Hemophagocytic Lymphohistiocytosis Associated with Histiocytic Necrotizing Lymphadenitis: A Clinical Study of 13 Children and Literature Review

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Objective To analyze the clinical characteristics and prognosis of pediatric hemophagocytic lymphohistiocytosis (HLH) associated with histiocytic necrotizing lymphadenitis (HNL).

Study design We retrospectively collected the clinical data of all children with HNL-HLH enrolled in Beijing Children's Hospital from 2007 to 2019. The control patients with Epstein-Barr virus-associated HLH and simple HNL (not associated with HLH) were case matched (1:2). The clinical features and prognosis were analyzed by case-control study. Cases of HNL-HLH in the literature were reviewed.

Results The male-to-female ratio of the 13 patients in our center was 9:4. The mean age of the patients at disease onset was 8.1 ± 1.2 years, younger than that of the 16 patients in the literature ($P = .017$). Clinical presentations, especially rash and splenomegaly, and laboratory examination of HNL-HLH group were statistically different from Epstein-Barr virus-HLH group, simple HNL group, and patients reported in the literature ($P < .05$). Three patients were treated with immunosuppressive drugs or chemotherapy owing to poor control of HLH. One patient died, and all 12 remaining patients survived, 2 of which developed autoimmune diseases. Kaplan-Meier survival curves showed no statistical difference among the 3 groups ($P > .05$).

Conclusions HNL-HLH is more common in school- and preschool-age children. Most patients have a favorable prognosis. Some patients suffer from relapses or develop autoimmune diseases. Prolonged follow-up should be carried out for patients with HNL-HLH. *(J Pediatr 2021;229:267-74)*.

Histiocytic necrotizing lymphadenitis (HNL), also known as subacute necrotizing lymphadenitis, or Kikuchi-Fujimoto disease, is a self-limited inflammatory disease of the lymph nodes with a subacute onset that is common in young women and rare in children. HNL is considered to be triggered by either viral infection or an autoimmune factor. However, the specific pathogen associated with HNL remains unknown.[1] The typical manifestations of HNL include fever, leukopenia (especially neutropenia), and lymphadenopathy. Extranodal involvement such as rash and nervous system symptoms may also be observed.[2,3] Most patients have a favorable prognosis, although some may relapse or develop autoimmune diseases. Severe HNL may be complicated by hemophagocytic lymphohistiocytosis (HLH).[4,5]

HLH, also known as hemophagocytic syndrome, is a rare life-threatening hematologic disease characterized by immune dysfunction that can occur secondary to a variety of infectious diseases, rheumatic diseases, or malignancies. The clinical manifestations of HLH may include fever, anemia, hemorrhage, hepatosplenomegaly, and others, and diagnosis is based on the HLH 2004 criteria.[6,7]

HLH secondary to HNL (HNL-HLH) is rare in children. The purpose of this study was to improve the understanding of HNL-HLH and provide evidence for its clinical diagnosis and treatment.

CNS	Central nervous system
DIC	Disseminated intravascular coagulation
HLH	Hemophagocytic lymphohistiocytosis
HNL	Histiocytic necrotizing lymphadenitis
PVB19	Parvovirus B19
SLE	Systemic lupus erythematosus

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This work was supported by The Special Fund of The Pediatric Medical Coordinated Development Center of Beijing Municipal Administration of Hospitals (No. XTZD20180202); National Natural Science Foundation of China (No. 81800189, 81700186); Beijing Municipal Administration of Hospitals' Youth Programme (QML20181205); Scientific Research Common Program of Beijing Municipal Commission of Education (No. KM201910025011); Beijing Municipal Science & Technology Commission (No. Z171100001017050); The Capital Health Development Research Special Research Key Public Relations Project (No. 2020-1-2022); National Science and Technology Key Projects (No. 2017ZX09304029004); Funding for Reform and Development of Beijing Municipal Health Commission (Genetic and immunological pathogenesis of pediatric histiocytosis and its guiding role in clinical diagnosis and treatment). The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.08.063

Methods

General Information

This study was a retrospective, single-center case-control study. Enrolled patients were treated in Beijing Children's Hospital affiliated to Capital Medical University from January 2007 to October 2019.

Inclusion Criteria

The patients with HNL-HLH (developed HLH during the course of HNL) had HNL diagnosed by lymph node biopsy; and HLH was diagnosed according to the HLH 2004 criteria and was not associated with other causes.

Control patients in the EBV-HLH group and the simple HNL group (not associated with HLH) were matched (1:2) based on the age difference between the matched patients and the patients with HNL-HLH was less than 3 years; the difference of time since diagnosis between the matched patients and the patients with HNL-HLH was less than 5 years; and the matched patients with EBV-HLH had to meet the HLH 2004 diagnostic criteria with evidence of an active EBV infection, excluding primary HLH and HLH secondary to other causes, whereas the matched patients with simple HNL had to be diagnosed by lymph node biopsy, with exclusion of other primary diseases manifesting as fever, rash, and lymphadenopathy.

Randomization

According to the matching criteria, all patients with EBV-HLH and patients with simple HNL who could be matched with the corresponding patients with HNL-HLH were selected and reordered according to patient's identification numbers from smallest to largest. Two random numbers were generated by the Randbetween function in Microsoft Office Excel software (Microsoft Corporation). The patients with EBV-HLH and patients with simple HNL corresponding with random numbers were enrolled in the control groups.

Genetic Testing

Four patients in HNL-HLH group and 8 patients in EBV-HLH group did not undergo genetic test owing to the lack of genetic detection project before 2013 in our center. Whole exome sequencing was performed in the remaining patients with HNL-HLH and EBV-HLH, but not in all patients with simple HNL.

The patients with HNL-HLH from literature also had to have HNL diagnosed by biopsy examination and HLH diagnosed according to the HLH 2004 criteria.

Literature Review

A review of the literature was performed using PubMed, Web of Science, CNKI (Chinese), and WanFang (Chinese) online databases. The literature search was performed as follows: ((((((((haemophagocytic) OR (hemophagocytic)) OR (Hemophagocytic Lymphohistiocytosis)) OR (Hemophagocytic Syndrome)) OR (Erythrophagocytic Lymphohistiocytosis)) OR (Histiocytic Reticulosis)) OR (Hemophagocytic Reticulosis)) OR (Hemophagocytic Histiocytosis)) AND (((((((Histiocytic Necrotizing Lymphadenitis) OR (Kikuchi Disease)) OR (Kikuchi Necrotizing Lymphadenitis)) OR (Nosocomial Kikuchi Disease)) OR (Kikuchi-Fujimoto Disease)) OR (Kikuchi Fujimoto Disease)) OR (Histiocytic Necrotising Lymphadenitis)).

Statistical Analyses

IBM SPSS (24.0; IBM) software was used for the statistical analysis. The count data were expressed by the number of cases or percentages, and the Fisher exact test was used for the categorical variables. The measurement data with normal distribution is expressed by the mean ± SD, and the measurement data with non-normal distribution is expressed by median (minimum-maximum). For continuous variables, data were analyzed using the *t* test and Mann-Whitney *U* test, depending on the data distribution. Survival curves were estimated using the Kaplan-Meier method, and the log-rank test was used to estimate the differences among the groups. A *P* value of less than .05 was considered statistically significant.

Results

Characteristics of the Patients with HNL-HLH in Our Center

The electronic medical records of our center were searched and yielded 13 patients with HNL-HLH (**Table I** and **Table II** [available at www.jpeds.com]). For the literature review, a total of 16 cases in 11 studies were included (**Figure 1** [available at www.jpeds.com] and **Table III**).[8-18]

General Characteristics of Patients with HNL-HLH

The male-to-female ratio of the 13 patients in our center was 9:4. The mean age of disease onset was 8.1 ± 1.2 years, and the median follow-up time was 22.2 months (IQR, 1.9-107.2 months). All of the patients were Han Chinese children. Compared with the EBV-HLH and simple HNL groups, there were no significant differences in sex or age (**Figure 2**, A and B [available at www.jpeds.com] and **Table I**).

Clinical Presentations of HNL-HLH

The 13 patients in our center had fever and multiple enlarged superficial lymph nodes at the onset of HNL-HLH. Skin rash, hepatomegaly, and (mild) splenomegaly were observed in most patients. During the course of the disease, 8 patients had central nervous system (CNS) symptoms (61.5%), including convulsions, drowsiness, conscious disturbance, irritability, and projectile vomiting. No primary diseases of the CNS were observed by cerebrospinal fluid examination and craniocerebral imaging (**Figure 2**, C-F).

Compared with the EBV-HLH group (n = 26), the incidence of skin rash (10 vs 3) and CNS symptoms (8 vs 5) was higher in the HNL-HLH group ($P < .001$), and splenomegaly was less common ($P = .039$). In contrast, the

Table I. Comparison of clinical characteristics among HNL-HLH, EBV-HLH, and simple HNL groups in our center

Characteristics	HNL-HLH (n = 13)	EBV-HLH (n = 26)	HNL-HLH vs EBV-HLH		HNL (n = 26)	HNL-HLH vs simple HNL	
			Test value	*P* value		Test value	*P* value
Male-to-female ratio	9:4	13:13	–	.318*	17:9	–	>.999*
Age of onset	8.1 ± 1.2	8.7 ± 0.8	−0.467†	.643	9.1 ± 0.8	0.204†	.839
Skin rash	10 (76.9%)	3 (11.5%)	–	<.001*	8 (30.8%)	–	.015*
Hepatomegaly	10 (76.9%)	23 (88.5%)	–	.380*	7 (26.9%)	–	.005*
Splenomegaly	7 (53.8%)	23 (88.5%)	–	.039*	2 (7.7%)	–	.003*
CNS symptom	8 (61.5%)	5 (19.2%)	–	.013*	1 (3.8%)	–	<.001*
Leukopenia/neutropenia	10 (76.9%)	14 (53.8%)	–	.295*	17 (65.4%)	–	.714*
At diagnosis of HLH							
Leukopenia/neutropenia	13 (100.0%)	22 (84.6%)	–	.281*	–	–	–
Decreased hemoglobin	6 (46.2%)	16 (61.5%)	–	.497*	–	–	–
Thrombocytopenia	6 (46.2%)	20 (76.9%)	–	.163*	–	–	–
CRP >8 mg/L	4 (30.8%)	10 (38.5%)	–	>.999*	11 (42.3%)	–	>.999*
ESR (mm/h)	25.0 (2.0-124.0)	14.0 (2.0-78.0)	−1.574‡	.115	36.0 (8.0-94.0)	−1.312‡	.190
FIB (g/L)	1.6 (0.3-2.5)	1.1 (0.6-4.3)	−2.309‡	.021	–	–	–
DIC score	4 (2-11)	5 (2-11)	−1.535‡	.125	0	–	–
TG (mmol/L)	4.0 (2.0-5.8)	4.0 (1.1-15.1)	−0.894‡	.371	–	–	–
AST (U/L)	376.9 (53.8-3427.0)	258.2 (28.3-2991.9)	−1.281‡	.200	38.1 (20.9-275.0)	−4.439‡	<.001
ALT (U/L)	176.0 (49.4-2174.4)	143.3 (5.1-1788.5)	−0.596‡	.551	22.8 (7.7-244.0)	−3.873‡	<.001
LDH (U/L)	1360.0 (622.0-5706.0)	1020.5 (228.0-8181.0)	−0.924‡	.356	375.0 (128.0-1449.0)	−4.618‡	<.001
Serum ferritin (ng/mL)	3687.0 (1020.0-83 400.0)	6657.0 (283.5-77 070.0)	−0.119‡	.905	–	–	–
Hemophagocytosis in bone marrow	9 (69.2%)	23 (88.5%)	–	.194*	–	–	–
Lymphocyte subsets in peripheral blood							
Increased proportion of $CD8^+$ T lymphocytes	9 (69.2%)	18 (69.2%)	–	>.999*	6 (23.1%)	–	.013*
Decreased ratio of $CD4/CD8^+$ T lymphocytes	7 (53.8%)	18 (69.2%)	–	.482*	9 (34.6%)	–	.312*
Decreased proportion of natural killer cells	7 (53.8%)	17 (65.4%)	–	.508*	14 (53.8%)	–	>.999*
Cytokines§							
IFN-γ (pg/mL)	4.32 (0.00-36.22)	14.86 (0.00-1492.70)	−0.692‡	.489	–	–	–
TNF-α (pg/mL)	0.00 (0.00-7.54)	1.05 (0.00-77.93)	−1.318‡	.188	–	–	–
L-10 (pg/mL)	9.15 (3.42-104.15)	79.49 (3.44-855.73)	−2.668‡	.008	–	–	–
IL-6 (pg/mL)	45.44 (1.73-199.00)	19.14 (0.00-370.01)	−1.173‡	.241	–	–	–
IL-4 (pg/mL)	0.03 (0.00-1.94)	0.06 (0.00-558.83)	−0.340‡	.734	–	–	–
Unfavorable event¶	3 (23.1%)	9 (34.6%)	–	.714*	3 (11.5%)	–	.380*
Event-free survival			0.533**	.465		0.729**	.393
2-year	91.7%	62.2%			100%		
5-year	55.0%	62.2%			72.9%		
Overall survival			2.313**	.128		1.750**	.186
2-year	100%	64.8%			100%		
5-year	75.0%	64.8%			100%		

–, Not available; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *FIB*, fibrinogen; *IFN-γ*, interferon gamma; *LDH*, lactate dehydrogenase; *TG*, triglyceride; *TNF-α*, tumor necrosis factor alpha.
*Fisher exact test.
†*t*-value.
‡Z-value.
§Cytokine profile was detected in 9 patients with HNL-HLH and 24 patients with EBV-HLH. Cytokines were not detected in all of the patients in the simple HNL group.
¶Unfavorable events include progression, developing into autoimmune diseases, relapse, and death.
**χ^2-value in log-rank test.

incidence of skin rash (10 vs 8), hepatomegaly (10 vs 7), splenomegaly (7 vs 2), and nervous system symptoms (8 vs 1) was higher in the HNL-HLH ($P < .001$) group than in the simple HNL group (n = 26).

Examination and Pathology of the Patients with HNL-HLH

At the diagnosis of HNL-HLH, leukopenia (leukocytes $<4 \times 10^9$/L) and/or neutropenia (neutrophils $<1 \times 10^9$/L) were observed in all cases, and in 10 of 13 patients (76.9%) at the onset of the disease. Most patients had elevated levels of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and serum ferritin. When the HLH 2004 criteria were met, the median soluble CD25 and natural killer cell activity was 7209 pg/mL (IQR, 2445-36 512 pg/mL) and 16.92% (IQR, 11.30%-20.09%), respectively.

Hypofibrinogenemia was milder ($Z = -2.309$; $P = .021$) and the level of serum IL-10 was significantly lower in the patients with HNL-HLH than in the EBV-HLH group. Disseminated intravascular coagulation (DIC) scores were calculated according to Chinese DIC scoring system; however, no significant difference was observed between HNL-HLH group and EBV-HLH group ($P = .125$).[19] All patients with simple HNL had a score of 0. We did not observe the association of DIC score with HLH prognosis either ($Z = -0.233$; $P = .816$).

Table III. Clinical characteristics of patients with HNL-HLH reported in the literature

Cases	Age (years)	Sex	Race	Rash	CNS symptom	Hepatomegaly	Splenomegaly	At diagnosis of HLH: Leukopenia/neutropenia	At diagnosis of HLH: Decreased hemoglobin	At diagnosis of HLH: Thrombocytopenia	LDH (U/L)	Serum ferritin (ng/mL)	Infection of EBV	Autoantibodies
1	14	Male	Asian	N	N	Y	N	Y	N	Y	1238	128	Past infection	ANA 1:40
2	10	Female	Asian	N	N	N	N	Y	N	N	852	1083	Past infection	ANA 1:40
3	4	Male	Asian	Y	Y	N	N	Y	N	N	8340	35 500	–	Negative
4	13	Female	Asian	Y	Y	N	N	Y	N	Y	–	14 955.2	Past infection	Negative
5	15	Female	Caucasian	N	N	N	N	–	N	Y	1136	22 090	–	–
6	6	Female	Caucasian	N	N	Y	Y	Y	Y	Y	–	–	–	–
7	17	Female	Asian	N	Y	N	N	Y	N	N	1573	1000	Negative	ANA 1:160, negative dsDNA
8	12	Female	Asian	N	N	N	N	Y	N	N	1105	1003	–	–
9	14	Female	Asian	N	N	N	N	Y	N	N	682	2541	–	–
10	5	Male	Asian	N	N	Y	Y	Y	Y	N	1540	3371	–	–
11	14	Male	Asian	N	N	N	N	Y	N	N	627	472	–	–
12	8	Female	Asian	N	N	Y	Y	Y	N	N	1308	1168	–	–
13	15	Female	Asian	N	N	Y	Y	Y	Y	N	1941	2500	Negative	ANA 1:40
14	16	Male	Asian	Y	N	N	Y	Y	N	N	–	892.9	Current infection	Negative
15	13	Male	Asian	N	N	Y	Y	Y	N	N	–	–	Negative	Negative
16	16	Female	Caucasian	N	Y	N	N	Y	Y	N	2150	619	Negative	Negative

Case	Hemophagocytosis: Bone marrow	Hemophagocytosis: Lymph node	Treatment	Prognosis	Others	Reference
1	Y	N	IVIG + prednisone	Survival	–	Chen JS, et al[8]
2	Y	N	IVIG + prednisone	Survival	–	Chen JS, et al[8]
3	Y	N	VP16 + dexamethasone + CsA, prednisone	Survival	Relapsed HNL complicated with HLH Suspected to have a family history	Mahadeva U, et al[9]
4	Y	N	VP16 + dexamethasone, IVIG, methylprednisolone	Survival	–	Kim YM, et al[10]
5	–	N	CsA, anakinra, methylprednisolone	Survival	*Ala91Val* heterozygous mutation	Marsili M, et al[11]
6	Y	N	VP16 + dexamethasone + CsA	–	*RAB27A* homozygous mutation	Listernick R[12]
7	Y	N	IVIG	Survival	–	Kelly J, et al[13]
8	Y	N	Prednisone	Relapse	–	Lim GY, et al[14]
9	Y	N	VP16 + dexamethasone, IVIG	Relapse	–	Lim GY, et al[14]
10	Y	N	VP16 + dexamethasone, prednisone	Death	–	Lim GY, et al[14]
11	Y	N	VP16 + dexamethasone + CsA, IVIG	Survival	–	Lim GY, et al[14]
12	Y	N	Prednisone	Survival	–	Lim GY, et al[14]
13	Y	Y	Prednisone	Survival	IgM, IgG and DNA of PVB19 was positive	Yufu Y, et al[15]
14	Y	–	Symptomatic treatment	Survival	HNL diagnosed by skin biopsy	Lee HY, et al[16]
15	Y	N	Prednisone	Survival	–	Lin YW, et al[17]
16	Y	Y	Symptomatic treatment	Survival	–	Sykes JA, et al[18]

–, Not available; *ANA*, antinuclear antibody; *dsDNA*, double-stranded DNA; *IVIG*, intravenous immunoglobulin; *N*, no; *Y*, Yes.

In addition, the leukocyte ($Z = -3.412$; $P = .001$) and/or neutrophil ($Z = -2.681$; $P = .007$) counts were significantly decreased and the aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase levels were increased ($P < .001$) in the patients with HNL-HLH compared with patients with simple HNL. An increased proportion of $CD8^+$ T lymphocytes occurred more frequently in the HNL-HLH group than in the simple HNL group (9 vs 6, respectively; $P = .013$). There was no statistically significant difference in other presentations among the 3 groups (Table I).

None of the patients with HNL-HLH in our center had any evidence of an active EBV infection, and they were all negative for other pathogenic agents including cytomegalovirus, rubella virus, parvovirus B19 (PVB19), bacteria, fungi, and parasites.

Lymph node biopsies were performed in all patients with HNL-HLH. Necrotic areas could be seen in the paracortex of lymph nodes, surrounded by histiocytes with plasmacytoid or crescentic nuclei (Figure 3). Hemophagocytosis was found in 4 cases of biopsied lymph node tissues (30.8%) and 9 cases of bone marrow smears (69.2%).

None of the patients met the diagnostic criteria for systemic lupus erythematosus (SLE) (American College of Rheumatology 1997 criteria) or Sjogren syndrome (American-European Consensus Criteria for Sjögren's Syndrome [2002]) at diagnosis of HNL-HLH. Whole exome sequencing was performed in 9 patients with HNL-HLH and 18 patients with EBV-HLH. No primary HLH-related mutation was found.

Treatment and Prognosis of HNL-HLH

Among the 13 patients in our center, HLH was controlled by symptomatic and supportive treatment in 3 patients, by gamma globulin alone (total dose was 2 g/kg, infused intravenously for 4 or 5 days) in 1 patient, and by methylprednisolone (total dose was 2-20 mg/kg per day, infused intravenously) combined with gamma globulin in 5 patients. In addition, 1 patient was treated with ruxolitinib (a Janus kinase 1/2 inhibitor, 5 mg/kg per treatment, once every 12 hours) orally after the diagnosis of HLH, and her prolonged fever, the cytokine levels (interferon-γ, IL-10, and IL-6), and hemogram recovered after 1 week of treatment. Moreover, her serum ferritin decreased from 6069 ng/mL to 987.4 ng/mL. After completion of the 1-week target therapy, methylprednisolone (10 mg/kg per day) was added over the course of 3 days and tapered off within 8 weeks. During the 2-month follow-up, the patient's temperature and superficial lymph nodes were normal without new rashes.

The remaining 3 patients were treated with immunosuppressive drugs or chemotherapy (methylprednisolone + cyclosporine A [CsA] (3mg/kg per day), methylprednisolone+CsA+etoposide (150mg/m^2 per time)+dexamethasone (10mg/m^2 per time)+cyclophosphamide (1g/m^2 per time), and methylprednisolone+dexamethasone (4mg per time, intrathecal injection)+methotrexate (12mg per time, intrathecal injection), respectively) owing to poor control of the HLH. Two of the 3 patients had a favorable prognosis (follow-up period was 3.0 and 15.6 months); the third was treated with dexamethasone + CsA for 52 weeks. Then, after 9 months of drug withdrawal, the HLH relapsed and was treated with a 5-month course of etoposide (discontinued owing to economic difficulties). Eleven months later, the HLH relapsed again with a diagnosis of SLE. This patient experienced no improvement after treatment with methylprednisolone + CsA + cyclophosphamide and died of pulmonary hemorrhage (genetic testing was not performed).

Except for the patient who died of recurrent HLH, all the patients had survived at the end of follow-up. One patient suffered from SLE with Sjogren syndrome 3 months after the diagnosis of HNL-HLH. In another patient, the HNL relapsed (without HLH), as verified by lymph node biopsy, with fever and enlarged cervical lymph nodes 19 months after the HNL-HLH diagnosis. Subsequently, Sjogren syndrome was diagnosed at 26 months of follow-up. The survival analysis showed that the differences in event-free survival and overall survival were not statistically significant among 3 groups (Figure 4).

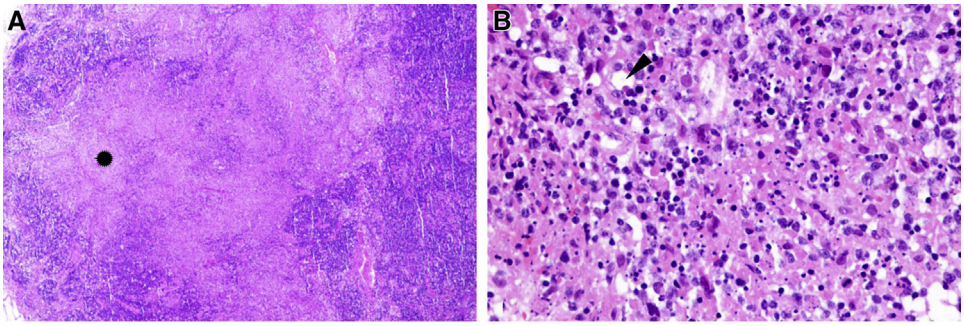

Figure 3. Pathologic images of lymph node from a patient with HNL-HLH microscopically (hematoxylin and eosin stain). **A,** original magnification ×4, patchy coagulative necrosis in the paracortex of lymph node was observed in low-power field (*). **B,** original magnification ×40, a lot of nuclear debris, proliferation of diverse histiocytes and hemophagocytosis (*arrow*) could be seen in high-power field.

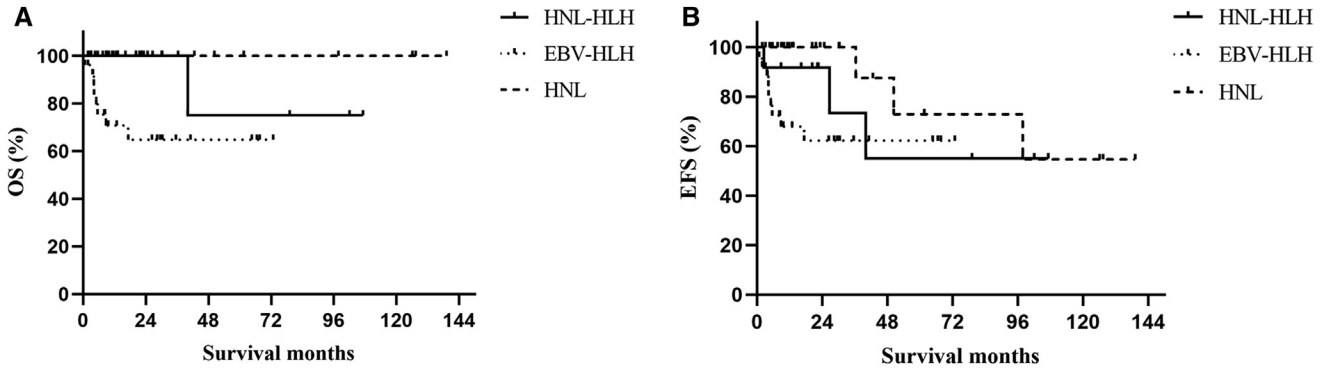

Figure 4. Survival analysis of HNL-HLH, EBV-HLH and simple HNL group in our center. *EFS*, event-free survival; *OS*, overall survival.

Comparison of Clinical Features and Treatment Outcomes Between the Patients with HNL-HLH Enrolled in Our Center and Those Reported in the Literature

Among the 16 patients reported in literature review, the ratio of male to female was 6:10. The mean age of disease onset was 11.3 ± 1.2 years; 13 of 16 were Asian and 3 were Caucasian (**Table III**). There was no significant difference in the sex ratio between the patients in our center and those reported in the literature (P = .139). However, the age at diagnosis of our patients was younger than that of the patients in the literature (t = −2.543; P = .017; **Figure 2**, G and H).

All 16 patients had fever and enlarged superficial lymph nodes, and 93.8% of the patients had leukopenia and/or neutropenia at the time of HNL-HLH diagnosis. Moreover, a higher level of triglycerides (P = .005) and incidences of skin rash (P = .003) and increased trend of CNS symptoms (P = .067) and hepatomegaly (P = .061) were found in our patients. No significant difference in any other clinical features, including the incidence of splenomegaly (P = .467), was observed between the patients in our center and those in the literature (**Figure 2**). Two cases had current EBV and PVB19 infections, respectively. Hemophagocytosis could be seen in the bone marrow of 15 cases and in the lymph node biopsies of 2 cases. One patient was diagnosed with HNL by skin instead of lymph node biopsy. The autoantibody titers were tested in 9 patients, and 8 of them had lower antinuclear antibody titers (<1:80) or negative results. The antinuclear antibody titer in 1 patient was 1:160, although the diagnostic criteria for SLE were not met.

Two patients were treated with supportive therapy, and 5 patients were treated with glucocorticoids or gamma globulin alone and 2 with glucocorticoids combined with gamma globulin to control the disease. The other 7 patients were treated with immunosuppressive drugs (**Table III**). Although 75% of the patients had a favorable prognosis, 2 patients experienced recurrent episodes of HLH. One patient died of DIC. The prognosis of 1 patient was unreported. Compared with the patients with HNL-HLH in our center, there was no significant difference in the incidence of unfavorable events (P > .999; **Figure 2**, S).

Discussion

Based on the literature review and the patients with HNL-HLH in our center, there is no significant difference in the male-to-female ratio. HNL-HLH can occur in different phases of childhood, though it is more common in school- and preschool-age children.[20] The age at diagnosis of our patients was younger than that of the patients reported in the literature. This may be due to the fact that most patients with HNL-HLH admitted to our center underwent biopsies of enlarged lymph nodes at an early stage to screen HLH secondary to malignancy such as lymphoma; therefore, many younger patients with HNL-HLH were identified.

Although the pathogenesis of HNL is unclear, the disease may be related to the proliferation of $CD8^+$ T lymphocytes induced by infection, autoimmunity, and other factors. After apoptosis mediated by FasL/Fas and perforin, activated T lymphocytes are phagocytized by macrophages and typical HNL pathologic manifestations are observed in lymph nodes.[21] Owing to its short course and concomitant neutropenia, a potential correlation between HNL and viral infection has been put forward.[22] EBV and PVB19 are both viral inducing factors of HLH. Because anti-dsDNA and autoantibodies of lymphocyte can be induced by PVB19 infection, it may be involved in the pathogenesis of HNL or HNL-HLH.[15,23] Some patients in our center had a history of EBV infection, but there was no evidence of active infection. Although 2 patients in the literature had current infections of EBV and PVB19, it is unclear whether a virus is a direct pathogenic factor of HNL. In contrast, there is a close relationship between HNL and autoimmune diseases, and HNL may be considered a potential manifestation of certain autoimmune diseases. Some research has shown that 30% of patients with HNL are positive for autoantibody detection at diagnosis are at high risk of developing SLE over time.[2,24] Some patients with simple HNL may develop other

autoimmune diseases, such as Sjogren syndrome, adult-onset Still disease, and Behcet disease. In addition, glucocorticoid therapy for patients with HNL and patients with HNL-HLH may alleviate the symptoms, which corresponds with the treatment of some autoimmune diseases. The pathologic findings in HNL may be related to phagocytosis of apoptotic T lymphocytes by macrophages, induced by viral infection and autoimmune factors.

It is known that $CD8^+$ T lymphocytes, natural killer cells, and high levels of cytokines play a considerable role in the pathogenesis of HLH.[25] Our study showed that the proportion of $CD8^+$ T lymphocytes in peripheral blood nucleated cells was significantly higher in the HNL-HLH group than in the simple HNL group. We believe that $CD8^+$ T lymphocytes in patients with HNL-HLH may be excessively activated, which make the self-limited HNL progress along an uncontrollable course, resulting in the emergence of HLH.[17] Unfortunately, the role of cytokines played in HNL-HLH and simple HNL was unclear owing to the lack of cytokine detection in the simple HNL group. However, the IL-10 level in the HNL-HLH group was significantly lower than that in the EBV-HLH group, indicating the differential roles of some cytokines, such as IL-10 in different subtypes of secondary HLH, which needs further investigations.

It is suggested that pancytopenia in HLH is mainly related to the inhibition of high levels of cytokines, such as interferon-γ and tumor necrosis factor-α, on medullary hematopoiesis.[26] Although the degree of leukopenia and neutropenia was similar between the patients with HNL-HLH and the patients with EBV-HLH, the incidence of leukopenia or neutropenia at the onset of the disease was higher in the patients with HNL-HLH. In addition to the induction of leukocyte apoptosis by cytokines, patients with HNL may also have antileukocyte autoantibodies owing to the special relationship between HNL and autoimmune disease, in which apoptosis of leukocytes is induced by autoimmune response.

DIC score has been reported to be a better indicator of disease activity in patients with HLH.[27] However, no significant difference was observed between the HNL-HLH group and the EBV-HLH group. Similarly, DIC score was not related to the outcome of treatment of patients with HLH, possibly owing to the sample size in this study.

Skin rash may occur at the beginning or during the course of the disease, and it is mainly characterized by transient red, millet-size maculopapules. The incidence of skin rash in our patients was higher than that in the literature review, which may be due to the fact that rash was not interpreted as the main observation indicator in most reports.

HNL-HLH may be controlled by symptomatic treatment, glucocorticoids, and immunoglobulin therapy in most patients. A few patients need chemotherapy owing to aggressive or relapsed HLH. Resolution was obtained in 1 patient in our center after ruxolitinib treatment. It is suggested that individualized treatments should be adopted for patients with HNL-HLH.

In terms of prognosis, there was no significant difference in event-free survival and overall survival among the 3 groups. Although the HNL-HLH is not as clinically severe as EBV-HLH, delayed diagnosis and treatment owing to an inadequate understanding of HNL-HLH among clinicians may be one of the reasons for similar prognosis.

In the 29 patients with HNL-HLH included in this study, 3 patients with an HLH relapse, 2 patients with an HNL relapse without HLH, and 2 patients with the development of autoimmune disease were observed.[9,14,17] It is reported that the recurrence rate of simple HNL in children is about 10.0%-42.4%.[2] However, no specific mutation related to recurrent and familial HNL has been found. Patients with relapsed HNL may have autoimmune disorders and suffer from relapse induced by infectious factors.[28] Retreatment with glucocorticoids and immunoglobulin may continue to be effective, and treatment should still focus on controlling the primary disease. If HLH cannot be controlled with general treatment, short-term chemotherapy such as etoposide can be used according to the appropriate regimen for HLH.

The major limitations of this study were its retrospective nature, small sample size, and the possibility of incomplete data. It is necessary to enlarge the sample size and conduct prospective research. Cytokine detection should be performed further in the simple HNL group.

In summary, there may be some unique clinical presentations in patients with HNL-HLH compared with patients with EBV-HLH and patients with simple HNL, which need to be further verified by a multicenter prospective clinical study with large sample size. Most of the patients with HNL-HLH showed a favorable prognosis without significant differences compared with the patients with EBV-HLH and patients with simple HNL. Some patients suffered from relapse or developed autoimmune diseases. Prolonged follow-up should be carried out for patients with HNL-HLH. ■

Submitted for publication Apr 26, 2020; last revision received Jul 14, 2020; accepted Aug 21, 2020.

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Data Statement

Data sharing statement available at www.jpeds.com.

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Table II. Clinical characteristics of patients with HNL-HLH in our center

Cases	Age (years)	Sex	CNS symptom	Rash	Hepatomegaly	Splenomegaly	At diagnosis of HLH: Leukopenia/ neutropenia at the onset	At diagnosis of HLH: Leukopenia/ neutropenia	At diagnosis of HLH: Decreased hemoglobin	At diagnosis of HLH: Thrombo-cytopenia	Increased CRP	ESR (mm/h)	FIB (g/L)	TG (mmol/L)	AST (U/L)	ALT (U/L)	LDH (U/L)	Serum ferritin (ng/mL)	Infection of EBV
1	8.9	Male	Y	Y	Y	N	Y	Y	N	Y	Y	41	1.4	2.0	398.7	125.4	3301	12 337	Past infection
2	2.1	Male	Y	N	Y	N	N	Y	Y	Y	N	2	1.6	4.6	611.0	176.0	2105	2536	Past infection
3	5.3	Male	Y	Y	Y	Y	N	Y	Y	Y	Y	73	0.3	5.4	1122.0	133.0	5706	83 400	Negative
4	13.9	Male	Y	N	Y	N	Y	Y	Y	N	N	17	1.8	3.0	482.0	277.0	908	1500	Past infection
5	9.9	Female	N	N	Y	Y	Y	Y	N	Y	N	4	2.1	2.6	156.8	57.5	1031	2516	Negative
6	11.6	Female	Y	Y	Y	Y	Y	Y	N	N	N	17	2.5	5.3	360.6	218.4	1507	10 230	Past infection
7	14.0	Male	Y	N	N	N	Y	Y	N	N	Y	33	2.5	2.9	170.5	253.5	622	1319	Past infection
8	3.8	Male	Y	Y	Y	Y	Y	Y	Y	Y	Y	29	0.8	3.7	376.9	236.3	1683	16 200	Past infection
9	5.3	Male	N	Y	N	N	Y	Y	N	N	N	2	1.2	5.8	295.5	413.9	2121	3687	Past infection
10	6.0	Female	N	N	Y	Y	Y	Y	N	N	N	19	1.9	4.0	53.8	49.4	801	1020	Past infection
11	8.3	Male	Y	Y	Y	N	Y	Y	Y	Y	Y	124	1.5	5.5	124.9	53.3	1256	2439	Past infection
12	12.7	Male	Y	Y	Y	Y	N	Y	N	Y	N	25	1.3	2.7	3427.0	2174.4	1360	15 000	Past infection
13	3.0	Female	Y	Y	N	Y	Y	Y	Y	N	N	38	1.8	4.0	497.4	65.7	910	6069	Past infection

Case	sCD25 (pg/mL)	NK activity (%)	ANA (titers)	IFN-γ (pg/mL)	TNF-α (pg/mL)	IL-10 (pg/mL)	IL-6 (pg/mL)	IL-4 (pg/mL)	Hemophagocytosis: Bone marrow	Hemophagocytosis: Lymph node	Treatment	Prognosis	Others
1	11 444	17.27	0	0	6.78	34.27	45.44	0	Y	N	IVIG + methylprednisolone	Survival	
2	–	–	1:320	–	–	–	–	–	Y	N	IVIG + methylprednisolone	Survival	
3	–	–	0	–	–	–	–	–	N	N	IVIG + methylprednisolone	Survival	
4	–	–	0	–	–	–	–	–	Y	Y	CsA + dexamethasone, VP16, methylprednisolone + CsA + cyclophosphamide	Death	HLH relapsed, then died
5	4531	11.30	0	35.14	1.26	10.22	56.61	0	Y	N	Symptomatic treatment	Relapse	HNL relapsed (without HLH), then developed Sjogren's syndrome
6	9926	14.62	0	36.22	0	12.48	52.1	0	Y	Y	IVIG	Survival	–
7	2445	14.21	1:10	4.32	7.54	3.42	199	0.74	Y	Y	Symptomatic treatment	Survival	–
8	–	–	0	–	–	–	–	–	N	N	IVIG + methylprednisolone	Survival	–
9	4249	18.82	0	2.3	1.11	4.01	1.73	1.94	Y	N	Methylprednisolone, CsA	Survival	–
10	7209	16.92	1:1280	0.61	0	4.15	3.6	0.03	Y	N	Symptomatic treatment	Develop autoimmune diseases	developed SLE with Sjogren's syndrome
11	5589	18.25	1:80	0	0	9.15	4.99	0.15	N	N	Methylprednisolone + dexamethasone (IT) + MTX (IT)	Survival	–
12	36 512	20.09	1:1280	32.18	0	104.15	101.12	0.41	N	Y	IVIG + methylprednisolone	Survival	–
13	15 641	15.52	1:80	28.95	0	4.97	40.24	0	Y	N	Ruxolitinib, methylprednisolone	Survival	–

–, Not available; *ALT* alanine aminotransferase; *ANA*, antinuclear antibody; *AST*, aspartate aminotransferase; *CRP*, C-reactive protein; *EBV*, Epstein-Barr virus; *ESR*, erythrocyte sedimentation rate; *FIB*, fibrinogen; *IFN-γ* interferon gamma; *IT*, intrathecal injection; *IVIG*, intravenous immunoglobulin; *LDH*, lactate dehydrogenase; *MTX*, methotrexate; *NK*, natural killer; *sCD25*, soluble CD25; *TG*, triglyceride; *TNF-α*, tumor necrosis factor alpha; *VP16*, etoposide.

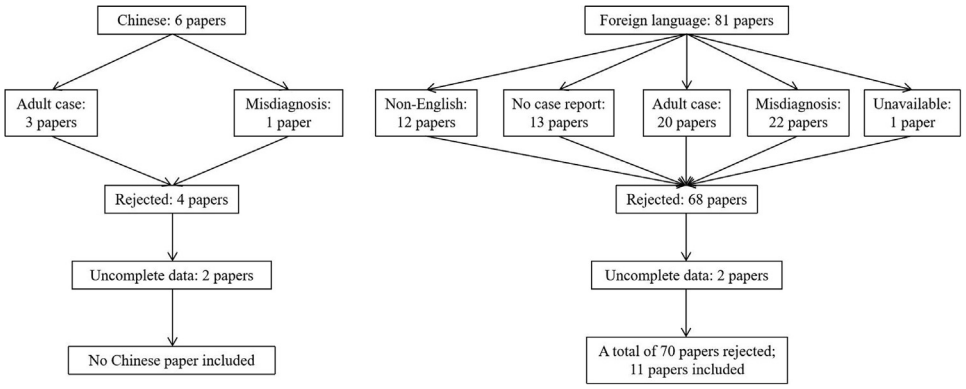

Figure 1. Procedure of literature screening in Chinese and English databases.

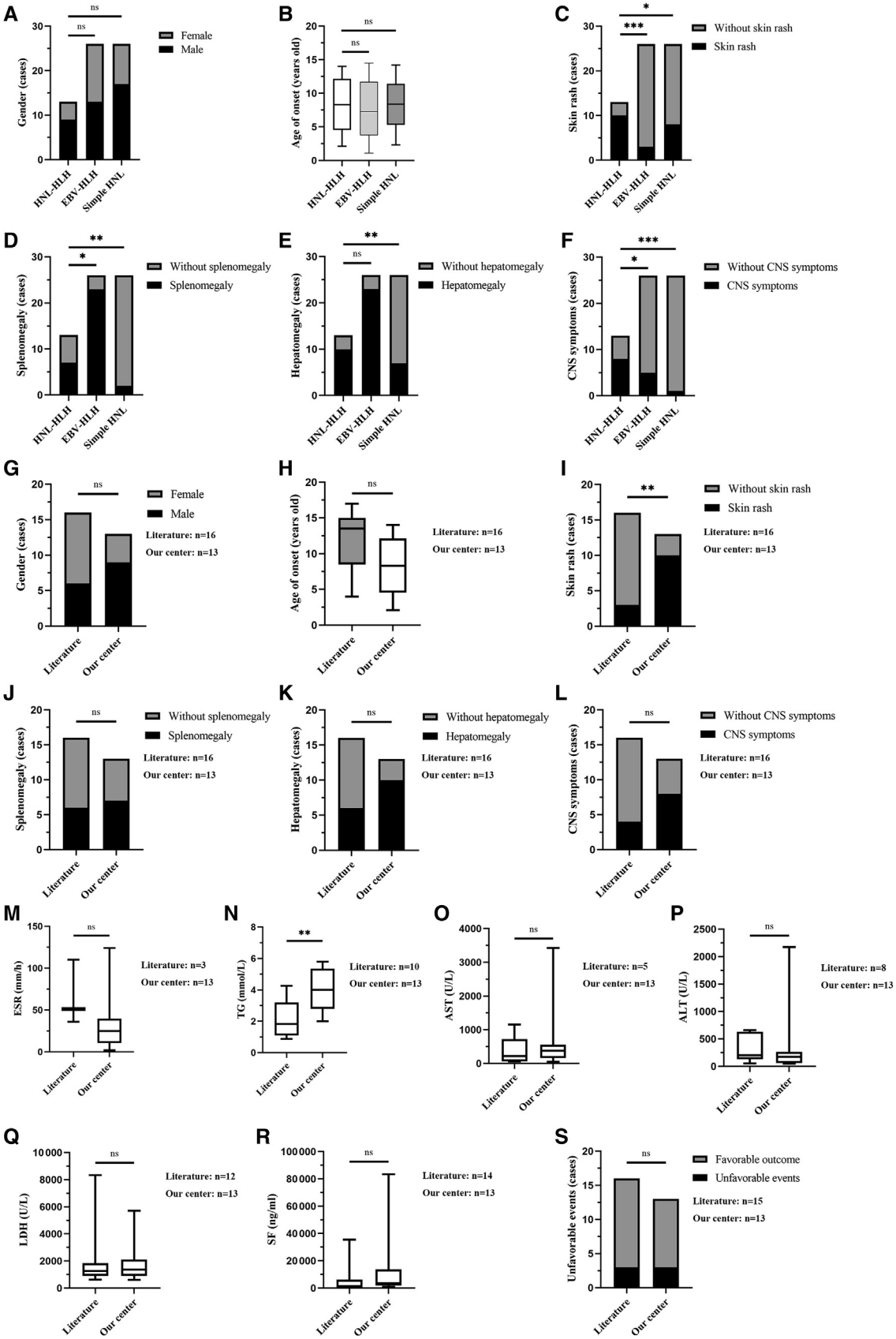

Figure 2. Comparison of characteristics among HNL-HLH, EBV-HLH, simple HNL groups in our center, **A-F,** and between patients with HNL-HLH in our center and cases from literature, **G-S**.