio increases in areas where consanguinity marriages are high (21% in Turkey in general and up to 42% in the southeast region) due to autosomal recessive inheritance.[1-8]

Corresponding author: Tiraje Tülin Celkan, Division of Pediatric Hematology-Oncology, İstinye Faculty of Medicine, İstanbul, Turkey
e-mail: tirajecelkan@yahoo.com
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ORCID iDs of the authors: A.G.K. 0000-0002-2848-3978; T.T.C. 0000-0001-7287-1276.

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Although few studies have reported the frequency of secondary HLH, it seems more than primary HLH. Janka et al. found that the prevalence of malignancy-associated pediatric HLH is 8.4%, and they confirmed that the results probably even underestimate the prevalence.[1-8] Machaczka et al.[52] reported malignancy-associated HLH in adults with an incidence rate of 0.36/100.000. As symptoms of HLH are almost the same as those of sepsis, HLH is underdiagnosed, especially in the adult population.[53-55] The classification of HLH is usually challenging, as secondary HLH beyond infancy might be a late-onset familial hemophagocytic lymphohistiocytosis (FHL).[9,11,56,57]

Eighty percent of patients with HLH are infants, especially babies aged 1-6 months. In less than 10% of cases, symptoms manifested during the neonatal period, whereas 20% were diagnosed during adolescence or adulthood.[51,58]

PATHOPHYSIOLOGY

When an infection is caused by intracellular pathogens, infected cells activate CTLs and NK cells by contact interactions, forming an immunological synapse. Perforin and granzymes, (cytoplasmic granule toxins) are released into the infected cells and begin their cytolytic activity.[59] Commonly, a viral trigger is required for HLH to develop. Another mechanism of HLH is the non-antigen-specific form through receptors of the innate immune system. Toll-like receptors (TLRs) are the primary receptor.[60] TLR signaling is also an important factor in genetic HLH. Impaired function of NK cells and CTLs is the hallmark of genetic and transient HLH. The activation of Fas ligand and perforin-dependent pathway leads to the death of the infected cells. NK cells and CTLs have cytotoxic granules that contain perforin and granzymes. After the activation of these cells, the granules secrete their contents through the immunologic synapse[3] and kill the target cells. When the trigger is abolished, the immune system returns to its normal state, maintaining immune homeostasis. Perforin has an important role in this process. If cytotoxic cells cannot eliminate the infected antigen-presenting cell (APC), continuous immune stimulation causes HLH. In all genetic defects in FHL and granule-related syndromes such as Griscelli syndrome type II (GS-2), Chediak-Higashi syndrome (CHS), and Hermansky-Pudlak type 2 (HPS2), the formation, trafficking, docking, or exocytosis of granules (FHL3-5, GS-2, CHS, HPS2, and FHL-2) is defective. Immune response is controlled by perforin and CTLs by killing Fas-associated APCs and NK cells that destroy activated CD4 cells. Impaired function of cytotoxic CD4+ T-regulatory cells that remove the expanded CD8+ T-cell population is another cause of HLH.[1-3,59,60]

Recently, CD 47 was reported to inhibit phagocytosis by interacting with signal regulatory protein α. During HLH, CD 47 is downregulated, and it activates histiocyte- and lymphocyte-infiltrated organs.[61]

Lymphocyte cytotoxicity is also directed against APCs. After APCs are destroyed by NK cells, T-cell-mediated immune responses become dominant. Nevertheless, compared with NK cells, CTLs are more prominent in the pathogenesis of HLH.[3,60] Ineffective cytotoxicity cause APCs to stimulate CTL constantly and increase the production of cytokines. Cytokines, primarily, interferon (IFN)-γ, induced macrophage activation. Tissues, bone marrow, liver, and central nervous system (CNS) are infiltrated by T cells and macrophages by secreting cytokines and starting the phagocytic activity.[62-65] IFN-γ and TNF-α affecting hematopoietic cells result in cytopenia. Increased IL-1, IL-6, and TNF-α levels cause prolonged fever. TNF-α causes hypertriglyceridemia by inhibiting lipoprotein lipase.[1-8] High ferritin levels are caused by the secretion of activated macrophages. They also secrete plasminogen activator, which is associated with hypofibrinogemia. IL-2 receptors are secreted to the plasma by activated T- and NK cells, which is a characteristic laboratory abnormality of HLH.

HLH is particularly triggered by Epstein-Barr virus (EBV) infection. Primary immuno-deficiencies tend to result in HLH, including X-linked disorders such as signaling lymphocytic activation molecule associated protein (SAP) and X-linked inactivator of apoptosis (XIAP) deficiency and the autosomal recessive IL-2 inducible T-cell kinase (ITK) and CD27 deficiencies.[66-69] NK and T-cell development, or T-cell-B-cell interaction, and the ability of cytotoxic T-cells to lyse B-cells are impaired in these diseases.

FHL associated with albinism is found as having abnormal lymphocyte cytotoxicity. Similarities were noted between molecular vesicle trafficking, especially pigment transport in the skin and hair. Moreover, the degranulation of platelets, mast cells, and perforin was shown to be impaired.[60]

In acquired HLH, the mechanisms of hemaphocytosis are not fully understood yet, as underlying conditions are varied. Malignancies, iatrogenic immune suppression, human immunodeficiency virus (HIV) infection or autoinflammatory diseases are all candidates for HLH. Nevertheless, the mechanism leading to HLH is not known yet. Polymorphisms in cytokine genes can cause severe inflammatory response or inhibition of NK cell activity by cytokines, and there is a temporary disproportion between immune cells and infected cells. Furthermore, low number of NK cells is detected in these patients.[1-4,60]

GENETIC EVALUATION

Several genetic defects that cause HLH were recently discovered, although 1/3 of patients showed no known mutations yet. FHL is an autosomal recessive disorder. Its incidence in Sweden was estimated to be 1 in 50,000 births. Moreover, 90% of familial cases have different genetic defects with respect to cytotoxic granule function or exocytosis (Table 1). The genetic defects are associated with proteins perforin, MUNC 13-4, Syntaxin-11, and MUNC18-2, which have a critical role in lymphocyte cytotoxicity. Patients with FHL-2 have a deficiency in perforin, the most important molecule in cytotoxic granules for immune response. In patients with FHL 3-5 (Munc 13-4, STX-11, and STXBP2 mutations), impaired granule exocytosis leads to the same clinical symptoms as FHL2 (perforin mutation). UNC 13D mutation reflects the inability of vesicles to adhere to the cell membrane.[50,56,70-74] An interaction problem also exists between dendritic cells and NK cells in Syntaxin 11 gene defects. Granule exocytosis pathways are also active in mast cells,

neutrophils, platelets, and skin cells besides the immune system. As a result of the abnormal functions of these cells, a patient with FHL may complain of bleeding, immune deficiency, or albinism.

Genetic cases can also be encountered in adults. Mutations in FHL 2-5 and X-linked proliferative (XLP) can be seen in adult patients with HLH. Biallelic or monoallelic mutations or polymorphisms in genes of familial HLH were found among adults with HLH.[11] They also have hypomorphic mutations in PRF1, MUNC13-4, and STXBP2, which causes the milder and atypical forms of HLH beyond infancy.[75-77] The FHL associated genes depend on the geographical and ethnic origin of the patient. For example, perforin 50 delT mutations are found in African–American patients, 1090-1091 delCT in Japanese, and Trp374 stop (W374X) in Turkish patients with HLH. Patients with (W374X) mutant are usually diagnosed <6 months and have a poor prognosis. Moreover, generally, patients with Syntaxin 11 mutations are from Turkey.[78-83]

Complex granule-associated syndromes (GS2, CHS, and HPS2) can also cause HLH.[1-3] The third group of genetic diseases that lead to HLH are immunodeficiencies associated with impaired control of EBV infection. This group of disorders are XLP 1 and 2 (XLP1 SAP), XLP2 (XIAP), ITK, and CD27 deficiency (Figure 1).

In summary, genetic diseases that are inclined to HLH can be grouped into three categories:

1. Familial HLH (FHL2-5)

2. Granule defects that are associated with impaired lymphocyte cytotoxicity (CHS, GS, and HPS)

3. EBV-associated immune deficiencies with impaired lymphocyte cytotoxicity

The age of symptom onset is usually an important clue for the genetic differential diagnosis. In most patients of the first group (FHL), HLH occurs in the early days of life; however, they seldom remain asymptomatic until adulthood. According to our experience, HLH onset in granule-associated diseases tends to be later in familial forms.

Another clue for the classification of HLH is the occurrence of relapses. A recurrent disease is usually a result of genetic problems rather than secondary forms, and hematopoietic stem cell transplantation (HSCT) is the only curative treatment; thus, HSCT must be performed immediately.

CLINICAL EVALUATION

The main symptoms of HLH are hepatosplenomegaly, pancytopenia, and prolonged fever that is often unresponsive to antibiotic therapy.

Hepatitis and neurological symptoms are secondary findings. Characteristic laboratory features are increased levels of ferritin, triglycerides, transaminases, bilirubin, lactate dehydrogenase, and soluble IL-2 receptor α-chain and decreased levels of fibrinogen (Tables 1 and 2).

The clinical symptoms are characteristic but nonspecific, and there is no clear-cut clinical difference between familial and acquired forms of HLH. Fever is usually higher than 38.5 °C and unresponsive to antibiotic treatment. Specifically, lymphadenomegalies, edema, and different skin rashes accompany fever. The uncontrolled inflammatory response leads to ascites and pleural effusion, as histiocytes and activated lymphocytes invaded all tissues, just like leukemia, and clinical findings are multisystemic. In cases of hepatic, CNS, renal, and lung involvements, the disease progresses very rapidly, and mortality is inevitable. As clinical signs varied, the diagnosis is very challenging.[1-8] Generally, patients are misdiagnosed, and they are evaluated for hepatic or renal insufficiency, encephalitis, or lung abnormalities. Infants with CNS involvement experienced discomforts, convulsions, and fontanel bulging at the beginning, whereas opisthotonus, cranial nerve palsies, ataxia, hemiplegias, loss of vision and consciousness, and increased intracranial pressure may develop during diagnostic evaluations.[84-87] Uncommonly, CNS involvement may begin before organomegalies and cytopenias, as isolated HLH of the CNS can be misdiagnosed as acute disseminated encephomyelitis until other symptoms appeared.[86] Neurologic symptoms are found in more than 30% of cases. Seizures, meningismus, decreased consciousness, irritability, and hyper- or hypotonia may be present. Hyperbilirubinemia, thrombocytopenia, hyperferritinemia, and cerebrospinal fluid infiltration are indicative of poor prognosis. In addition, the persistence of anemia, hypofibrinogenemia, thrombocytopenia, and fever after starting the therapy are early clues for a dismal end. In EBV-associated HLH, the persistence of high viral load is a sign of morbidity and mortality.[50,88]

Infections are usual triggers of HLH. The identification of an infectious organism cannot be used to distinguish familial HLH from acquired HLH, as both of them might be triggered by

TABLE 1. Symptoms of Hemophagocytic Lymphohistiocytosis and Relation with Hypercytokinemia

• Fever	IL-1, IL-6, and TNF
• Profound cytopenias	TNF, IFN-γ, hemophagocytosis, hyperferritinemia, increased sIL-2 receptor
• Hypertriglyceridemia	TNF-α, suppressed lipoprotein lipase by cytokines
• Hyperfibrinolysis	Activated macrophages and increased plasminogen activator
• Hyperferritinemia	GDF15 upregulation of ferroportin
• Elevated LDH	Cell death
• Elevated D-dimer	Hyperfibrinolysis
• Elevated CSF cells/protein	Central nervous system infiltration

IL, interleukin; LDH, lactate dehydrogenase; IFN, interferon, TNF: Tumor necrosis factor, CSF: Cerebrospinal fluid

infectious agents. Thus, HLH therapy must not be stopped when an infectious agent is detected. Infectious organisms are mostly viruses, especially EBV and cytomegalovirus, but bacteria, protozoa, and fungi can also cause HLH. EBV and leishmania infections are the most frequent triggers. Although Leishmania is an important trigger, it may not be diagnosed if hematologist did not suspect and investigate bone marrow aspirations carefully due to histological similarities with platelets. Before 2000, HLH was named a virus-associated hemophagocytic syndrome or infection-associated hemophagocytic syndrome, as cases were usually from Japan and far-east Asia and ¾ of cases were associated with EBV. In Japan, 90% of children with HLH were found to have acquired forms.[50,89]

Neonates with HLH have a dismal prognosis. The babies in their first week of life rarely have all the features of HLH. Sometimes, clinical symptoms of HLH begin in the prenatal period, leading to non-immune hydrops.[90]

Sepsis/systemic inflammatory response syndrome is usually the reason for misdiagnosis. HLH and sepsis can both have extreme inflammation, and many similar laboratory findings such as cytopenias, low fibrinogen, and elevated levels of triglycerides,

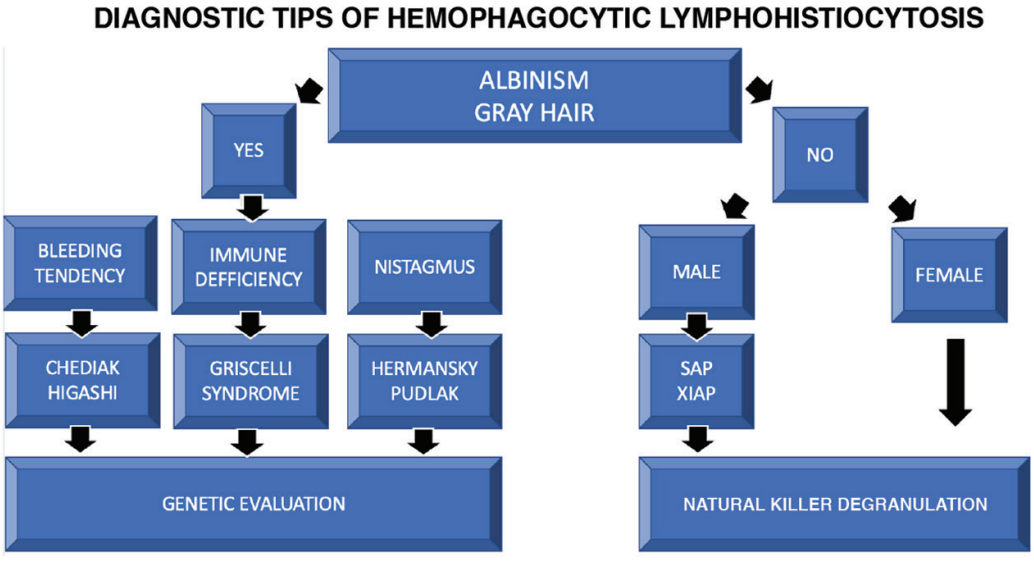

FIG. 1. Clinical clues for differential diagnosis of hemophagocytic lymphohistiocytosis[1-3,60]

TABLE 2. Hemophagocytic lymphohistiocytosis-2004 Criteria (CSF: cerebrospinal fluid)

Features	Cutoff
Fever	
Splenomegaly	
Cytopenia	>/=2 cell lines
Hemoglobin	<90 g/L (neonates <100 g/L)
Platelets	100 x 10^9/L
Neutrophils	<1 x 10^9/L
Hyperferritinemia	>500 µg/ L
Hypofibrinogenemia	1.5 g/L
Hypertriglyceridemia	3 mmol/L
Elevated soluble CD25	>2,400 U/mL
Hemophagocytosis	Bone marrow, other tissues
Reduced or absent NK cytotoxicity	
Elevated transaminases, bilirubin	
Elevated LDH	
Elevated D-dimer	
Elevated CSF cells or CSF protein	

NK: natural killer, CSF: cerebrospinal fluid, LDH: lactate dehydrogenase

ferritin, and soluble IL-2 receptor make the differential diagnosis difficult. Therefore, each patient with sepsis should be considered at risk of HLH.[53-55]

Autoinflammatory and autoimmune conditions form a special subgroup of HLH, which is named macrophage activation syndrome (MAS). The incidence rate is high in systemic juvenile idiopathic arthritis, Still's disease, and systemic lupus erythematosus. Repeated stimulations of immune response cause HLH. MAS may be clinically evident either during active disease or during treatment, especially with anti-TNF-α. MAS is a form of HLH in rheumatologic diseases. Typical findings are low leukocyte and thrombocyte counts accompanied by hyperferritinemia, hypofibrinogenemia, hemophagocytosis, elevated liver enzymes, hypertriglyceridemia, and low erythrocyte sedimentation. MAS, a form of secondary HLH, does not generally fulfill the HLH criteria; thus, its diagnosis is challenging.[91-93]

The next subgroup of HLH includes both children and adults with malignancies. Lymphomas and leukemia are the common causes of HLH. Malignant cells secrete proinflammatory cytokines, and an increased risk of cancer development in patients with HLH is hypothesized as a cause of familial HLH and cancer.[3,37,48]

Patients with HIV infection and iatrogenic immune deficiencies (chemotherapy or transplantation associated) are prone to develop HLH.[94]

HLH is also common in metabolic disorders such as lysinuric protein intolerance, sulphatase deficiency, Wolman's disease, and propionate metabolism disorders.[39-45]

LABORATORY FINDINGS

The most common manifestation of HLH includes cytopenias that involve at least two hematopoietic cell lines. Cytopenias generally began with thrombocytopenia and can progress to severe pancytopenia accompanied by hyperferritinemia, elevated transaminases and LDH, hypofibrinogenemia, hypertriglyceridemia, hypoalbuminemia, and hyponatremia.[1-4] Immunologically, CD25 is elevated, and NK cell cytotoxicity is reduced. Patients with HLH might also complain of disseminated intravascular coagulation.

The lack of histomorphological evaluation in hemophagocytosis cannot rule out its diagnosis. At the early stage of disease development, it may not be seen, so bone marrow aspiration can be repeated several times to check for hemophagocytosis (Figure 2).[29-31]

Interstitial opacities, pulmonary edema, and pleuritis could be seen in plain lung radiography. Hypertrophy of the liver, spleen, and kidneys could be detected by abdominal ultrasonography.

In CNS HLH, lymphocytes, histiocytes, macrophages, and high protein content may be detected in cerebrospinal fluid (CSF). Diffuse signals and hyperintense lesions in the white and gray brain matter, delayed myelinization, calcifications in the parenchyma, and atrophy could be seen in T2 magnetic resonance imaging.

TREATMENT

Familial HLH can lead to severe organ damage and death if left untreated.[95,96] Therefore, treatment should be started immediately to suppress the severe hyperinflammation that causes mortality. This blocks the activation of T cells with impaired functions.[97] The treatment option for HLH depends on the underlying disease and severity of the patient's clinical condition. Treatment is challenging, and there is no clear-cut regimen.[4]

In HLH triggered by infections, infection-directed therapy is recommended. The treatment of EBV-related HLH is controversial because of its variable clinical course. In a brief report, Belyea presented two cases of EBV-HLH that spontaneously recovered without the need for HLH therapies.[98] However, in the study by Imashuku et al., EBV-related HLH cases have multiorgan failure that is caused by hypercytokinemia.[99,100] The treatment modality should be decided according to the cytokine levels and clinical status.

The mainstay treatment of HLH is the use of epipodophyllotoxin derivatives (etoposide and teniposide) and steroids. They relieve clinical symptoms of HLH.[100,101] In HLH-2004, these drugs were combined with immunosuppressive drugs such as cyclosporine (CSA), which is also effective in FHL.[100-103] CNS HLH may cause serious irreversible damage, and reactivations are common.[3,104,105] Therefore, dexamethasone is used as a first-line therapy because its blood-brain barrier penetration is better than prednisolone. Intrathecal administration of methotrexate must begin after the second week of therapy in children with abnormal CSF findings.[5] After 8 weeks of initial therapy, treatment is terminated in patients without a proven family history and who achieved complete remission. Primary HLH is verified by genetic testing, and persistent and reactivated secondary HLH should receive continued therapy with etoposide, dexamethasone, and CSA. HSCT should be performed as soon as possible.[5] During treatment, prophylactic cotrimoxazole, antimycotic, and antiviral therapy for ongoing viral infections, and intravenous immunoglobulin G (IVI; 0.5 g/kg IV) once every 4 weeks is recommended as supportive care.

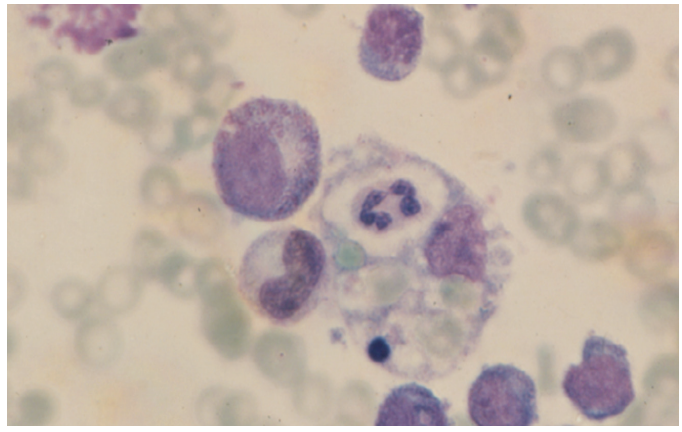

FIG. 2. Hemophagocytosis in bone marrow aspiration
(Foamy macrophage is engulfing neutrophil and precursor erythrocyte)[29-31]

Reactivation of HLH occurs in patients who have a familial form or treated by a reduced intensity regimen. Infections and vaccination can also trigger an abnormal immune response. The intensification of therapy could be restarted from week 2 in patients who received protocol less than 8 weeks and then continued with modified continuation therapy. In CNS reactivation, additional intrathecal treatments are recommended.[106,107] Despite these treatments, 20% of cases are unresponsive and are grouped as refractory. Different salvage treatments are mentioned in the literature in the form of single case reports. There are cases treated with anti-thymocyte globulin, alemtuzumab (Campath), daclizumab (Zenapax), ruxolitinib, and anakinra.[107-111] HSCT has high priority in reactivation cases rather than as salvage treatment.[112]

Allogeneic HSCT is the only definitive therapy for HLH. The long-term survival rate is 50-70%, depending on the donor type and intensity of the conditioning regimen.[113-115] The HLH 2004 study is the largest prospective study on HSCT in primary/secondary HLH, including 187 children aged <18 years who fulfilled the study inclusion criteria and underwent 209 transplants from 2004 to 2011. They have familial/genetic, relapsing, or severe/persistent disease. After HSCT, the 5-year overall survival (OS) and event-free survival (EFS) were 66% and 60%, respectively. The 5-year OS was 81% in children with a complete response and 59% (95% CI, 48-69) in those with a partial response. For children with genetically verified FHL, the 5-year OS and EFS rates were higher than those without verified FHL because the age of patients at the beginning of HLH-2004 treatment was significantly higher in children without verified FHL and their median time to HSCT was significantly longer.[116] Prolonged disease activity increases the risk of irreversible CNS damage and affects the success of HSCT. The 5-year OS of children with complete remission (using the criteria of ferritin cutoff of 500 mg/L) at HSCT conditioning was better (81%) than of those with partial response (59%; $p = 0.035$)

Although fludarabine-based reduced intensity conditioning regimen is reported to have less transplant-related mortality (TRM) than busulfan-based regimen, mixed chimerism, secondary graft failure, relapse rates are more frequently seen in fludarabine-based regimen.[117-120] This regimen is the most appropriate treatment with a low incidence of TRM. Mixed chimerism is not a serious problem because stable chimerism with 10-20% of donor cells may be enough for being asymptomatic.[121]

NK cell activity can transiently decline in active secondary HLH (sHLH). Cytotoxic function (CD107a mobilization, perforin expression, and SAP/XIAP expression) should be investigated before transplantation to identify subclinical cases and avoid unnecessary HSCT and its serious side effects.[122-124]

Monoclonal CD20 antibody (rituximab) can be a treatment for in HLH with high EBV load. In the retrospective study of Chellapandian et al.[125], 42 patients had a median decrease of EBV load by 2-3 logs and a reduction of ferritin after rituximab treatment. Etoposide is an effective cytotoxic drug in EBV-related HLH. It inhibits the synthesis of EBV nuclear antigen and clonal expansion of EBV-infected T-cells. Virus-infected immune cells are also eradicated by rituximab. This prolonged immunosuppressive treatment can activate the primary or a new triggering agent. However, pathogen-directed therapy is usually not sufficient to control hyperinflammation, except amphotericin B that is used effectively in leishmaniasis.[3,126] Thus, therapeutic agents must be selected rationally, and treatment modalities should proceed together.

In malignancy-related HLH, our first recommendation is to start chemotherapy rapidly. However, if pancytopenia and multiorgan failure are severe, adding dexamethasone to the treatment would be appropriate. Steroids are the mainstay of treatment in HLH and support the recovery of the bone marrow. IVIG can be also applied in cases with signs of infection. It would be appropriate to apply the HLH 2004 scheme in cases where there is no clinical response despite this treatment. If clinical and laboratory findings (pancytopenia, coagulopathy, organ failure, and neurological findings) regress after 4 weeks of treatment, it can be continued with only planned chemotherapy. However, since NK and T-cell functions are impaired in these patients, the presence of infection and chemotherapy response should be followed carefully, and HLH recurrence should be kept in mind when an unexpected finding is present.[48]

In MAS HLH (e.g., reactivating autoimmune/autoinflammatory diseases), pulse steroids with or without CSA therapy is effective in most patients. Recently, anticytokine treatment is used with marked clinical efficacy.[127]

Emapalumab is an anti-IFN-γ human immunoglobulin that is approved in November 2018 for familial, refractory, and recurrent HLH. Before the initiation of therapy, latent tuberculosis infection must be investigated with an IFN-γ release assay or purified protein derivative placement. During the treatment, prophylaxis for herpes zoster and *Pneumocystis jirovecii* should be started.[128,129] While emapalumab reduces hyperinflammation by suppressing IFN-γ, other cytokines become active. Etoposide and dexamethasone eliminate activated APC and CD8+ T-cells; thus, proinflammatory cytokines are reduced at their source. For this reason, combination therapy with emapalumab became more effective in the treatment of HLH. This agent is very efficacious in adults with sHLH. In pediatric patients, emapalumab is generally used as a bridging therapy to HSCT. Nevertheless, further studies are required to verify that it can result in complete remission without HSCT.[128,129]

HLH should be considered in the differential diagnosis of children with persistent fever, liver-spleen enlargement, pancytopenia, clinically severe or devastating infections, malignancy or rheumatological cases, which are resistant to therapies, and family history of sibling death and consanguineous marriage. For differential diagnosis, laboratory tests (especially fibrinogen, ferritin, and triglyceride) and bone marrow and organ biopsies should be planned if necessary. All infections should be investigated as a triggering factor. Delayed diagnosis adversely affects the course and prognosis of the disease.

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