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ORIGINAL ARTICLE

Clinical characteristics and follow-up analysis of adult-onset Still's disease complicated by hemophagocytic lymphohistiocytosis

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Abstract We evaluated clinical characteristics and prognosis for adult-onset Still's disease (AOSD) complicated by hemophagocytic lymphohistiocytosis (HLH). We retrospectively identified cases of AOSD with ($n = 10$) and without ($n = 305$) HLH complications. We reviewed their medical records, completed follow-up through outpatient clinic and telephone interviews, and analyzed their clinical symptoms, signs, laboratory test results, treatments, and prognosis. More AOSD patients with HLH developed hepatomegaly, bleeding, serositis, and neurologic symptoms than those without HLH, and they more commonly presented with leukopenia, thrombocytopenia, severe anemia, severe liver function abnormalities, decreased fibrinogen, elevated immunoglobulin, and bone marrow hemophagocytosis. The ten patients with AOSD complicated by HLH were treated with high-dose steroids or pulse steroid therapy, and eight of them also received cytotoxic drugs, while biological agents showed poor response. Follow-up results indicated that AOSD patients overall had good prognosis, while those with HLH showed worse prognosis, including higher relapse and readmission rates and increased mortality. In patients with AOSD, unexplained decreased blood cells, severe liver dysfunction, and/or hemophagocytosis in the bone marrow should be considered as signs of HLH complication. Patients with AOSD complicated by HLH have worse prognosis and higher relapse rates compared to AOSD patients without HLH complications. Thus, these patients should undergo frequent and careful follow-up.

Keywords Adult-onset Still's disease · Complication · Follow-up · Hemophagocytic lymphohistiocytosis

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Introduction

Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis (HLH), is an aggressive and life-threatening syndrome of excessive immune activation and cytokine storm [1]. It is a rare disease and is more commonly observed in children than in adults. HLH can be secondary to a variety of events that disrupt immune homeostasis, such as malignancies, infections, and autoimmune diseases [2, 3]. Among the autoimmune diseases, it is most common for adult-onset Still's disease (AOSD) to be complicated by HLH, and there have been several case reports describing their co-occurrence [4–6]. However, no reports have compared cases of AOSD with HLH to those without HLH, have analyzed the clinical characteristics, or have conducted follow-ups of patients with the condition. Thus, we reviewed and analyzed cases of AOSD in order to determine information related to early detection of this complication.

Materials and methods

Study subjects

We conducted a search of the electronic medical records of Peking Union Medical College Hospital (PUMCH) and identified 463 cases of AOSD diagnosed from August 2004 to July 2014. Each case of AOSD was diagnosed by at least two qualified rheumatologists in PUMCH together, according to the criteria described below. Among these cases, there were 315 patients older than 14 years (according to the classification criteria for AOSD in 1992 [7]) of age with detailed and reliable medical records, including 10 patients who also met the diagnostic criteria for HLH and 7 patients suspected to have HLH complication but who did not meet the diagnostic criteria.

Study methods

We retrospectively evaluated patients' medical records to analyze the clinical manifestations, physical examination results, laboratory results, treatments, and prognoses of these patients.

Diagnostic criteria

To diagnose HLH, we used the diagnostic criteria used in the HLH-2004 trial, as described in Table 1 [8]. And, to diagnose AOSD, we used the diagnostic criteria known as the Yamaguchi criteria, established in 1992, as shown in Table 2 [7, 9].

Table 1 Diagnostic criteria from HLH-2004

Molecular identification of an HLH-associated gene mutation (i.e., *PRF1*, *UNC13D*, *STX11*, *STXBP2*, *Rab27A*, *SH2D1A*, or *BIRC4*). Children require documentation of homozygosity or compound heterozygosity for HLH-associated gene mutations. By comparison, heterozygosity may be sufficient for adults if they have clinical findings associated with HLH.

OR

5 of the following 8 findings:

- Fever ≥38.5 °C
- Splenomegaly
- Peripheral blood cytopenia, with at least two of the following: hemoglobin <9 g/dL (for infants <4 weeks, hemoglobin <10 g/dL); platelets <100,000/μL; absolute neutrophil count <1000/μL
- Hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent NK cell activity
- Ferritin >500 ng/mL (the author prefers to consider a ferritin >3000 ng/mL as more indicative of HLH)
- Elevated soluble CD25 (soluble IL-2 receptor alpha) two standard deviations above age-adjusted laboratory-specific norms

Diagnostic criteria are from the HLH-2004 trial [8]

HLH hemophagocytic lymphohistiocytosis, *NK* natural killer

Statistical analysis

SPSS 18.0(SPSS Inc., Chicago, IL) was used to analyze the statistics. For statistical analysis, categorical data are presented. Statistical comparisons between experimental groups were analyzed by Fisher's exact test, and a two-tailed $p < 0.05$ was taken to indicate statistical significance.

Results

Patient characteristics

Among the 315 patients enrolled in the study, there were 89 men and 226 women, with a median age of 33.2 years (range, 14–76 years), and the number of diagnosed cases increases each year. Among the ten patients with AOSD complicated by HLH (3.2 % of all AOSD patients in the study), there were two men and eight women, with a median age of 25.5 years (range, 14–38 years). There were no significant differences between the two groups with respect to sex ratio and age.

Clinical features

We reviewed and compared the clinical features of the 305 patients with AOSD without HLH with those of the 10 patients with AOSD complicated by HLH (Table 3). The results suggest that, compared with AOSD patients without HLH,

Table 2 Classification criteria for adult-onset Still's disease

Yamaguchi criteria: The Yamaguchi criteria require the presence of five features, with at least two being major diagnostic criteria. In addition, the presence of any infection, malignancy, or other rheumatic disorder known to mimic AOSD in its clinical features precludes the diagnosis of AOSD, at least for the purpose of research.

The four major Yamaguchi criteria are as follows:

- Fever of at least 39 °C (102.2 °F) lasting at least 1 week
- Arthralgia or arthritis lasting two weeks or longer
- A non-pruritic macular or maculopapular skin rash that is salmon-colored in appearance and usually found over the trunk or extremities during febrile episodes
- Leukocytosis (10,000/μL or greater), with at least 80 % granulocytes

The minor Yamaguchi criteria include the following:

- Sore throat
- Lymphadenopathy
- Hepatomegaly or splenomegaly
- Abnormal liver function studies, particularly elevations in aspartate and alanine aminotransferase and lactate dehydrogenase concentrations
- Negative tests for antinuclear antibody (ANA) and rheumatoid factor (RF)

Classification of AOSD is based on the Yamaguchi criteria [7, 9]. AOSD, adult-onset Still's disease

Table 3 Clinical features of AOSD with and without HLH

Manifestation	AOSD with HLH $N=10$	AOSD without HLH $N=305$	p value
Fever	10 (100 %)	305 (100 %)	No
Jaundice	3 (30 %)	27 (8.9 %)	0.059
Hepatomegaly	6 (60 %)	57 (18.7 %)	0.006
Splenomegaly	7 (70 %)	132 (43.3 %)	0.113
Lymphadenopathy	6 (60 %)	102 (33.4 %)	0.097
Neurologic symptoms	4 (40 %)	13 (4.3 %)	0.001
Bleeding tendency	3 (30 %)	9 (3.0 %)	0.004
Rash	9 (90 %)	223 (73.1 %)	0.464
Serositis	6 (60 %)	33 (10.8 %)	<0.001
Arthralgia/arthritis	2 (20 %)	144 (47.2 %)	0.113
Myalgia	2 (20 %)	78 (25.6 %)	1.000
Sore throat	1 (10 %)	97 (31.8 %)	0.182

Data are presented as *n* (%)

AOSD adult-onset Still's disease, *HLH* hemophagocytic lymphohistiocytosis

those with HLH presented more hepatomegaly, splenomegaly, lymphadenopathy, jaundice, bleeding, serositis, and neurological symptoms, with hepatomegaly, bleeding, serositis, and neurological symptoms being the most significant. In contrast, they presented with less arthritis and sore throat, although these differences were not significant.

Laboratory results

The typical laboratory findings of the two groups are summarized in Table 4. Compared with AOSD patients with HLH, those without HLH rarely presented with leukopenia, thrombocytopenia, severe anemia, severe liver function abnormalities, decreased fibrinogen levels (in contrast, fibrinogen levels were elevated in 248 [81.3 %] patients with AOSD), and bone marrow hemophagocytosis. Notably, if patients presented with severe liver dysfunction or hemophagocytosis in bone marrow, the possibility of HLH complications was even higher.

Diagnosis

Of the ten patients diagnosed with AOSD complicated by HLH, four were diagnosed with HLH before they were diagnosed with AOSD, and all had fever for more than 1 month before diagnosis. In the other six cases, two developed HLH more than 1 year after being diagnosed with AOSD (4 years and 15 months, respectively; since both of them had elevated standardized uptake value (SUV) in positron emission tomography/computed tomography (PET/CT), a diagnosis

Table 4 Laboratory results for patients with AOSD with and without HLH

Manifestation	AOSD with HLH $N=10$	AOSD without HLH $N=305$	p value
Leukopenia	7 (70 %)	0 (0 %)	<0.001
Anemia	8 (80 %)	210 (68.9)	0.729
Thrombocytopenia	8 (80 %)	0 (0 %)	<0.001
Liver function abnormalities	10 (100 %)	171 (56.1 %)	0.007
Coagulation abnormalities	8 (80 %)	248 (83.1 %)	1.000
Bone marrow hyperplasia	10 (100 %)	105[a] (89.0 %)	0.597
Bone marrow hemophagocytosis	10 (100 %)	0 (0 %)	<0.001
Elevated ferritin level	10 (100 %)	285 (94.8 %)	1.000
ESR and CRP elevation	10 (100 %)	296 (97.0 %)	1.000
Fibrinogen decrease	7 (70 %)	2 (0.6 %)	<0.001
Immunoglobulin elevation	5 (50 %)	261 (85.6 %)	0.010

Data are presented as *n* (%). AOSD, adult-onset Still's disease

HLH hemophagocytic lymphohistiocytosis, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

[a] 118 patients with AOSD not complicated by HLH underwent bone marrow

of lymphoma was suspected), and the other four patients developed HLH within 3 months after being diagnosed with AOSD. The average course of AOSD for these ten patients was 9.45 months, while the average course after their HLH diagnosis was 43.9 days.

Treatment

All ten patients with AOSD complicated by HLH received broad-spectrum antibiotic treatment for possible pulmonary infections (six had pleuritis and four showed patches on CT). Two of them had cytomegalovirus infection complications, and anti-virus treatments were demonstrated to be effective. All ten also received high-dose glucocorticoids (>1 mg/kg prednisone), and four received cyclosporine after 1–2 weeks of taking glucocorticoids. Three received cyclophosphamide, which was well tolerated, and one received VP-16. Nine patients underwent blood transfusion for supportive care. After treatment, eight patients demonstrated decreases in erythrocyte sedimentation rate and C-reactive protein levels, and four patients demonstrated a rapid decrease in ferritin level (>50 %). However, the other two patients did not respond well to therapy and demanded discharge.

Follow-up

We performed a follow-up of all 305 AOSD patients without HLH and 10 with HLH, as shown in Fig. 1.

In the AOSD without HLH group ($n=305$), 14 died in the hospital, and the direct causes of death were severe infection ($n=11$), pulmonary hypertension ($n=2$), and uncontrolled bleeding and shock ($n=1$). Of the 47 patients readmitted to the hospital, the average time to remission was 13 months (range, 1–37 months). Overall, up until most recent follow-up, 183 patients have remained stable and in remission; disease progression has occurred in 35 patients, 22 patients have died, and we lost contact with 51 patients. We identified 28 patients with new diagnoses: 8 were ultimately diagnosed with systemic lupus erythematosus, 17 were diagnosed with pathologically confirmed lymphoma, 2 were diagnosed with lung cancer, and 1 was diagnosed with a gastrointestinal tumor.

In the AOSD with HLH group, all ten patients were critically ill while in the hospital. One died in the hospital, and three demanded discharge after getting critically ill; two of them died 1 week after discharge, and the other one was readmitted due to severe aplastic anemia. That patient's disease was controlled after using anti-thymocyte globulin (ATG) and cyclosporine for 3 months. Thus, as of the most recent follow-up, seven patients were taking steroids and/or immunosuppressant drugs and remained stable and in remission and stable. However, four were readmitted due to disease flare, 1–4 months after discharge.

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation and cytokine storm. The excessive activation of lymphocytes and macrophages could be triggered by several pathologic conditions. Autoimmune-disease-associated hemophagocytic syndrome (AAHS) is a relatively common cause of secondary

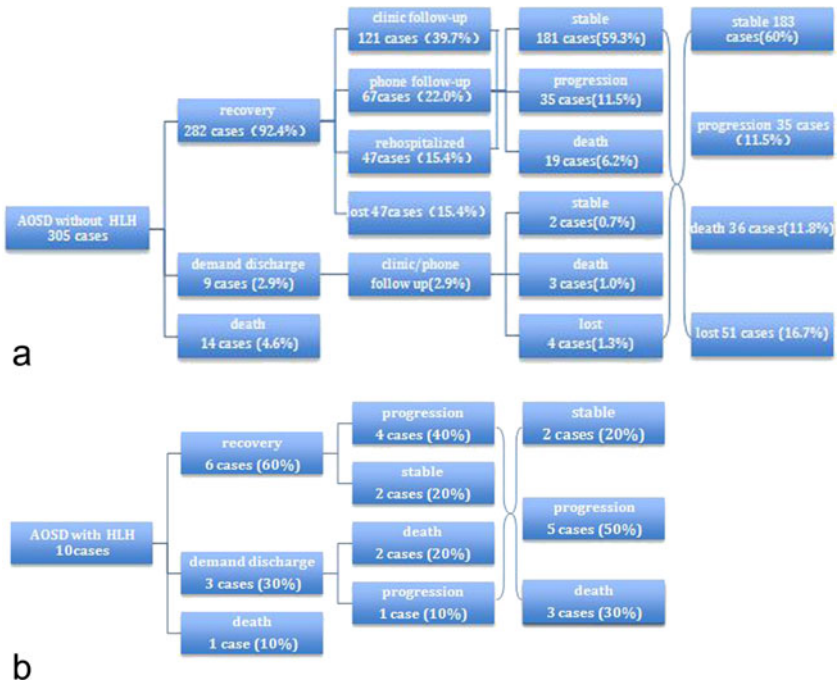

Fig. 1 Flowchart showing patient follow-up. **a** Follow-up of patients diagnosed with adult-onset Still's disease (AOSD) without hemophagocytic lymphohistiocytosis (HLH). **b** Follow-up of patients diagnosed with AOSD complicated by HLH

HPS, but even so, the incidence is not high. In a review of the published literature, we found that of the adult autoimmune diseases, AOSD complicated by HLH is the most common manifestation, followed by systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis, polyarteritis nodosa, etc. In this study, we also reviewed cases of HLH treated at PUMCH and reached similar conclusions; of the autoimmune diseases complicated by HLH, the diseases from most to least frequent were AOSD, systemic lupus erythematosus, vasculitis (including Bechet's disease, polyarteritis nodosa, antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, and Takayasu's arteritis), Sjögren's syndrome, rheumatoid arthritis, dermatomyositis, and mixed connective tissue disease.

AOSD has a similar pathophysiological process to that of HLH. Both involve massive macrophage activation and cytokine storm, so they have several similar clinical manifestations, such as fever, enlargement of the liver and spleen, and elevated serum ferritin levels. Thus, it is difficult to differentiate whether AOSD is complicated by HLH [10–14]. Studies have suggested that pleuritis, acute respiratory distress syndrome, leukopenia, and thrombocytopenia are rare in AOSD [14, 15]. Another study indicated that serum triglyceride level is helpful in both diagnosing HPS and evaluating its prognosis, as a high serum triglyceride level is more typical in AOSD with than without HLH, and its level can decrease with effective treatment; thus, it could be used as a prognosis laboratory marker [16]. Two recent articles noted that serum β2-microglobulin level could be a good predictor of systemic lupus erythematosus complicated by HLH [17, 18]; thus, we examined whether it had similar results for AOSD complicated by HLH. However, unfortunately, in the cases we reviewed, only a few had serum β2-microglobulin level test results, so no significant results could be determined.

PUMCH has diagnosed several AOSD cases in recent years. However, there have only been 10 cases of AOSD complicated by HLH in the past 10 years, with an incidence of 3.2 %. Overall, the clinical manifestations of these cases were non-specific, but the disease progression has been rapid, with a high mortality rate, and has been associated with greater treatment expenses, similar to results that had been reported earlier [19]. Nevertheless, through our study, we concluded that some markers could be highly suggestive of early HLH complications; thus, earlier intervention might be possible.

With respect to basic characteristics, the average age of AOSD patients with HLH was significantly younger than that of those without. With respect to clinical features, the presence of hepatomegaly, bleeding, serositis, and neurological symptoms was significantly higher in AOSD with than without HLH, while the presence of arthritis and sore throat was much lower. With respect to laboratory results, AOSD patients with HLH were more likely to develop leukopenia, thrombocytopenia, severe anemia, and decreased fibrinogen. Significantly, when severe liver dysfunction and bone marrow hemophagocytosis occur, HLH complications should be highly suspected. With respect to treatment, our study suggests that AOSD alone or in combination with infection can both lead to HLH. Additionally, infection could also trigger an AOSD flare and HLH [19, 20]; thus, differentiation would be difficult. Several studies have demonstrated that for patients complicated by HLH, removing the trigger, such as a viral infection, could be vital, and treating the underlying trigger is as important as supportive care; successfully managing them both could decrease disease mortality [20–23]. Notably, previous studies have reported therapeutic responses using clarithromycin in some patients with AOSD, which might be effective both as an antibiotic and as an anti-inflammatory agent. Thus, evaluating the possible roles of clarithromycin and other macrolide antibiotics in AOSD treatment could be intriguing in further studies [24, 25]. In the six cases of patients who recovered, inflammatory markers, such as erythrocyte sedimentation rate, C-reactive protein level, serum triglycerides, and serum ferritin level, obviously decreased. However, for those who responded poorly, having nearly no change in serum ferritin level was associated with a very poor prognosis. Previous studies comparing erythrocyte sedimentation rates and C-reactive protein levels also had similar results, and serum ferritin level may more accurately predict the prognosis of patients with HLH [17, 18, 26, 27]. Thus, it seems crucial to control the hyperinflammatory state in the early stage of treatment for AOSD complicated by HLH.

Currently, there is no international guideline for treating autoimmune diseases associated with HLH. Kumakura et al. performed a meta-analysis of treatment reports for AAHS in PubMed since March 2013, and they concluded that 98.3 % cases received steroids, 24.1 % received intravenous immune globulin (IVIG), 20.7 % received cyclosporine, 14.7 % received cyclophosphamide, and a few patients received biological agents, such as infliximab, etanercept, and rituximab. In their study, 95.7 % of patients received steroids or steroids with immunosuppressant as the first-line treatment; the rate of steroid plus immunosuppressant use was 75 %, higher than the rate of 52.9 % for steroid use only. Those who did not respond well to steroid treatment were administered cyclophosphamide, cyclosporine, or IVIG. The authors found that the response rate of cyclophosphamide was 91.6 %, significantly higher than 35.7 % for cyclosporine and 8.3 % for IVIG. Their study also showed a good response to treatment with biological agents [28]. In the HLH-2004 trial, the basic treatment was etoposide, dexamethasone, and cyclosporine. Etoposide is a cytotoxic agent that can suppress the mononuclear phagocytic system, suppress viral duplication, and enhance cell apoptosis, making it a crucial agent for treating HLH. Intrathecal therapy is recommended for patients with CNS involvement. Some experts think that a serum ferritin level beyond 10,000 μg may be an indicator to use IVIG

[21, 22, 26]. All ten patients in our study received high-dose steroids, four received cyclosporine, three received cyclophosphamide and showed good tolerance, one received etoposide, and four received IVIG. Only one patient received an anti-TNF agent, and this patient showed a poor response.

Our study showed that AOSD patients had a good prognosis overall, but some patients may develop other diseases, become unresponsive to treatment, or even die, suggesting that even when AOSD is diagnosed without other complications, regular follow-up is recommended, and ruling out an underlying infection, tumor, or other autoimmune disease should be always considered. Meanwhile, if AOSD patients have HLH complications, the prognosis is much worse. A multi-center survey in France showed that the mortality rate of AAHS could be as high as 38.5 % [4]. Recently, another case review in China indicated that the prognosis of AOSD with HLH may be favorable to other diseases complicated by HLH (e.g., tumor and infection). In our study, the prognosis for AOSD complicated by HLH was worse than that for HLH secondary to other autoimmune diseases (17 cases, with a remission rate of 77 %).

In recent years, along with more physicians' acknowledgment of HLH and AOSD, the diagnosis of AOSD complicated with HLH has increased. In the past 10 years, PUMCH has diagnosed 315 AOSD cases, and of those, 86 cases were diagnosed in 2013 and 2014. Of the ten cases of AOSD with HLH, only one case was diagnosed in 2006; the other nine were all diagnosed in 2013 and 2014. Our results indicate that for AOSD patients, if there is recurrence, unexplained blood cell decrease, obvious reticuloendothelial system activation, unexplained severe liver dysfunction, coagulation abnormalities, bleeding, or more importantly hemophagocytosis observed in the bone marrow, complication with HLH should be seriously suspected. We also conclude that besides these changes, serum ferritin levels should be monitored, as they could predict prognosis. We believe that the results of our study provide methods for distinguishing this critical complication during the disease's early stage, facilitating early intervention.

In our study, the overall disease course has not been long, and some of the patients could develop other diseases in the future, as it has been shown that AOSD patients with HLH complications have a high likelihood of being diagnosed with other conditions, such as lymphoma [14]. AOSD patients overall have a high rate of recurrence and readmission, and AOSD patients complicated by HLH have even higher rates of recurrence and readmission, making regular follow-up more important for this group. We will continue to follow these patients and monitor their symptoms and changes in laboratory results. Furthermore, a greater number of cases of AOSD with HLH may lead to more significant conclusions, and we will continue to enroll such cases for further study.

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Compliance with ethical standards All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All study participants provided their written informed consent prior to inclusion in the study.

Conflict of interest The authors declare no conflicts of interest. The authors confirm that they have full control of all primary data and that they agree to allow the journal to review their data if requested.

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