

Intrathoracic infections in Hodgkin lymphoma (HL) patients may cooperate with HL to trigger hemophagocytic lymphohistiocytosis

A retrospective study

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Abstract

Hodgkin lymphoma (HL)-related hemophagocytic lymphohistiocytosis (HLH) has been reported in the literature; however, there is almost no literature on the factors related to HL triggering HLH.

One hundred forty patients with HL were retrospectively analyzed. The incidence of HL-related HLH (we call HL-related HLH as HL-HLH). And all HL-HLH patients in our cohort had HLH as the first manifestation and its clinical characteristics and the role of intrathoracic infection (ITI) in triggering HLH are discussed.

The 140 patients with HL mainly included mixed-cellularity classic HL (MCCHL) in 81 (57.9%), nodular sclerosis classic HL (NSCHL) in 36 (25.7%), and lymphocyte-rich classic HL in 14 (10.0%) patients. Of the 137 patients who underwent chest computed tomography scans on admission, 44 had ITI, and most of these ITI were mildly ill and had no respiratory symptoms. Among 140 HL patients, 8 patients from MCCHL were diagnosed as HL-HLH. Among 81 MCCHL patients, 26 patients with ITI had a significantly higher incidence of HL-HLH than those without ITI (26.9% vs 1.8%, $P = .002$). The median survival time of 8 cases of HL-HLH was only 2 months.

When HL patients were first admitted to the hospital, 5.7% had HLH as the first manifestation, and 32.1% had ITI. These ITI can cooperate with HL to trigger HLH, despite their mild illness. The prognosis of HL-HLH was poor.

Abbreviations: HL = Hodgkin lymphoma, HL-HLH = Hodgkin lymphoma-related hemophagocytic lymphohistiocytosis, HLH = hemophagocytic lymphohistiocytosis, MCCHL = mixed-cellularity classic Hodgkin lymphoma, NSCHL = nodular sclerosis classic Hodgkin lymphoma, ITI = intrathoracic infections, NHL = non-Hodgkin Lymphoma, EBV = Epstein-Barr virus, CR = complete remission, LRCHL = lymphocyte-rich classical Hodgkin lymphoma, LDCHL = lymphocyte-depleted classical Hodgkin lymphoma.

Keywords: antibiotic treatment, hemophagocytic lymphohistiocytosis, Hodgkin lymphoma, intrathoracic infections

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH), also known as hemophagocytic syndrome, is a clinical syndrome characterized by a pathological inflammatory response caused by hereditary or acquired immune dysfunction.^[1,2] Secondary HLH can be triggered by infection, malignant tumors, and immune diseases,^[2,3] of which tumor-related HLH accounts for about 20% of secondary HLHs. More than 90% of tumors related to HLH are hematopoietic tumors, especially lymphomas.^[2-4] At present, it is known that lymphomas that cause secondary HLH are mainly aggressive lymphomas, such as natural killer

(NK)/T-cell lymphoma and diffuse large B-cell lymphoma, while secondary HLH caused by indolent lymphomas are less common.^[5-7]

In comparison with non-Hodgkin lymphoma (NHL), the progress of Hodgkin lymphoma (HL) is slow and its prognosis is good; however, to the best of our knowledge, there are few reports on HL-related HLH, hereby referred to as HL-HLH. Therefore, we sought to investigate clinical factors related to HL-HLH. To address this question, we analyzed retrospective clinical data of HL patients and found that intrathoracic infection (ITI) in HL patients is associated with the development of HL-HLH.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The study was approved by the First Affiliated Hospital of Guangxi University Ethics Committee (2020 KY-E-169). The need for patient consent was waived.

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2. Materials and methods

2.1. Diagnosis and treatment of HL patients

We collected clinical data of HL patients admitted to our hospital from January 2010 to December 2018. Data included gender, age, clinical stage, Epstein-Barr virus (EBV) in situ hybridization test results, chest computed tomography (CT) findings, and HLH-related clinical manifestations. For the patients with HL-HLH, we further analyzed their clinical characteristics and possible causes of HLH. All HL patients were diagnosed by histopathological examination. The monoclonal antibodies used in immunohistochemistry included CD3, CD4, CD7, CD10, CD15, CD19, CD20, CD21, CD30, CD38, CD 45Ro, CD68, CD79a, AAT, ALK, BCL-2, BCL-6, C-MyC, MUM, PAX-5, Ki67, and EMA. The chemotherapy for HL should have lasted no <6 cycles, with ABVD (adriamycin + bleomycin + vinblastine + dacarbazine) (or bleomycin + etoposide + adriamycin + cyclophosphamide + vincristine + procarbazine + prednisone [BEACOPP]) regimen in adult patients and an A regimen in children. If the patient did not achieve complete remission (CR) after 4 cycles of chemotherapy, a second evaluation was required after the sixth cycle of chemotherapy. The original regimen of 2 courses of chemotherapy was still required if the patient achieved CR during the second evaluation. Otherwise, second-line regimens were used for further treatment. HL efficacy was evaluated according to a previous report.^[8] The study was approved by the First Affiliated Hospital of GuangXi University Ethics Committee (2020 KY-E-169). The need for patient consent was waived.

2.2. Diagnosis and treatment of HLH

The diagnosis of HLH was based on the criteria of HLH 2004, that is, those who met ≥ 5 of the 8 characteristics of HLH were diagnosed as HLH.^[9] Treatment of HLH included chemotherapy with the HLH-2004 regimen or an intravenous drip of dexamethasone for a few days (20–40mg/d), after which we began treatment for HL as soon as possible based on the above principles. We did not evaluate the efficacy of HLH because it was secondary to HL.

2.3. Definition of ITI

Patients in our cohort underwent a chest CT scan on admission, and those who met the following 3 criteria were diagnosed with ITI: chest CT showed increased lung density or/and pleural effusion; anti-infection treatment could make the lesions disappear quickly; otherwise, the lesions did not disappear; the image findings were not likely to be tumors or tuberculosis, and anti-lymphoma treatment alone was not effective.

2.4. Statistical analysis

SPSS 19.0 was used for data analysis, the relative number of categorical data was given as percentage, chi-square test was used for their comparison, with P value of $<.05$ as significant difference, and GraphPad Prism V.7.0 (LA Jolla, CA) was used to draw survival curve.

3. Results

3.1. Types and basic characteristics of HL

From January 2010 to December 2018, a total of 140 patients with HL were admitted to our hospital. Among them, 3 cases (2.1%) were nodular lymphocyte-predominant HL, 81 (57.9%) were mixed-cellularity classical HL (MCCHL), 36 (25.7%) were nodular sclerosis classical HL (NSCHL), 14 (10.0%) were lymphocyte-rich classical HL (LRCHL), 4 (5.7%) were lymphocyte-depleted classical HL (LDCHL), and 2 (1.4%) were undetermined.

The more common HL in our cohort were MCCHL, NSCHL, and LRCHL, and their characteristics are shown in Table 1. Table 1 shows that EBV infection in patients with MCCHL was significantly higher than that found in patients with NSCHL or LRCHL, while there was no significant difference in the composition ratio of stage III and IV and the incidence of ITI.

3.2. Incidence and clinical characteristics of HL-HLH

Of the 140 cases of HL in our cohort, 8 patients had HLH as the first manifestation of HL, while the prevalence of HL-HLH was 5.7%. Interestingly all patients with HL-HLH were MCCHL, therefore the incidence of HL-HLH in MCCHL was 9.9%. The clinical characteristics of HL-HLH patients in our cohort are shown in Table 2. Among them, there were 5 males and 3 females, the age range was 15 to 75 years, and the median age was 42.5 years. All 8 patients were in stage IV and presented with fever, splenomegaly, and hemopenia. Seven patients showed hemophagocytosis, 3 showed hypertriglyceridemia, and 1 showed hypofibrinogenemia. Serum ferritin and NK-cell activity were detected in 5 of 8 patients with HL-HLH, of which serum ferritin was increased in 5 and NK-cell activity was decreased in 3 patients. We were unable to detect sCD25 in our cohort.

A follow-up was conducted in December 2018. All 8 patients with HL-HLH died. Among them, No.2, No.6, and No.7 did not receive treatment and survived for 1, 2 and 1 months, respectively. No.1 and No.3 first received dexamethasone for HLH, and then received 1 course of ABVD chemotherapy for HL, and survived for 2 months and 1 month, respectively. No.5 first received dexamethasone for HLH and then received 2 courses of BEACOPP regimen for HL. This patient survived for 3 months. Of the remaining 2 patients, No.4 first received HLH-2004 regimen for HLH, then received 2 courses of BEACOPP regimen and 1 course of DHAP chemotherapy regimen for HL. This patient survived for 4 months. No.8 used the ABVD regimen to treat HL, but only achieved partial remission after 5 courses of chemotherapy. This patient survived for 9 months. The median survival time of the 8 patients with HL-HLH was only 2 months, and their survival curve is shown in Figure 1.

3.3. The occurrence of ITI and its association with HL-HLH

Among the 140 patients in our cohort, 2 cases of NSCHL and 1 case of LRCHL did not undergo chest CT. Therefore, out of 137 patients that performed chest CT, 44 (32.1%) had ITI. Among the 44 patients with ITI, 26 had MCCHL, 13 had NSCHL, 4 had LRCHL, and 1 had LDCHL. This represented 32.1% of MCCHL patients, 38.2% of NSCHL patients, 28.6% of LRCHL patients and 25.0% of LDCHL patients being diagnosed with ITI.

Patients with ITI presented mild infection, with few respiratory symptoms, small lung lesions, and few pleural effusions (Fig. 2A–F), which were quickly reversed with antibiotic treatment (Fig. 2C, D). However, these intrathoracic lesions persisted if antimicrobial treatment was not employed, independent of the patient's HL (Fig. 2E, F).

We divided our MCCHL (the only HL in our cohort that presented HL-HLH) patients into 2 groups according to the presence or absence of ITI. The clinical characteristics of these 2 groups are shown in Table 3. The prevalence of HL-HLH in patients with ITI was significantly higher than that found for the group without ITI (26.9% vs 1.8%, $P = .002$). However, there was no significant difference in the composition ratio of stage III and IV and EBV infection rates between the 2 groups.

Table 1
The common HLs and their characteristics.

Group	N	Median age (years)	Stage III and IV	EBV positive*	ITI
MCCHL	81	37.0	50.6%(41/81)	73.5%(36/49)	32.1%(26/81)
NSCHL	36	37.0	50.0% (18/36)	30.0% (6/20)	25.0%(9/36)
LRCHL	14	26.5	42.9% (6/14)	41.7% (5/12)	35.7%(5/14)

*: chi-square test, MCCHL group, and NSCHL group, $P = .001$. MCCHL group and LRCHL group, $P = .035$.

EBV positive = EBV positive in situ hybridization, HL = Hodgkin lymphoma, ITI = intrathoracic infection, LRCHL = lymphocyte-rich classical HL; MCCHL = mixed-cellularity classic Hodgkin lymphoma, NSCHL = nodular sclerosis classic HL.

Table 2
Clinical characteristics of 8 patients with HL-HLH.

	No.1	No.2	No.3	No.4	No.5	No.6	No.7	No.8
Gender	F	M	F	M	M	M	M	F
Age (y)	44	52	75	41	47	15	31	26
Stage	IIIB	IVB	IVB	IVB	IVB	IVB	IIIB	IVB
HS criterion								
A	+	+	+	+	+	+	+	+
B	+	+	+	+	+	+	+	+
C	+	+	+	+	+	+	ND	+
D	-	-	+	-	-	+	+	-
E	-	-	-	-	-	-	+	ND
F	+	-	+	+	+	+	+	+
G	+	+	+	+	+	ND	ND	+
H	+	+	-	-	+	ND	ND	ND
I	ND	ND	ND	ND	ND	ND	ND	ND
Treatment 1	DXM	NT	DXM	2004 regimen	DXM	NT	NT	NT
Treatment 2	1 ABVD	NT	1 ABVD	2 BEACOPP + 1 DHAP	2 BEACOPP	NT	NT	5 ABVD
Efficacy 2	NR		NR	NR	NR			PR
Status	Died	Died	Died	Died	Died	Died	Died	Died
Cause of death	DP	UNK	UNK	INF	DP	UNK	UNK	DP
Survival time, mo	2	1	1	4	3	2	1	9

HS criterion—A: fever (>38.5°C for at least 7 d), B: splenomegaly, C: cytopenia (at least 2 of 3 cell lines), D: hypertriglyceridemia, E: hypofibrinogenemia, F: hemophagocytosis, G: elevated ferritin, H: low or absent NK-cell activity, I: elevated sCD25.

+ = patient present this criterion, - = patient did not present this criterion, 2004 regimen = 2004 regimen for treating HLH, ABVD = adriamycin + bleomycin + vinblastine + dacarbazine, BEACOPP: bleomycin + etoposide + adriamycin + cyclophosphamide + vincristine + procarbazine + prednisone, DHAP = cisplatin + cytarabine + dexamethasone, DP = disease progression, DXM = dexamethasone, Efficacy 2 = efficacy of HL, HL, Hodgkin lymphoma, HLH = hemophagocytic lymphohistiocytosis, INF = infection, ND = no detection, NK = natural killer, NT = no treatment, PR = partial remission, Treatment 1 = the treatment of HLH, Treatment 2 = the treatment of HL, UNK = unknown.

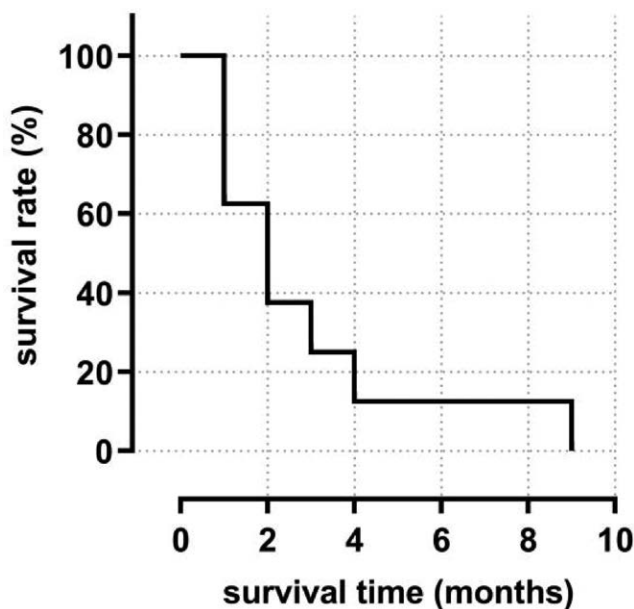


Figure 1. The survival curve of 8 HL-HLH patients. HL = Hodgkin lymphoma, HLH = hemophagocytic lymphohistiocytosis.

4. Discussion

4.1. The characteristics and distribution of HL types

Previous literature indicates that the most frequent types of HL are NSCHL (70%) and MCCHL (25%), while nodular lymphocyte-predominant HL, LRCHL, and LDCHL are less frequent.^[10] Unlike previous reports, the most frequent forms of HL found in our cohort were MCCHL (57.9%), NSCHL (25.7%), and LRCHL (10.0%), while other LDCHL (5.7%) and LCPHL (2.1%) were rare. Importantly, the geographical distribution of HL subtypes may vary.

4.2. The prevalence of HL-HLH and HL associated with HLH

There are currently few reports assessing HL-HLH. In our cohort, up to 5.7% of HL patients had HLH as their first presentation, suggesting that the prevalence of HLH in indolent lymphomas such as HL is not low. To the best of our knowledge, this is the first report on the frequency of HL-HLH.

Previous literature reports the presence of HL-HLH in various types of HL,^[11-14] which may be related to the situations upon the diagnosis of HL-HLH. For example, some developed HLH as the first symptom, others had HLH during the treatment of HL, while others presented other related factors that triggered HLH. Flew et al reported a patient with HL-HLH whose associated HL was LDCHL. The patient was diagnosed

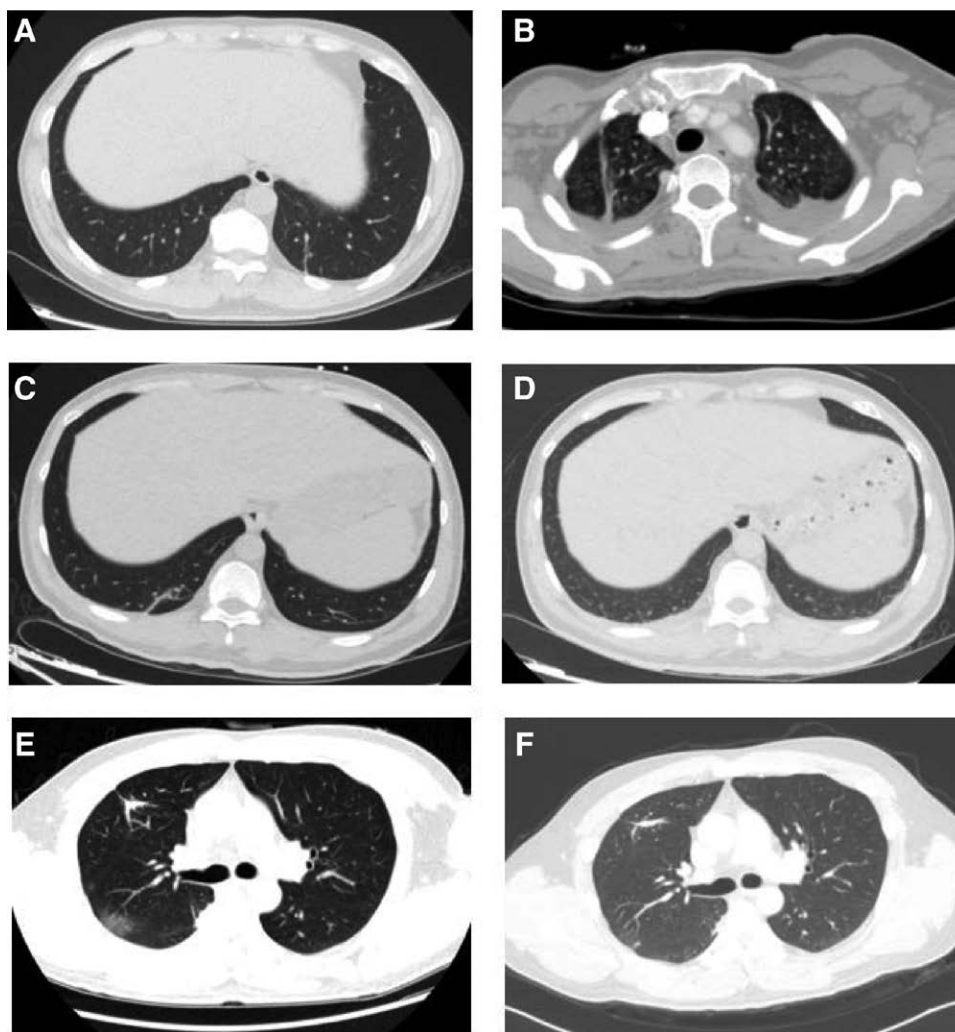


Figure 2. ITI in patients with HL. (A) No.2 in Table 2, when the patient was diagnosed with HL-HLH, chest CT showed a cord-like high-density shadow on the basal segment of his left lung (January 13, 2014). (B) No.8 in Table 2, when the patient was diagnosed with HLH, his chest CT showed a high-density cord-like shadow on the upper lung and an arc-shaped liquid density shadow in both chests (March 8, 2015). (C and D) No.4 in Table 2, when the patient was diagnosed with HLH, chest CT showed a high-density cord-like image on his lower left lung (January 26, 2017) (C). After antibiotic treatment, chest CT showed that the above lesions had disappeared, but nodular high-density shadows appeared on his lungs, and these new lesions were suspected of HL lung invasion (February 7, 2017) (D). (E and F) When a patient was diagnosed with HL (he had no HLH), chest CT showed a patchy, cord-like high-density shadow on his right lung, with blurred edges (March 24, 2017) (E). The patient was not treated with antibiotics, and chest CT showed that the above lung lesions still existed after 19 mo (October 11, 2018). CT = computed tomography, HL = Hodgkin lymphoma, HLH = hemophagocytic lymphohistiocytosis, ITI = intrathoracic infection.

with human immunodeficiency virus (HIV) infection in 2003 and was diagnosed with HL-HLH in 2009. Therefore, in addition to HL, the HIV infection could have also triggered HLH in this patient.^[13] Chaker et al reported another patient with HL-HLH. This patient was first diagnosed with chronic lymphocytic leukemia and was diagnosed with HL-HLH after receiving chemotherapy in which fludarabine was used. It is worth noting that HL, chronic lymphocytic leukemia, and even related therapeutic drugs can trigger HLH.^[14–16] Other reports showed that HL-HLH was mainly found in LDCHL

and MCCHL,^[11,12,17,18] but these reports did not indicate whether these patients had HLH as the initiating symptom of HL.^[17]

Unlike the literature, all HL-HLH in our cohort were found in MCCHL. MCCHL belongs to classic HL, and its histological feature is the presence of multiple cellular components in the diseased tissue. Its incidence is low in European and American countries but high in developing countries and HIV-infected people. MCCHL is closely related to EBV infection because EBV can be detected in up to 75% of patients.

Table 3
Clinical characteristics of 81 patients with MCCHL.

Group	N	Median age (years)	Stage III and IV	EBV positive	HLH incidence※
With ITI	26	45.5	57.7% (15/26)	70.0% (14/20)	26.9% (7/26)
Without ITI	55	33	47.3% (26/55)	75.9% (22/29)	1.8% (1/55)

※: chi-square test, with ITI group and without ITI group, $P = .002$.

EBV positive = EBV positive in situ hybridization, ITI = intrathoracic infection, MCCHL = mixed-cellularity classic Hodgkin lymphoma.

Indeed, only MCCHL triggered HLH in our cohort, but this does not mean that HL-HLH only comes from MCCHL. This is because MCCHL was the most common type of HL in our cohort. The number of other HL types was so small that the HLH they trigger was not found; the high frequency of EBV infection in our cohort of MCCHL patients could trigger HLH; and objectively, patients who presented HLH as the initial symptom were mainly MCCHL.

4.3. ITI associated with HL and its role in triggering HLH

The ITI in our cohort was not the same as the HLH pulmonary involvement described by Seguin et al. This report observed a group of 219 patients with HLH, 118 of whom had lung involvement. These patients showed coughing or difficulty breathing. Chest x-rays showed interstitial infiltrates with centrilobular nodules, ill-defined consolidation, or focal ground-glass opacity, and pleural effusion and lymphadenopathy were seen in roughly half of the patients. Of the 118 patients, 52 could be identified as having an infection, 34 could be identified as having pulmonary edema, and 22 could be identified as having a tumor (mainly lymphoma).^[19]

The intrapleural lesions in our cohort were characterized by small lung lesions and small pleural effusions, which can appear in many diseases and even in healthy people. These intrapleural lesions were diagnosed as “pneumonia disease” and “pleural effusion” by radiologists. An accidental discovery led us to observe that these lesions responded well to antibiotics since our antibiotic treatment was exclusive for the fever of HLH (suspected as infectious fever before the diagnosis of HLH) rather than to treat these small lesions. Moreover, these lesions were not lymphoma or tuberculosis because they continued to exist without antibiotic treatment, and they would not worsen with high-dose corticosteroid treatment without antituberculosis treatment. The above observation led us to consider these lesions as infectious lesions and define them as ITI. The ITI in our cohort was relatively mild, which makes it difficult to determine ITI as the only trigger of HLH, as the infections that trigger HLH tend to be more severe.^[20] Therefore, we speculate that ITI may cooperate with other clinical features in HL to trigger HLH.

Among the patients in our cohort who were tested for EBV, the incidence of EBV infection in the MCCHL group was significantly higher than that in the NSCHL and LRCHL groups, suggesting that MCCHL is more closely related to EBV infection. We cannot directly observe the relationship between EBV infection and HLH, because only some patients in our cohort had been tested for EBV. The ITI lesions in our cohort responded well to antibiotic (not antiviral) treatment, indicating that the ITI lesions we observed were caused by bacterial infection rather than EBV infection.

4.4. The treatment of ITI may be beneficial to HL-HLH

It is currently believed that the treatment of lymphoma-related HLH should be based on the treatment of lymphoma itself. The mortality rate after the diagnosis of HLH was 28.8%, and the OS at 6 months was 45.7%, suggesting that lymphoma-related HLH responded poorly to treatment and the patients had a poor prognosis.^[5,7,21] In addition, there are reports that the prognosis of HLH caused by T-cell lymphoma is poor, while HLH caused by B-cell lymphoma is less aggressive.^[22] Our HL-HLH has a very poor prognosis, which may be related to the following: the prognosis of MCCHL is inherently poor,^[10] all MCCHL with HLH were stage IV, the HL-HLH in our cohort received insufficient treatment, and in particular, HLH may be an extremely important factor in the poor prognosis of HL.

The treatment of HL-HLH patients in our cohort was irregular, and we are unable to make a treatment recommendation.

Since ITI could trigger HLH and responded well to antibiotics, we recommend antibiotic therapy for patients with both HL-HLH (or HL close to the diagnostic criteria for HLH) and ITI to prevent ITI from triggering HLH or making HLH refractory.

5. Conclusion

In summary, we found that 5.7% of HL patients in our cohort had HLH as the initial symptom. We also found that ITI in HL patients may trigger HLH in conjunction with other clinical factors associated with HL. To the best of our knowledge, this is the first report on how ITI is related to HL-HLH. However, the number of cases in our cohort was not large enough, and we cannot determine the pathogenic microorganisms that caused ITI. Further research is needed to clarify these questions.

Author contribution

Yan Huang and Bin-Bin Tan participated in the study design, did lab detection and helped to collect the data.

Ji-Cheng Zhou conceived the study, drafted the first version of the article, and did data analyses.

Yin-Ying Wu helped to collect the data and did data analyses.

Zhen-Jie Bai helped to collect the data and did data analyses.

Min-Lan Liang helped to collect the data and did data analyses.

Wei-hua Zhao helped to collect the data and did data analyses.

All authors contributed to the interpretation of data and read and approved the final article.

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