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A Clinical Analysis of 52 Adult Patients With Hemophagocytic Syndrome: The Prognostic Significance of the Underlying Diseases

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Abstract

We retrospectively analyzed 52 adult patients with hemophagocytic syndrome (HPS). The underlying diseases were heterogeneous, including malignant lymphoma (lymphoma-associated hemophagocytic syndrome [LAHS]) in 26 patients, systemic lupus erythematosus in 3 patients, viral infections in 7 patients, and bacterial or fungal infections in 6 patients. More than 83% of patients received prednisolone as an initial treatment. Multiple-agent chemotherapies (cyclophosphamide, doxorubicin, and vincristine) were administered to 96% of LAHS patients after a histopathological diagnosis of lymphoma. HPSs were controllable and remissions were achieved except for those patients with LAHS, fulminant Epstein-Barr virus–associated HPS, and an immunosuppressive state. Twenty-one (81%) of the LAHS patients had uncontrollable HPS and died of multiple organ failure and disseminated intravascular coagulation. The median survival time of LAHS patients was 83 days. In contrast, 3 (12%) of the other HPS patients died of multiple organ failure within 44 days. The clinical manifestations and the laboratory findings of LAHS and the other HPSs were too variable to establish the prognosis based only on the findings at the onset of HPS. The prognostic factors of adult HPS were found to be the underlying diseases, notably malignant lymphoma and infections, accompanied by the immunosuppressive state. *Int J Hematol.* 2001;74:209-213.

Key words: Hemophagocytic syndrome; Underlying disease; Therapy; Prognosis

1. Introduction

Hemophagocytic syndrome (HPS) is a clinicopathological entity characterized by histiocytic proliferation with marked hemophagocytosis in bone marrow. Clinical features of HPS comprise high-grade fever, cytopenias, liver dysfunction, and coagulopathy. Patients with HPS often undergo an aggressive clinical course resulting in a poor prognosis [1]. Adult HPS is caused by various diseases [2,3], eg, viral infections (virus-associated hemophagocytic syndrome [VAHS]) [4]; bacterial infections (bacteria-associated hemophagocytic syndrome [BAHS]) [5], including tuberculosis [6]; fungal infections [7]; autoimmune disorders (autoimmune-associated hemophagocytic syndrome [AAHS]) [8,9]; and malignant lymphoma. Among this wide range of clinical diseases causing HPS, malignant lymphoma is one of the most frequently occurring [10,11]. We previously reported the clinical features and pathophysiological findings of lymphoma-associated hemophagocytic syndrome (LAHS). We found that the overall survival rate of LAHS was low and that the patients died within several months unless they received chemotherapy [12,13]. Although the prognosis of VAHS was originally described as poor by Risdall et al [4], this prognostication has become a controversial issue in more recent studies [2,14]. Some patients with VAHS survive without any treatment. Moreover, despite the underlying disorders of HPS being variable [1], the differences in the clinical characteristics between LAHS and the other types of adult HPS have not been studied extensively.

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Table 1.
Classification of Hemophagocytic Syndrome in Adults

Underlying Disease	No. of Cases
Lymphoma-associated hemophagocytic syndrome (LAHS)	
T/natural killer lymphoma	12
B lymphoma	12
T/B unknown	2
Virus-associated hemophagocytic syndrome (VAHS)	
Epstein-Barr virus	4
Measles	1
Parainfluenza	1
Hepatitis A	1
Not identified	10
Bacteria-associated hemophagocytic syndrome (BAHS) and fungal infections	
Mycobacterium tuberculosis infection	2
Staphylococcus aureus infection	1
Pseudomonas aeruginosa infection	1
Corynebacteria infection	1
Candida albicans infection	1
Autoimmune-associated hemophagocytic syndrome (AAHS)	
Systemic lupus erythematosus	3

In the present study, we examined the clinical features and outcomes of 52 adult patients with HPS.

2. Materials and Methods

We retrospectively analyzed adult patients older than 15 years with hemophagocytosis in bone marrow smears between January 1990 and October 2000 in Akita University Hospital and affiliated hospitals. For making the diagnosis of HPS, we applied the following criteria proposed by Tsuda [2]: (1) High fever for more than a week, (2) unexplained progressive cytopenia affecting at least 2 cell lineages, and (3) bone marrow showing mature histiocytes ≥3% or 2500 cells/mL with prominent hemophagocytosis and/or hemophagocytosis in the liver, spleen, or lymph nodes. According to these criteria, 52 cases were diagnosed as HPS. To make a diagnosis of the underlying disease, the following examinations were performed: biopsies of organs, cultures from body fluids or organs, measurements of autoantibody titers, and measurements of antibody titers for Epstein-Barr virus (EBV) and cytomegalovirus. Paraffin sections from lymphoma tissues were immunostained with 2 monoclonal antibodies, UCHL-1 (T-cell marker) and L26 (B-cell marker) (Dako, Glostrup, Denmark). The laboratory findings were analyzed by Student *t* test, chi-square test, or Fisher's test, and survival curves were made using Kaplan-Meier's method and evaluated by the Log rank test.

3. Results

3.1. Underlying Diseases

The details of the underlying diseases of HPS are listed in Table 1. Among 52 patients with HPS, 26 patients (50%) had LAHS. Among the other 26 patients, 13 patients had documented infections. Neither underlying infection nor neoplasm could be identified in the other 13 patients. Although antibodies against viral antigens were not detected, 10 of the 13 patients were also presumed to have VAHS because they did not have autoimmune disease and showed an improvement in their clinical symptoms with steroid therapy. In the other 3 patients, the underlying disease was diagnosed as active systemic lupus erythematosis (SLE) according to the criteria of the American Rheumatism Association, and 2 of the 3 SLE patients received steroids. Prior immunosuppressive states were present in the following 4 patients: irradiation for laryngeal cancer (1 patient), a cytostatic drug (5-fluorouracil) for gastric cancer (1 patient), acute lymphoid leukemia (1 patient), and uncontrollable diabetes mellitus (1 patient). All 4 of these cases were subsequently classified as BAHS.

3.2. Clinical Features

The median age at diagnosis of LAHS was the highest among HPS patients (Table 2). The ratio of males to females was not significantly different. High-grade fever and hepatosplenomegaly were common at the onset of HPS. However, hepatosplenomegaly was more frequent in LAHS than the other types of HPS. The differences in laboratory findings between LAHS and the other HPSs were not significant except for hemoglobin level, platelet counts, lactate dehydrogenase levels, and ferritin levels.

3.3. Therapy for HPS

All patients were treated with broad-spectrum antibiotics because of fever and leukopenia. A diagnosis of HPS was made within 2 weeks in more than 50% of the patients. More than 83% of patients were treated with prednisolone (0.5-1 mg/kg) as an initial therapy for HPS. In addition, methylprednisolone (mPSL) pulse therapy (mPSL pulse: 500-1000 mg/d for 3 days) was administered to more than 47% to 83% of patients according to the severity of the initial symptoms of HPS. Twenty-one patients (40%) were administered γ-globulin (5 g/d for 2-3 days). Only 1 patient with LAHS was administered high-dose γ-globulin (10-20 g/d for 5 days). Cyclosporin A was also administered to 2 LAHS patients. Multiple-agent chemotherapy, including cyclophosphamide, doxorubicin, vincristine, and prednisolone, was administered to the LAHS patients. One LAHS patient did not receive chemotherapy because her illness was too severe to allow a diagnostic procedure for LAHS before an autopsy. However, 3 patients whose disease was classified as VAHS had received vincristine a few times before their condition had improved.

3.4. Clinical Outcomes

Twenty-three patients (88%) with LAHS died of multiple organ failure and disseminated intravascular coagulation combined with uncontrollable HPS. The ratio of immunophenotypes among the 23 patients with LAHS was not significantly different (B-LAHS, 10/12 patients; T/natural killer [NK]-LAHS, 11/12 patients; others, 2/2 patients). However, 3 non-LAHS patients (12%) died of multiple organ failure. In the other patients, HPSs were treated successfully and these

Table 2.
Patient Characteristics*

	LAHS (n = 26)	VAHS (n = 17)	BAHS (n = 6)	AAHS (n = 3)	*P*†
Age, y, median (range)	68.5[a,b] (17-82)	48.0[a] (18-66)	66 (39-71)	33.0[b] (19-64)	<.05[a,b]
Men/women, n	17/9	6/11	4/2	2/1	NS
Clinical manifestations at onset of HPS					
Fever	100	100	100	100	
Hepatomegaly	88[a,b]	59[a]	33[b]	67	<.05[a,b]
Splenomegaly	77[a]	65	33[a]	100	<.05[a]
Jaundice	35	13	33	0	NS
Skin rash	15	24	17	33	NS
Laboratory findings at the onset of HPS					
WBC, median, /μL	1750	2700	2085	1900	NS
WBC, range, /μL	0-64,100	1300-15,500	700-7200	1390-1900	
Neutrophils < 1000/μL	62	35	33	33	NS
Hb, median, g/dL	8.4[a]	11.2[a]	9.9	10.1	<.05[a]
Hb, range, g/dL	6.3-12.2	5.5-17.7	6.7-14.0	9.4-11.3	
Hb < 10 g/dL	77[a]	29[a]	50	33	<.01[a]
Plt, median, $\times 10^5$/mL	3.6	5	3	6.1	NS
Plt, range, $\times 10^5$/mL	0.4-10.5	0.7-16.8	0.4-22.7	6.0-25.7	
Plt < 10^5/mL	100[a,b]	88	83[a]	66[b]	<.05,[a] <.001[b]
LDH‡, median × upper limit	3.8	2.71	1.75	2.86	NS
LDH‡, range × upper limit	0.4-34.5	0.6-11.9	0.8-5.8	1.9-4.9	
LDH > 2× upper limit	88[a]	76	50[a]	100	<.05[a]
Ferritin, range, ng/mL	489-26,180	218-44,080	300->3000	460-34,746	
Ferritin > 1000 ng/mL	88[a]	41[a]	50	66	<.01[a]
FDP, range, μg/mL	<10-42.6	<10-203	10.9-106	10.6-223.9	
FDP > 10 μg/mL	55	43	100	100	NS
Bone marrow findings					
Cellularity, n					
Hypocellular	19	10	4	3	
Normocellular	5	7	2	0	
Hypercellular	2	0	0	0	NS
Histiocytes, median	6.0	8.4	7.1	4.0	NS
Histiocytes, range	2.6-28	2.0-23	6.8-10.2	2.0-7.4	
Duration from the onset to the diagnosis of HPS					
<3 d	8	17	0	0	
<1 wk	31	29	17	0	
<2 wk	19	29	50	67	NS
<1 mo	38	24	33	33	
≥1 mo	4	0	0	0	
Treatment for HPS					
Antibiotic drugs	100	100	100	100	NS
mPSL pulse	58	47	83	67	NS
Prednisolone	96	88	83	100	NS
γ-Globulin (2.5 g for a few days)	27[a]	59[a]	50	67	<.05[a]
High-dose γ-globulin	4	0	0	0	NS
G-CSF	27[a]	0[a]	17	33	<.05[a]
Plasma exchange	4	0	0	0	NS
Cyclosporin A	8	0	0	0	NS
Anticancer drugs	96[a]	18[a]	0	0	<.001[a]
Clinical outcome					
Remission	12	94	67	100	
Death	88	6	33	0	

*Values are percentages unless otherwise indicated. LAHS indicates lymphoma-associated hemophagocytic syndrome; VAHS, virus-associated HS; BAHS, bacteria-associated HS; AAHS, autoimmune-associated HS; WBC, white blood cell count; Hb, hemoglobin level; Plt, platelet count; LDH, lactate dehydrogenase level; FDP, fibrin degradation product level; mPSL, methylprednisolone; G-CSF, granulocyte colony–stimulating factor; NS, not significant.

†*P* values are for data with the same superscript letter on the same line.

‡LDH values relative to the upper limit of the normal range.

patients achieved remission. The underlying diseases of the 3 patients who had died with non-LAHS were fulminant EBV infection, laryngeal cancer, and diabetes mellitus with alcoholism.

Figure 1 shows the overall survival curves of HPS patients, determined using Kaplan-Meier's method. LAHS patients showed a lower survival rate than non-LAHS patients. The median survival time of LAHS patients was 83 days, and the

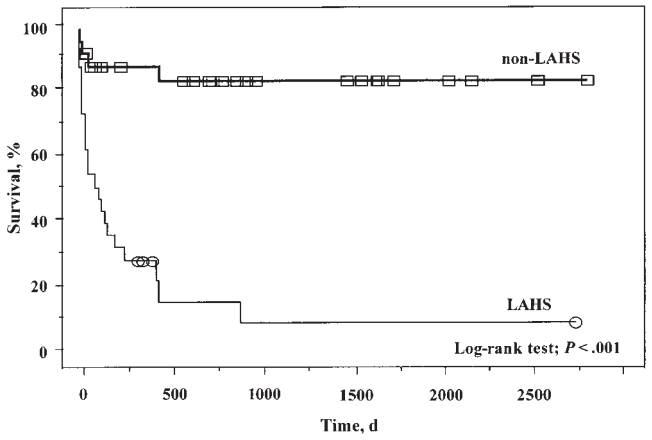

Figure 1. Overall survival (OS) curves of patients with hemophagocytic syndrome, determined using Kaplan-Meier's method. Lymphoma-associated hemophagocytic syndrome (LAHS) patients showed a lower survival rate than non-LAHS patients. The median survival time of LAHS patients was 83 days, and the OS rate showed a plateau at 8%. In contrast, the OS rate of non-LAHS patients showed a plateau at 83%. Log-rank test results showed significant differences between the 2 groups ($P < .001$).

overall survival rate showed a plateau at 8%. In contrast, the overall survival rate of non-LAHS patients showed a plateau at 83%. Log-rank test results showed significant differences between the 2 groups ($P < .001$).

4. Discussion

To the best of our knowledge, this is the largest study reporting the occurrence of adult HPS using strict diagnostic criteria. According to the latest studies, mainly from Asian countries, the incidence of LAHS is more common than that of other types of HPS [10,11]. The present retrospective observations demonstrated that half of the adult cases of HPS are associated with malignant lymphoma (26/52 cases).

In previous studies, many of the adult patients with VAHS had fulminant clinical courses and had underlying diseases resulting in immunodeficiency and/or treatment with immunosuppressive drugs [4]. In the present series, none of the patients with VAHS, including 5 with EBV-associated hemophagocytic syndrome (EBV-AHS), had any underlying diseases causing immunosuppressive states, and of these patients, all achieved remissions except for 1 patient with fulminant EBV-AHS. It follows, therefore, that VAHS could occur in healthy adults with a mild clinical course and a good outcome, even without any treatment for HPS [14].

EBV-AHS is a subtle disease with a clinical course ranging from mild/self-limiting to severe/aggressive and fatal [15]. Even a case of self-limiting infectious mononucleosis without cytopenias showed marked histiocytosis and hemophagocytosis [16]. However, the prognosis of EBV-AHS associated with the terminal phase of chronic active EBV infection is particularly poor [17,18]. EBV-AHS in children is often fatal and has a relatively high mortality rate [19]. Imashuku estimated that the mortality rate of EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH) in children was almost 41% [15]. In comparison with the disease in children, adult fulminant EBV-AHS is very rare, especially following primary EBV infection [20]. The difference in outcomes in EBV-AHS between children and adults may be explained by differences in their immunodeficiencies [21]. The good prognoses of VAHSs in this study are partly explained by the fact that only 1 patient had fulminant EBV-AHS, and patients with chronic active EBV infection were not included. Many cases, especially those in apparently immunocompetent adults, were suggested to show mild/self-limiting courses in the present study as well as in previous studies [2,14].

The past histories of all 14 patients with VAHS were not significant, whereas 4 of 6 patients with BAHS showed a prior immunosuppressive state. According to several studies, BAHS cases occasionally occur in patients with underlying diseases that cause a prior immunosuppressive state, and these cases show a severe/aggressive clinical course [5,6]. Likewise, the present study also revealed that the BAHS patients who had died of HPS had a prior immunosuppressive state.

Kaito et al analyzed 34 adult cases of HPS and proposed risk factors associated with death that were as follows: patient age older than 30 years, presence of disseminated intravascular coagulopathy, increased ferritin and β_2-microglobulin levels, and anemia accompanied by thrombocytopenia and jaundice [22]. However, Kaito et al only partly listed the underlying diseases and the relationship between prognoses and underlying diseases. Although we applied their risk factors to our patients, the outcomes did not always correspond with these factors (data not shown). The clinical manifestations and the laboratory findings were highly variable among each patient at the onset of HPS, and so we could not rely completely on these findings to establish the correct prognosis. However, these findings play an important role in indicating the severity of HPS and, therefore, assist in choosing the appropriate initial therapy.

There were no significant differences between LAHS and non-LAHS in the duration from the onset to the diagnosis of HPS or in the initial treatment. All patients received antibiotic therapy and more than 83% of patients received steroid therapy. This study showed that steroid treatment including mPSL pulse therapy was useful for an initial therapy of HPS regardless of underlying diseases, even though some previous studies concluded that steroid therapy is contraindicated in patients with an infection-associated hemophagocytic syndrome [4,23]. High-dose γ-globulin therapy [24,25], cyclosporin A supported by granulocyte colony–stimulating factor [26], and plasma exchange are useful as initial therapies for all types of HPS when the degree of HPS is severe or aggressive based on the clinical and laboratory findings at presentation. Unfortunately, however, the treatment has transient effects in LAHS.

To make a differential diagnosis of LAHS from the other types of HPS is difficult in most cases. In particular, a lack of histological proof of lymphoma delays the choice of appropriate treatments for LAHS at the initial stage [27]. Early diagnosis of aggressive or refractory cases may be supported by molecular studies of the EBV genome, T-cell–receptor

rearrangement, and immunoglobulin heavy-chain rearrangement in addition to a histopathological analysis of samples from bone marrow and/or liver biopsy [21].

Imashuku et al proposed 3 steps for an optimal treatment strategy for EBV-HLH [28]: (1) control of the cytokine storm, including coagulopathy and multiple organ failure; (2) control of opportunistic infections; and (3) eradication of clonally proliferating EBV-containing T cells or NK cells by immunochemotherapy and, if necessary, hemopoietic stem cell/bone marrow transplantation. Although this strategy was intended for children with EBV-HLH, it may also be applied to adults with HPS, including LAHS.

In conclusion, HPS is associated with heterogeneous diseases, and it was difficult to estimate the prognosis based on the clinical features and laboratory findings at the onset of HPS. A prognosis of adult HPS may be evaluated by underlying diseases, especially malignant lymphoma and infections accompanied by an immunosuppressive state.

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