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ORIGINAL ARTICLE

Causes, clinical symptoms, and outcomes of infectious diseases associated with hemophagocytic lymphohistiocytosis in Taiwanese adults

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Outcome

Background: Hemophagocytic lymphohistiocytosis (HLH) is an uncommon but a potentially life-threatening condition. Few systematic reviews have been published on the clinical manifestations, causes, and indicators for prognosis of HLH caused by infections.
Methods: We retrospectively reviewed the medical records of patients diagnosed with HLH documented by bone marrow study at a teaching hospital between 2000 and 2007. HLH was defined according to the HLH-2004 diagnostic guidelines, which include fever; splenomegaly; cytopenia; hypertriglyceridemia; hypofibrinogenemia; and hemophagocytosis evident on pathological examination of bone marrow, spleen, or lymph node tissue; low or absent natural killer cell activity; hyperferritinemia; and high serum levels of soluble CD25. The demographic characteristics, clinical presentations, laboratory results, and final outcomes were recorded. The cause of HLH was diagnosed by microbiological, pathological, serological, and molecular biological methods.
Results: Among the studied patients, 66 had HLH because of noninfectious causes and 30 because of infections. Compared with patients with HLH related to noninfectious causes, those with HLH related to infections had lower mortality (70% *vs.* 47%, $p = 0.03$). The most common causative pathogens causing HLH were virus (41%), mycobacteria (23%), bacteria (23%), and fungi (13%), in that order of frequency. Clinical presentations of HLH were variable and included fever (90%), tachypnea (83%), tachycardia (80%), hepatosplenomegaly (40%), lymphadenopathy (27%), and altered consciousness (23%). Laboratory findings revealed thrombocytopenia in 93%, hyperferritinemia in 90%, elevated serum lactate dehydrogenase levels in

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80%, anemia in 67%, and leukopenia in 60% of the patients. Fourteen patients (47%) died. In multivariate analysis, age more than 50 years ($p = 0.05$; odds ratio [OR], 3.46; 95% confidence interval [CI], 1.00–15.73), fever not subsiding within 3 days of diagnosing HLH ($p = 0.003$; OR, 2.38; 95% CI, 1.21–11.25), and occurrence of disseminated intravascular coagulation as a complication ($p = 0.009$; OR, 3.22; 95% CI, 1.68–10.01) were found to be statistically significant indicators of mortality in patients with HLH.

Conclusions: The infectious diseases associated with HLH were diverse and resulted in a high mortality rate. Cases in which the patients were aged more than 50 years, developed DIC, and had persistent fever even after 3 days of being diagnosed with HLH showed poor prognosis.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an important hematological presentation of various diseases. The incidence of HLH in bone marrow studies of critically ill patients with cytopenia was 0.8%–4%.[1] Hemophagocytosis can be classified into familial and secondary or acquired types.[2] Familial HLH (FHLH) is associated with a group of inherited immunodeficiencies, including autosomal recessive inherited Chediak-Higashi syndrome and Griselli syndrome, as well as the X-linked proliferative syndrome. Virus infection is usually the most common factor triggering FHLH. The causes of secondary hemophagocytosis include malignancies, autoimmune diseases, and infections.[2] Sometimes, infection may concurrently be associated with malignancy in patients presenting with HLH.[3]

HLH is pathologically characterized by a defect in the cytotoxicity of natural killer (NK) cells or cytotoxic T cells and overactivation of macrophages, leading to the engulfment of other blood cells, including erythrocytes, platelets, leukocytes, and other precursor cells. The pathogenesis of secondary HLH is not well understood but is believed to involve dysfunction of NK-T cells and cytolytic T cells and regulation of macrophages.[1,4] This dysfunctional immune system is activated by various factors, such as malignancies and infections, which in turn trigger a cytokine storm.

Common pathogens reported to cause HLH include Epstein-Barr virus (EBV),[3,5] cytomegalovirus,[6] human immunodeficiency virus (HIV),[7,8] hepatitis A virus,[9,10] bacteria,[11] parasites,[12] mycobacterium,[13–15] and fungus.[16] Furthermore, reports have been published on HLH caused by malignancy, especially leukemia or lymphoma,[6,17,18] and autoimmune diseases, such as systemic lupus erythematosus (SLE).

In this study, we aim to investigate the clinical characteristics, treatment, and outcome of patients with HLH because of infections and analyze the indicators associated with mortality.

Patients and methods

Patients

We enrolled adult patients (≥16 years) who had hemophagocytosis proved by bone marrow biopsy/aspiration at the National Taiwan University Hospital between January 1, 2000 and December 31, 2007 (Fig.). Patients were diagnosed with HLH if they satisfied at least five of the following eight criteria of HLH-2004 diagnostic guidelines[19]: (1) fever with temperature ≥38°C; (2) splenomegaly; (3) cytopenia affecting at least two of three lineages of cells in the peripheral blood (red blood cells, i.e. hemoglobin level of <9 mg/dL; platelet count of <100,000/μL; neutrophils of <1,000/μL); (4) hypertriglyceridemia (fasting serum triglyceride level of ≥265 mg/dL) and/or hypofibrinogenemia (fibrinogen ≤1.5 g/L); (5) pathological evidence in samples of the bone marrow, spleen, or lymph nodes; (6) low or absent NK-cell activity; (7) hyperferritinemia (ferritin level of ≥500 mg/L); and (8) high levels of soluble CD25 (≥2,400 U/mL).

The clinical data of patients, including age, sex, presence or absence of underlying systemic illness, dates of hospitalization and intensive care unit admission, sites of infection, diagnosis of causes, invasive procedures, antibiotic use, physical findings, results of blood biochemical tests, and duration of hospitalization were recorded from the medical records by using a standardized data collection format.

For patients with underlying autoimmune diseases, the symptoms, signs, or laboratory results were recorded to exclude the possibility of HLH being related to autoimmune activity. We enrolled only patients who were followed up regularly and had no symptoms or signs or laboratory tests indicating flare of autoimmune diseases during hospital admission. Patients with a history of autoimmune diseases or active flare-up of autoimmune activity were excluded.

Diagnosis of infectious diseases

The infections were diagnosed on the basis of microbiological, pathological, serological, or molecular biological methods. HLH because of *Mycobacterium tuberculosis* infection was defined by (1) positive results of culture of sputum, blood, bone marrow, or ascitic fluid or (2) positive results of the sputum acid-fast stain but negative results of culture and response to antituberculosis treatment. Patients with bacterial or fungal infection were defined as those having clinical symptoms or signs of infections and who showed bacteria or fungi in clinical specimens obtained from sterile sites (such as blood, ascitic fluid, pleural effusion, cerebrospinal fluid, and joint effusion); pus, tissue, or fluid obtained during surgery or needle aspiration; or serological tests (cryptococcal antigen). HLH related to cytomegalovirus or EBV infection were confirmed

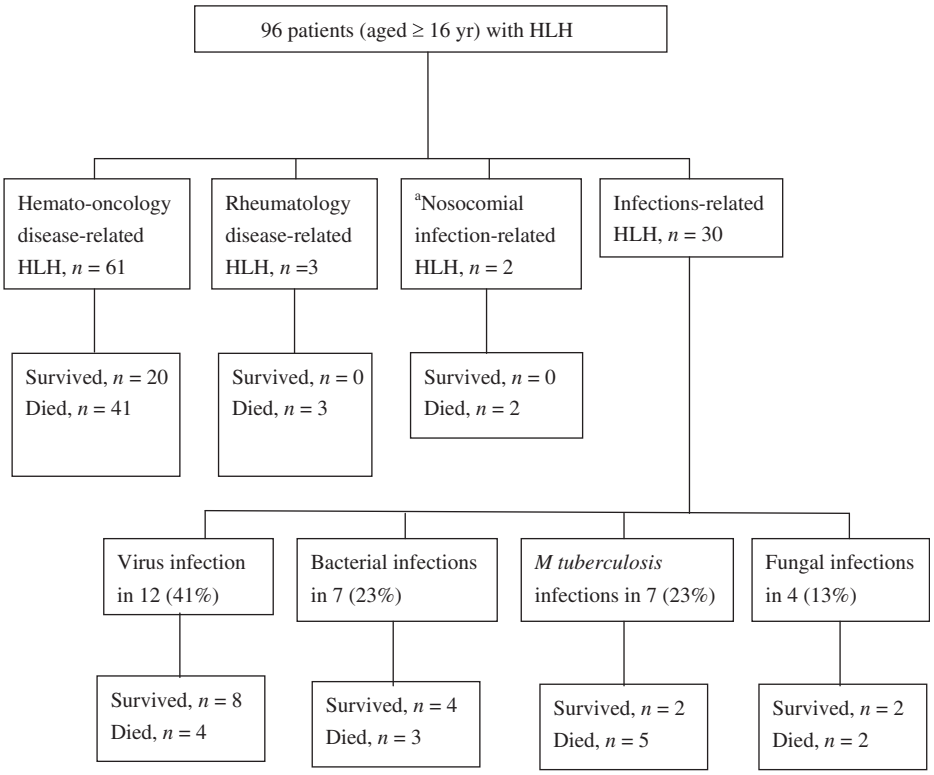

Figure 1. Patient flow chart in this study. [a]Nosocomial infections related to HLH included *Burkholderia cepacia* ($n = 1$) and *Acinetobacter baumannii* ($n = 1$).

by abnormal measurements of the antibody titer, which included elevation of serum IgG level to more than 4-fold in sequential tests, presence of serum IgM, and high titer of IgG ($\geq$1:2,560), high titer of serum viral load ($\geq 10^4$ copies/μL), or positive results of polymerase chain reaction of cerebrospinal fluid with encephalitis. Patients with clinical manifestations suggestive of viral infection and lymph node/tissue histopathological findings suggestive of viral infection were defined as having unknown viral infection. For cases in which more than two pathogens were identified as causing HLH, the classification of pathogens depended on the treatment response and the clinical courses.

Mortality was defined as death that occurred within 30 days of diagnosing infection, and death associated with infection during the same period of hospitalization was included as a case of mortality.

Statistical analysis

All statistical analyses were performed using the SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using the χ^2 or Fisher's exact test, whereas noncategorical variables were compared using Wilcoxon's rank-sum test. Variables in the univariate analysis with a p value less than 0.2 were considered in multivariate analysis by using the multiple logistic regression method to determine the independent variables that were associated with mortality. All tests were two-tailed, and a p value less than 0.05 was considered significant.

Results

In this study, we studied the records of 99 patients diagnosed with hemophagocytosis, which was confirmed by bone marrow aspiration study. A total of 96 patients met the HLH-2004 diagnostic criteria, including 30 patients with HLH related to infectious disease and 66 patients with HLH related to noninfectious diseases (61 with hematologic malignancies) (Fig. 1). The demographic characteristics of patients with infection-related HLH are shown in Table 1. They included 24 males (80%) and 6 females (20%), and 15 of these patients (50%) were aged more than 50 years. The underlying diseases diagnosed before admission included cardiovascular disease (eight patients), diabetes mellitus (six patients), and autoimmune disease (five patients). The latter included one patient each with adult-onset Still's disease, SLE, livedoid vasculitis, Sjogren's syndrome, and psoriasis.

The initial presentations and physical findings of the patients included fever (27, 90%), tachypnea (25, 83%), tachycardia (24, 80%), altered mental status (7, 23%), lymphadenopathy (8, 27%), hepatosplenomegaly (12, 40%), diarrhea (6, 20%), jaundice (6, 20%), and skin rashes (4, 13%). Twelve of the 30 patients (40%) with infection-related HLH presented with fever of unknown origin. The median duration from symptom onset to diagnosis of HLH was 34.5 days (range, 13–249 days). The laboratory tests showed leukopenia in 18 (60%) patients, with 9 of them developing neutropenia (absolute neutrophil count $< 500/\mu$L); anemia in 20 (67%) patients; thrombocytopenia in 28 (93%)

Table 1 Demographic characteristics, clinical manifestations, laboratory results, and clinical outcomes of 30 patients with infectious diseases associated with hemophagocystic lymphohistiocytosis

Characteristics	Overall ($n = 30$)	Patients died ($n = 14$)	Patients survived ($n = 16$)	p
Age, yr (mean, range)	52.4, 17–86	59.1, 23–86	44.4, 17–80	0.06
Age ≥50 yr	17 (57)	12 (86)	5 (31)	0.03
Gender, male, *n* (%)	24 (60)	10 (71)	14 (88)	0.5
Underlying diseases, *n* (%)				
Diabetes mellitus	6 (20)	3 (21)	3 (19)	>0.99
Cardiovascular diseases	8 (27)	5 (36)	3 (19)	0.53
Malignancy	2 (7)	2 (14)	0 (0)	0.65
Chronic obstructive pulmonary diseases	1 (3)	1 (7)	0 (0)	>0.99
Chronic kidney diseases	2 (7)	2 (14)	0 (0)	0.65
Cirrhosis of liver	2 (7)	1 (7)	1 (6)	>0.99
Autoimmune diseases	5 (17)	2 (14)	3 (19)	>0.99
HIV infection	2 (7)	0 (0)	2 (13)	>0.99
Initial presentations, *n* (%)				
Fever (>38°C)	27 (90)	13 (93)	14 (88)	>0.99
FUO[a]	12 (40)	8 (57)	4 (25)	0.07
Tachycardia (>100 beats/min)	24 (80)	12 (86)	12 (75)	0.4
Tachypnea (>20 cycles/min)	25 (83)	14 (100)	11 (69)	0.12
Altered mental status	7 (23)	2 (14)	5 (31)	0.51
Lymphadenopathy	8 (27)	3 (21)	5 (31)	0.85
Hepatosplenomegaly	12 (40)	5 (36)	7 (44)	0.7
Diarrhea	6 (20)	5 (36)	1 (6)	0.06
Skin rashes	4 (13)	1 (7)	3 (19)	0.71
Jaundice	6 (20)	2 (14)	4 (25)	0.79
Laboratory results, *n* (%)				
WBC (<4,000/μL)	18 (60)	7 (50)	11(69)	0.3
Neutropenia[b]	9 (30)	4 (29)	5 (31)	0.8
Hb (<9 g/dL)	20 (67)	10 (71)	10 (63)	0.9
Platelet count (<100,000/μL)	28 (93)	14 (100)	14 (88)	0.82
Platelet count (<50,000/μL)	23 (77)	13 (93)	10 (63)	0.12
Triglyceride (≥265 mg/dL)	9 (30)	2 (14)	7 (44)	0.17
LDH (≥1,000 U/L)	24 (80)	11 (79)	13 (81)	>0.99
Ferritin (>500 ng/mL)	27 (90)	13 (93)	14 (88)	>0.99
Ferritin (>10,000 ng/mL)	13 (30)	11 (79)	4 (25)	0.52
ALT (≥80 U/L)	19 (63)	8 (57)	11 (69)	0.51
ALP (≥400 U/L)	15 (50)	8 (57)	7 (44)	0.46
Infection type, *n* (%)				
Lymphadenitis	3 (10)	2 (14)	1 (6)	0.90
Pneumonia	7 (23)	4 (29)	3 (19)	0.84
Intraabdominal infection	2 (7)	0 (0)	2 (13)	0.95
Urinary tract infection	1 (3)	1 (7)	0 (0)	>0.99
Meningitis	1 (3)	1 (7)	0 (0)	>0.99
Systemic viral infection[c]	5 (17)	1 (7)	4 (25)	0.4
Organism from blood cultures	12 (40)	6 (43)	6 (38)	>0.99
Treatment, *n* (%)				
IVIG use	13 (30)	5 (36)	8 (50)	0.43
Immune modulator use[d]	17 (57)	7 (50)	10 (63)	0.5
Clinical course				
Became stable[e] ≤7 d	9 (30)	1 (7)	8 (50)	0.03
Fever subsided ≤3 d	11 (37)	2 (14)	9 (56)	0.02
DIC	11 (37)	9 (64)	2 (13)	0.003

[a] FUO: fever persisting for more than 14 days after visiting twice for medical help.
[b] Neutropenia, absolute neutrophil count less than 500/μL.
[c] Systemic viral infections include HIV ($n = 2$), Epstein-Barr virus ($n = 1$), and cytomegalovirus ($n = 2$) infection.
[d] Immune modulator use includes use of corticosteroid, IVIG, and chemotherapy agents, such as etoposide (VP-16).
[e] Stable condition was defined as vital signs (body temperature, pulse rate, and respiratory rate) being within the normal range.

ALP = alkaline phosphatase; ALT = alanine transaminase; DIC = disseminated intravascular coagulation; FUO = fever of unknown origin; Hb = hemoglobin; HIV = Human immunodeficiency virus infection; IVIG = intravenous immunoglobulin; LDH = lactate dehydrogenase; WBC = white blood cell count.

patients; elevation of serum alkaline phosphatase level to more than twice the upper limit of the normal range in 15 (50%) patients; elevation of serum lactate dehydrogenase level in 24 (80%) patients; hypertriglyceridemia in 9 (30%) patients; and elevation of serum ferritin level in 10 (33%) patients (Table 1).

The pathogens associated with HLH are shown in Table 2. The most common causes of HLH were virus infection (12 patients; 41%), bacterial infections (7 patients; 23%), *M tuberculosis* infections (7 patients; 23%), and fungal infections (4 patients; 13%), in that order of frequency. The most common identified viral pathogen was EBV ($n = 2$). Six patients had pathological findings and clinical presentation that was indicative of viral origin. The most common fungal pathogen causing HLH was *Penicillium marneffei* ($n = 2$). There were no differences between the different causative agents of HLH in terms of the presenting symptoms, laboratory findings, and outcomes.

Of the seven patients with *M tuberculosis*-related HLH, all were male, with median age of 44 years (range, 17—86 years). *M tuberculosis* was detected from the sputum culture by bronchoscopic examination ($n = 2$), or blood ($n = 3$), or bone marrow culture ($n = 2$). All patients with *M tuberculosis*- and fungi-related HLH had chronic systemic diseases, such as chronic hepatitis B, chronic hepatitis C ($n = 3$), alcoholic liver cirrhosis ($n = 2$), diabetes ($n = 2$), HIV infection ($n = 2$), SLE ($n = 1$), and end-stage renal disease because of bladder transitional cell carcinoma ($n = 1$). *M tuberculosis*-related HLH seemed to be associated with higher mortality rate (71% *vs.* 39%, $p = 0.14$) and longer duration of symptoms (more than 2 weeks) before diagnosis (67% *vs.* 48%, $p = 0.46$) than HLH caused by other infections. However, because the number of cases was small, the difference was not statistically significant. None of the seven patients with *M tuberculosis*-related HLH had respiratory symptoms or showed pulmonary infiltrations on chest radiographs. Three of these seven patients were diagnosed with disseminated intravascular coagulation because of *M tuberculosis* infection at the initial presentation.[20] Five out of the seven patients (71%) with *M tuberculosis*-related HLH died. Only three of the five patients received antituberculosis therapy before their death.

Table 2 Causative pathogens of hemophagocytic lymphohistiocytosis related to infectious disease

Causative pathogen	*n* (%)
Mycobacterium tuberculosis	7 (23)
Bacteria	7 (23)
Staphylococcus aureus	2 (7)
Klebsiella pneumoniae	2 (7)
Nontyphoid *Salmonella*	1 (3)
Aeromonas hydrophila	1 (3)
Escherichia coli	1 (3)
Fungi	4 (13)
Candida albicans	1 (3)
Penicillium marneffei	2 (7)
Cryptococcus neoformans	1 (3)
Virus	12 (41)
Hepatitis A virus	1 (3)
Human immunodeficiency virus[a]	2 (7)
Cytomegalovirus	1 (3)
Epstein-Barr virus	2 (7)
Suspect viral origin	6 (21)

[a] Both patients had primary human immunodeficiency virus infections.

The overall mortality rate of all-cause HLH was 63% (60 of 96 patients). Compared with patients with HLH because of noninfectious causes, those with HLH because of infections had lower mortality (70% *vs.* 47%, $p = 0.03$). The overall mortality of infection-related HLH was 47% (14 patients). Of the 14 patients who died, 3 received appropriate pathogen-specific therapy in the first week. In multivariate analysis, age more than 50 years [$p = 0.05$; odds ratio (OR), 3.46; 95% confidence interval (CI), 1.00—15.73], fever not subsiding within 3 days of diagnosing HLH ($p = 0.03$; OR, 2.38; 95% CI, 1.21—11.25), and occurrence of disseminated intravascular coagulation (DIC) as a complication ($p = 0.009$; OR, 3.22; 95% CI, 1.68—10.01) were significant factors associated with mortality (Table 3).

Previous reports have described three cases of HLH because of *M tuberculosis* infection; two of these were caused by HIV infection and one was caused by hepatitis A infection.[7,10,20]

Discussion

In this study, we showed that the infections causing HLH are diverse and have high mortality in adult Taiwanese patients. Patients with HLH because of infections had lower mortality than those who had HLH because of noninfectious causes (HLH in most such cases was caused by hematologic malignancies). Thorough investigations, including molecular biological, microbiological, pathological, and serological examinations, are recommended for the identification and early treatment of the cause of HLH. Patients aged more than 50 years, fever not subsiding within 3 days of diagnosing HLH, and occurrence of DIC have a high risk for mortality.

The infection-related HLH mortality rate in this study was 47%. In previous studies on patients with HLH because of various causes,[11,18—24] the overall mortality rates ranged between 30% and 80%. The comparison between studies is difficult because of differences in the study population (some studies are on children, whereas others are on adults); underlying diseases with autoimmune conditions,[25] malignancy, or lymphoma[11,18,24]; the diagnostic tools used; and the possibility of the initial bone marrow study being negative.[2,26] Compatible with other studies,[11,18—24] our results also show a high mortality rate associated with infection-related HLH.

The causes of infection-related HLH are diverse.[18,25] Bacterial, virus, or fungal infection could all be involved in the pathogenesis of HLH. In this study, *M tuberculosis* as well as other pathogens (*Staphylococcus aureus, Klebsiella pneumoniae*, *Penicillium marneffei*, and *Candida albicans*), were the common causes of infection-related HLH in adult patients. Although previous studies have reported that EBV infection is the most common cause of HLH,[2,5,19] it was diagnosed only in a few cases in our study, which may be attributed to the fact that most patients with EBV

Table 3 Multivariate analysis of factors associated with 30-day mortality in 30 patients with hemophagocytic lymphohistiocytosis

Factors	Patients died ($n = 14$)	Patients survived ($n = 16$)	Odds ratio (95% confidence interval)	p
Age $\geq$50 yr, *n* (%)				
Yes	12 (86)	5 (31)	3.46 (1.00–15.73)	0.05
No	2 (14)	11 (69)		
Defervescence $\leq$3 d after diagnosis, *n* (%)				
Yes	2 (14)	9 (56)	2.38 (1.21–11.25)	0.03
No	12 (86)	7 (44)		
Onset of DIC, *n* (%)				
Yes	9 (64)	2 (13)	3.22 (1.68–10.01)	0.009
No	5 (36)	14 (87)		

DIC = disseminated intravascular coagulation.

infection tended to be younger and we excluded this section of the population in this study. All patients with *M tuberculosis*- and fungi-related HLH were immunocompromised because of factors, such as diabetes, chronic liver and renal disease, HIV infection, or immunosuppresion therapy. In this study, we also noted that patients with *M tuberculosis*-related HLH who did not have the typical symptoms and signs of pulmonary infection were generally diagnosed late and received late treatment. Detailed investigations for detection of possible antimicrobial treatable diseases and administration of appropriate treatment might improve the prognosis of HLH.

Treatments of HLH include therapy targeted at the cause of HLH and immune modulators for cytokine storm, such as intravenous immunoglobulin, etoposide, dexamethasone, and cyclosporine A.[1,9,19] The HLH-2004 diagnostic and therapeutic guidelines suggest treatment of HLH with a combination of dexamethasone, etoposide, and cyclosporine A for 8 weeks. However, most evidence-based treatments for HLH have primarily been proposed for the treatment of FHLH. In some studies, treatment of the underlying disease has been suggested as the most efficient way to treat secondary hemophagocytosis.[16,26] There were no significant differences in the mortality rates between patients receiving immune modulators and those not receiving them. However, we examined only a few cases in this study and the patients usually received immune modulator treatment at the time of clinical progression of disease or at a late stage of the disease. It remains to be determined whether the routine use of immune modulators or not (cost benefits) or when to use it still remained debated.

Previous studies have reported the following as factors associated with mortality because of HLH: underlying diseases, old age, use of immunosuppressive agents, and laboratory findings (thrombocytopenia, anemia, DIC, and high serum ferritin level).[18,23–25] In our study, the factors associated with poor prognosis of infection-related HLH were age more than 50 years old, development of DIC, and fever not subsiding even 3 days after HLH was diagnosed. Patients with these factors should undergo extensive investigations and should be treated with both antimicrobial agents and immune modulators to improve the clinical outcome.

The most important limitations of our study are the small sample size and the retrospective nature of the study, which relied on the accurate and complete recording of many items, such as initial presentation and laboratory data. Furthermore, the results of the diagnostic tests performed to identify the pathogen may be influenced by the method used.

In conclusion, infectious diseases associated with HLH were diverse and resulted in a high mortality rate. Cases in which patients were elderly, developed DIC, and had persistent fever should be thoroughly investigated to identify the cause of HLH; treatment should be aimed at eliminating the causative agent and provide intensive supportive measures to improve the outcomes.

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