Clinical features and prognosis in 82 patients with adult-onset Still's disease

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Abstract

Objective

To assess the clinical features, laboratory findings, and response to therapy according to disease course, and analyse the predictive factors for unfavourable outcomes in patients with adult-onset Still's disease (AOSD).

Methods

We retrospectively reviewed the medical records of 82 patients from January 1992 to December 2010 at a single tertiary hospital. Thirty-three had monocyclic disease, 33 experienced at least one relapse, and 14 had chronic disease. Patients were divided into those with favourable (monocyclic, n=33) and unfavourable (polycyclic or chronic and death, n=49) outcomes.

Results

The major clinical features were high spiking fever (96.3%), polyarthralgia (85.4%), skin rash (80.5%), myalgia (70.7%), and sore throat (68.3%). Analysis of prognostic factors for the 2 groups showed that polyarthralgia, elevated erythrocyte sedimentation rate, high serum lactate dehydrogenase, and low dose of initial glucocorticoids were related with unfavourable outcomes. An insufficient starting dosage of prednisolone or its equivalent (<30 mg/day) was the most significant predictive factor (OR 6.476, p=0.007) for chronic and relapsing disease, markedly decreasing response rates.

Conclusion

Although AOSD is a benign disease, relapses are common and a chronic disease requires immunosuppressive therapy, that these unfavourable patients show significantly longer time from initiation of treatment to remission. Hence, it is important to control disease activity at the start of treatment with sufficient glucocorticoids.

Key words

adult-onset Still's disease, outcome, corticosteroid

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Introduction

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology, characterised by high spiking fever, evanescent rash, arthralgia, and leukocytosis (1). Serial cases of AOSD have been reported worldwide since it was first described by Eric Bywaters in 1971 (2), however, there is as yet no consensus on its prevalence, clinical manifestation and outcomes which are varied by geography and ethnic background (3-7).

Although AOSD is a relatively benign disease, relapses are common and chronic disease courses require prolonged glucocorticoids and immunosuppressive therapy. Previous studies have reported that arthritis (poly or root joint) or rash at disease onset are predictors of progression to chronic disease (8, 9), and that increased ferritin concentration to 5 times the upper limit of normal is associated with poor prognosis (10). Determination of the risk factors prognostic of disease activity and severity is important in patient diagnosis and treatment. We therefore evaluated the clinical features, disease course and long term outcomes in patients with adult-onset Still's disease diagnosed and treated at a single tertiary hospital, and analysed the factors predictive of unfavourable outcomes.

Patients and methods

Patient selection

We retrospectively reviewed the medical records of 82 patients (60 women, 22 men), diagnosed with AOSD according to the Yamaguchi (11) criteria in a single tertiary medical center between 1992 and 2012. All patients fulfilled the preliminary criteria for AOSD proposed by Yamaguchi *et al*., and were older than 16 years of age. Infections, malignancies, and other autoimmune disorders were excluded by cultures and by assaying for serologic markers of bacteria, viruses, fungi, and mycobacteria, and performed computed tomography (CT) scans ranging from the neck to the abdomen. Bone marrow or lymph node biopsies were done, if abnormal peripheral blood cell counts or palpable lymph nodes were noted. Lag time was defined as the mean duration of illness before diagnosis of AOSD, and follow-up time was defined as the period from diagnosis of AOSD to final visit to the outpatient clinic. All patients were observed for more than 12 months. The severity of AOSD was determined using the Pouchot score (9), which assigns 1 point to each of 12 manifestations: fever, typical rash, pleuritis, pneumonia, pericarditis, hepatomegaly or abnormal liver function tests, splenomegaly, lymphadenopathy, leukocytosis $\geq 15{,}000/mm^3$, sore throat, myalgia, and abdominal pain (maximum score, 12). Medical records describing disease duration and complications were also reviewed.

Demographic and clinical data

At diagnosis, the following clinical information was assessed: fever, typical rash, arthralgia or arthritis, myalgia, lymphadenopathy, sore throat, splenomegaly, hepatomegaly, abdominal pain, weight loss and GI symptoms. Pleural effusion or pleuritis and lung parenchymal involvement were evaluated by a chest radiograph or CT scan, and pericardial effusion or pericarditis were evaluated by echocardiography. Treatment regimens used in the course of disease were assessed. Steroid dosage was recorded as the initial starting dose and total cumulative dose; a low to moderate dose was defined as <0.5 mg/kg/day (<30 mg/day prednisolone) and a high dose as >0.5 mg/kg/day.

We also recorded total white blood cell and platelet counts; haemoglobin (Hb) concentration; erythrocyte sedimentation rate (ESR); and serum concentrations of C-reactive protein (CRP), creatinine, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), rheumatoid factor (RF), antinuclear antibody (ANA), and ferritin.

Remission was defined as the complete disappearance of systemic symptoms and normalisation of laboratory evidence of disease activity for at least 2 consecutive months, regardless of therapy. Recurrence was characterised by systemic flares occurring after remission and requiring additional therapy.

Patients were categorised into four groups as described by Cush *et al*. (12)

Table I. Baseline characteristics of patients with adult-onset Still's disease.

Variables	n=82
Age at onset, yrs	34.0 ± 14.9 (range, 16–74)
Onset between 16~35 yrs (%)	45/82 (54.8)
Sex, F/M (%)	60/22 (73.2)
Lag time, month*	1.0 ± 46 (range, 0.2–336)
Follow-up time, month	36.0 ± 42.5 (range, 12–215)
Pouchot score†	6.0 ± 1.9 (range, 1–12)

*Lag time: duration from onset of symptoms to diagnosis of AOSD.
†Scores (0~12) described by Pouchot, et al. Medicine (Baltimore) 1991;70:118-36. Numeric variables are expressed as number (%) of patients/total 82 patients. Continuous variables are expressed as median ± IQR (range).

depending on whether their disease course was monocyclic, polycyclic, or chronic and death. A monocyclic course was defined as a single episode for more than 2 months but less than 1 year followed by sustained remission through the entire follow-up period. A polycyclic course was characterised by recurrent systemic flares with remissions between flares. A chronic course was defined as at least one episode of persistent symptoms lasting longer than 1 year. Expired patients were defined as those who were diagnosed with AOSD and died during follow-up. Patients having a monocyclic disease course were regarded as having favourable outcomes, and those in the other three groups were regarded as having unfavourable outcomes.

Statistical analysis

All statistical analyses were performed using SPSS software 18. Descriptive statistics were reported as median ± IQR and probability values of $p<0.05$ was considered statistically significant. The odds ratio (OR) of parameters differing significantly between patients with favourable and unfavourable outcomes and the correlations between parameters were assessed by univariate logistic regression analyses. Clinically significant risk factors to predict poor outcomes were selected as covariates in multivariate logistic regression analyses and the results were expressed as the OR with its 95% confidence intervals (95%CI).

Results

Clinical characteristics and treatment

The 82 patients consisted of 22 men (26.8%) and 60 women (73.2%), with a median age at onset of 34.0±14.9 years (range, 16 to 74 years). Median lag time from symptom onset to diagnosis was 1.0±46 months (range 0.2–336 months) and median follow-up time was 36.0±42.5 months. The baseline characteristics of these patients are summarised in Table I.

Of the 82 patients, 79 (96.3%) had high spiking fever with body temperature ≥39°C for more than a few days, with the fever being remitting or irregular with 36 (43.9%) patients having significant weight loss at presentation. Sixty-six (80.5%) patients had a typical salmon-pink macular or maculopapular rash, mostly located in the trunk and the upper and lower extremities. Seventy patients (85.4%) had polyarthralgia, with six showing sacroiliac involvement. We found that 58 (70.7%) and 56 (68.3%) patients complained of myalgia and sore throat, respectively, symptoms that usually coincided with the fever spike and subsided when the body temperature returned to normal. Lymphadenopathy was noted in 45 (54.9%) patients, frequently involving the cervical region and hepatosplenomegaly in 36 (43.9%) patients. Pericarditis was present in 13 (15.9%) patients and pleural effusion in 25 (30.5%). Table II presents a comparison of the disease course and follow-up findings of our AOSD patients and previous series.

Bone marrow biopsy and/or aspiration were obtained from 56 of the 82 patients (68.3%) and the mean cellularity was 62.4±15.3 (15-90) with most showing granulocyte hyperplasia. Six (11%) patients had haemophagocytosis, 5 (9%) patients had chronic active EBV infection, and none had malignant cells. The 56 patients who underwent bone marrow biopsies were divided into 2 groups: those with and without reactive haemophagocytic syndrome (RHS) features. These groups were similar in sex and age distribution, whereas thrombocytopenia, lactate dehydrogenase, and Pouchot score were significantly higher in patients with than without RHS. Moreover, disease outcomes differed between these two groups, in that patients tended to have a chronic disease course and more complications (Table III). Lymph node biopsies were obtained from 20 patients, showing reactive lymphoid hyperplasia. Skin biopsies were obtained from 27 patients, showing perivascular inflammation by lymphocytes and neutrophils; and liver biopsies were obtained from 15 patients, showing mild periportal inflammation with lymphocytes.

Analysis of laboratory parameters at presentation revealed that the mean total white blood cell count in the 82 patients was 13,351.2 /mm^3, their haemoglobin concentration was 10.3 g/dl and their platelet count was 308,500 /mm^3. ESR was elevated in most patients and ranged from 4-130 mm/h with a mean of 70.1 mm/h. Mean serum CRP concentration was 11.6 mg/L and 71 patients (86.6%) had hepatic dysfunction. Serum ferritin concentration was increased in 77 patients, with 61 having a serum ferritin concentration >1,000 ng/ml.

Clinical outcome and prognosis

Of the 82 patients, 33 (40.2%) had monocyclic disease, 33 (40.2%) had at least one relapse and 14 (17.1%) had chronic disease. Two (2.4%) patients died, 1 from pulmonary hypertension and 1 from cholecystitis sepsis. We found that 38 patients (46.3%) relapsed at least once, with 19 (23.2%) having one relapse, 11 (13.4%) having 2, and 8 (9.6%) having 3 or more. Patterns observed at recurrence were similar to those observed initially.

Patients were divided into those with a favourable (monocyclic course; n=33) and those with an unfavourable (chronic, polycyclic, or death; n=49) course. We found that polyarthralgia ($p=0.01$), and high LDH ($p=0.03$) were significantly associated with an unfavourable disease course, otherwise the baseline patient characteristics were much the same in each group (Table IV). Eighty

Table II. Clinical characteristics of patients with AOSD in our study and previous series.

	Our series n=82	Zeng (4) n=61	Fautrel (20, 21) n=72	Pouchot (9) n=62	Yamaguchi (11, 22) n=90	Pay (23) n=95
Ethnicity	**Korean**	Chinese	French	Canadian	Japanese	Turkish
Female	**60 (73.2)**	45 (73.8)	NA	28 (45.9)	60 (66.7)	50 (52.6)
Onset between age						
17 and 35 years	**45 (54.8)**	29 (47.5)	NA	50 (80.6)	48/78 (61.5)	50 (52.6)
Fever ≥39 °C	**79 (96.3)**	61 (100.0)	61 (84.7)	62 (100.0)	63/83 (75.9)	94 (98.9)
Rash	**66 (80.5)**	54 (88.5)	51 (70.8)	54 (87.1)	72/83 (86.7)	78 (82.1)
Arthritis	**70 (85.4)**	50 (82.0)	64 (88.8)	58 (93.5)	62/86 (72.1)	81 (85.3)
Sore throat	**56 (68.3)**	44 (72.1)	38 (52.7)	57 (91.9)	58/83 (69.9)	63 (66.3)
Lymphadenopathy	**45 (54.9)**	32 (52.5)	32 (44.4)	46 (74.2)	59/86 (68.6)	35 (36.8)
Hepatomegaly	**19 (23.1)**	8 (13.1)	NA	27 (43.5)	42/87 (48.3)	43 (45.3)
Splenomegaly	**34 (41.4)**	23 (37.7)	32 (44.4)	34 (54.8)	56/86 (65.1)	40 (42.1)
Pericarditis	**13 (15.9)**	15 (24.6)	15 (20.8)	23 (37.1)	9/87 (10.3)	8 (8.4)
Pleuritis	**25 (30.5)**	11 (18.0)	NA	33 (53.2)	11/89 (12.4)	21 (22.1)
Myalgia	**50 (70.7)**	17 (27.9)	NA	52 (83.9)	50/89 (56.2)	66 (69.5)
Weight loss (>10 %)	**36 (43.9)**	7 (11.5)	NA	41 (66.1)	40/72 (55.6)	17 (17.9)
GI symptoms	**22 (26.8)**	NA	NA	30 (48%)	NA	NA

*NA : not available. Data are no. (%).

patients (97.6%) were treated with corticosteroids including prednisone, prednisolone, methylprednisolone, hydrocortisone, and triamcinolone at disease onset. Moreover, 53 patients (64.6%) received disease-modifying anti-rheumatic drugs (DMARDs) or immunosuppressive drugs, including methotrexate (n=49), hydroxychloroquine (n=10), sulfasalazine (n=5), leflunomide (n=2), infliximab (n=2), adalimumab (n=1), anakinra (n=1), cyclosporine (n=1), azathioprine (n=9), and IVIG (n=1) during the course of the disease. Table IV shows the clinical, laboratory and treatment response results of patients with favourable and unfavourable disease courses.

Table III. Characteristics of AOSD patients with and without reactive haemophagocytic syndrome (RHS).

	AOSD without RHS (n=50/56*)	AOSD with RHS (n=6/56*)	*p*-value
Sex	34 F 16 M	4 F 2 M	0.6
Mean age (years)	38 ± 15.6	35 ± 18.4	0.6
Leukocyte count†	12,850.0 ± 8500	11,150.0 ± 2025	0.2
Haemoglobin (g/dL)	10.5 ± 1.9	10.2 ± 1.4	0.7
Platelet count (/uL)	308,420 ± 148.2	228,330 ± 54.0	**0.01**
Ferritin (ug/mL)†	4,309.5 ± 10,468.5	6,935.8 ± 20,132.6	0.6
Creatinine (mg/dl)†	0.7 ± 0.2	0.7 ± 0.1	0.9
AST (IU/L)†	53 ± 46	87.5 ± 1,939	0.09
ALT (IU/L)†	37 ± 56	25.5 ± 576	0.9
LDH (IU/L)†	618 ± 512.7	1,313 ± 2,669.5	**0.05**
Haptoglobin (mg/dL)	314.2 ± 234.2	263 ± 38.4	0.7
Triglycerides (mg/dL)†	89 ± 114.5	100 ± 0.0	0.2
Fibrinogen (mg/dL)	506.5 ± 97.1	389 ± 223.4	0.2
D-dimer (ug/mL)†	3.3 ± 4.9	25 ± 53.6	0.2
Coagulopathy†	7/49 (14.2%)	3/6 (50%)	0.06
CRP (mg/dL)†	11.6 ± 14.5	7.6 ± 11.5	0.5
ESR (mm/h)†	67.5 ± 89	62.5 ± 50	0.6
Recurrence(s) •	19/50 (38%)	3/6 (50%)	0.4
Chronic course	6/50 (12%)	3/6 (50%)	**0.04**
Remission time (months)†	4.5 ± 5	9.0 ± 19.7	0.1
Pouchot score	6.0 ± 1.6	8.5 ± 1.8	**0.04**
Complications	3 (6%)‡	1 (16.6%)§	0.3

* Total number of patients who underwent bone marrow biopsy was 56;
†Continuous variables are expressed as median ± IQR;
• systemic flares occurring after remission and requiring additional therapy;
‡ sepsis, pneumonia, stress induced cardiomyopathy, §meningitis;
~ AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

To determine the risk factors predicting poor patient prognosis, and to assess the effectiveness of initial steroid doses, we compared outcomes in patients initially treated with low ~ moderate dose (≤0.5/kg mg/day) and higher dose (>0.5/kg mg/day) prednisolone or its equivalent. We found that lower steroid dose was significantly correlated with unfavourable outcomes (OR 5.0 (1.520-16.444) p=0.008), with a significantly longer mean time from the initiation of treatment to disease remission (p=0.02). Response rate was also lower in the low dose steroid groups, in that their duration of steroid use was longer (p<0.001) and they received more DMARDs (p=0.002). The odds ratio of risk factors for unfavourable outcome was analysed by multiple logistic regression analysis using clinical variables in relation to poor outcomes; arthralgia, rash, serositis, pouchot score, serum ferritin, and low-moderate steroids use. Initial steroid dosage was a significant predictive factor (OR 6.476, p=0.007) for poor prognosis and shown in Table V.

Table IV. Prognostic factors associated with unfavourable outcomes.

	Favourable (n=33)	Unfavourable (n=49)	OR (95%CI)	*p*-value
Age, years	34 ± 23	34±23	1.007 (0.978-1.038)	0.6
Sex, F/M (%)	20/13 (60)	40/9 (81)	**2.889 (1.057-7.894)**	**0.03**
Lag time, months	1 ± 12.8	3±6.5	1.014 (0.982-1.046)	0.3
Pouchot score	6 ± 2	6±2	1.160 (0.913-1.473)	0.2
Time to remission, months	4.6 ± 2.9	9.0±9.1	1.118 (1.017-1.229)	0.02
Follow-up time, months	26 ± 30.5	42±77	1.021 (1.006-1.037)	0.008
Complications (%) *	0 (0.0)	7 (14.2)	NA	>0.99
Clinical manifestations, n (%)				
Fever ≥39°C	32 (96.9)	47 (95.9)	0.734 (0.064-8.443)	0.8
Weight loss			0.596 (0.244-1.455)	0.2
Polyarthralgia	24 (72.7)	46 (93.8)	**5.75 (1.423-23.242)**	**0.01**
Rash	26 (78.7)	40 (81.6)	1.197 (0.397-3.610)	0.7
Myalgia	25 (75.7)	33 (67.3)	0.660 (0.244-1.785)	0.4
Sore throat	24 (72.7)	32 (65.3)	0.706 (0.269-1.854)	0.4
Lymphadenopathy			1.541 (0.633-3.748)	0.3
Hepatosplenomegaly			0.596 (0.244-1.455)	0.2
Serositis			1.660 (0.617-4.467)	0.3
GI symptom			0.579 (0.216-1.553)	0.2
Treatment regimens, n (%)				
NSAIDs	30 (90.9)	42 (85.7)	0.6 (0.143-2.511)	0.4
Steroids	31 (94)	49 (100)	NA	>0.99
Low ~ moderate (≤0.5 mg/kg)‡				
given as initial treatment	4 (12.1)	20 (40.8)	**5.0 (1.520-16.444)**	**0.008**
High (>0.5 mg/kg)‡				
given as initial treatment	27 (81.8)	29 (59.1)	**0.322 (0.113-0.923)**	**0.035**
Methotrexate	13 (39.3)	36 (73.4)	**4.26 (1.659-10.942)**	**0.003**
Hydroxychloroquine	0 (0)	10 (20.4)	NA	>0.99
Sulfasalazine	0 (0)	5 (10.2)	NA	>0.99
Leflunomide	0 (0)	2 (4)	NA	>0.99
Infliximab	0 (0)	2 (4)	NA	>0.99
Adalimumab	0 (0)	1 (2)	NA	>0.99
Anakinra	1 (3)	0 (0)	NA	>0.99
Cyclosporine A	0 (0)	1 (2)	NA	>0.99
Azathioprine	1 (3)	8 (16.3)	6.24 (0.742-52.523)	0.09
IVIG	0 (0)	1 (2)	NA	>0.99

Laboratory findings	Favourable (n=33)	Unfavourable (n=49)	OR (95%CI)	*p*-value
WBC/mm3†	12,000 ± 8,550	12,500±7,150	0.846 (0.320-2.235)	0.7
Hb, g/dl	10.5 ± 1.6	10.2±2.0	0.912 (0.714-1.166)	0.4
Platelet count (X1000/uL)	331.8 ± 153.2	292.9±115.9	0.998 (0.994-1.001)	0.1
ESR, mm/h	71 ± 70	63±70	0.997 (0.985-1.009)	0.5
CRP, mg/dL†	9.9 ± 16.4	7.9±9.3	0.917 (0.550-1.530)	0.7
ferritin, ng/ml†	2,641.2 ± 5,162	5,030±12,105.7	1.159 (0.894-1.503)	0.2
Ferritin > 1000 ng/ml (%)	25 (75.8)	37 (75.5)	0.987 (0.353-2.760)	0.9
LDH, IU/l†	539 ± 408	725.5±855.7	**2.523 (1.119-5.685)**	**0.02**
Albumin, mg/dl	2.9 ± 0.6	2.9±0.7	0.909 (0.474-1.743)	0.7
Creatinine, mg/dl†	0.7 ± 0.2	0.7±0.2	0.757 (0.122-4.675)	0.7
AST, IU/l†	52 ± 45	47±50	1.216 (0.745-1.986)	0.4
ALT, IU/l†	31 ± 45	29±43	0.998 (0.646-1.540)	0.9
ALP, IU/l†	121 ± 114	132±161	1.607 (0.754-3.424)	0.2
Total bilirubin, mg/dL†	0.6 ± 0.5	0.6±0.9	1.949 (0.994-3.823)	0.05

‡Steroid starting dosages equivalent to prednisolone.
*cellulitis (1), pneumonia (1), pericardiac tamponade (1), cholecystitis induced sepsis (1), pulmonary hypertension (1), stress induced cardiomyopathy (1), and HPS and aseptic meningitis (1), HPS (5).
~WBC: total white blood cells; Hb: haemoglobin; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase.
$p<0.05$ was considered statistically significant.
†Some continuous variables are analysed as log expression. By univariate logistic regression analyses.

Complications

At a median follow-up of 36.0±42.5 months (range 12–215 months), complications were seen in 7 patients, including one each with cellulitis, community acquired pneumonia, pericardiac tamponade, cholecystitis induced sepsis, pulmonary hypertension, stress induced cardiomyopathy, and aseptic meningitis. These complications were observed only in the unfavourable outcomes group (p=0.03). Moreover, two of these patients died, one each from biliary sepsis and severe pulmonary hypertension.

Discussion

This Korean study in 82 patients with AOSD is of interest since it is one of the largest study on the subject (only 5 other series with n >60, in the literature) and present additional datas on reactive haemophagocytosis. We analysed whether clinical manifestations, laboratory results and treatment responses were prognostic for poor outcomes in 82 patients with AOSD. Although, patients with unfavourable outcomes had higher proportion of polyarthralgia (p=0.01) similar to previous findings (8, 9, 13), the baseline patient characteristics were much the same between the 2 groups. We found that an insufficient initial dosage of steroids (≤0.5 mg/kg prednisolone) was the most significant predictive factor (OR 6.476, p=0.007) for chronic and relapsing disease courses, resulting in marked decreases in response rates.
Several clinical and laboratory features at onset of AOSD have been reported in association with unfavourable outcomes in literatures. Pleuritis is significantly associated with the use of biologics, which has been recognised as unfavourable factor that may identify AOSD patients with higher or persistent disease activity in the follow-up (14). Increased serum ferritin levels may correlate with poor characteristics in AOSD. In our study, the ferritin level was not significantly associated with poor outcome, however, patients in unfavourable group had a high median level of serum ferritin than favourable group (Table IV). The levels of macrophage migration inhibitory factor (MIF) has been recognised as

Table V. Odds ratios for unfavourable outcomes.

	Multivariate analysis		
	Odds ratio	95% CI	*p*-value
Arthralgia	4.699	1.060–20.830	0.042
Lnferritin	1.368	0.998–1.877	0.052
Low-moderate steroids	**6.476**	**1.663–25.226**	0.007

By multiple logistic regression analyses.
Clinically adjustable covariates were arthralgia, rash, serositis, pouchot score, ferritin, and low-moderate steroids use.

an important regulator of immune and inflammatory response in pathogenesis of AOSD. The serum MIF levels are higher in patients with sore throat, myalgias, splenomegaly, or pleuritis and closely related to disease severity and activity which may be used as a valuable marker for disease monitoring and evaluation in AOSD (15).

Haemophagocytic syndrome (HPS), also termed macrophage activation syndrome, is a clinicopathological entity characterised by fever, hepatosplenomegaly, lymphadenopathy, cytopenia, coagulopathy, elevated serum ferritin (>10,000 mg/ml), triglycerides (>160 mg/dl), fibrinogen (<250 mg/dl), liver enzyme elevation, and the activation of macrophages and/or histiocytes with prominent haemophagocytosis in bone marrow and other reticuloendothelial systems (16). HPS may be associated with AOSD in some patients (12~15.3%) (17-19) with an overall mortality rate of 20–38.5%. Of the 56 patients in our study who underwent bone marrow biopsies, 6 (10.7%) had AOSD complicated by HPS, with clinical findings predictive of poor prognosis. Since RHS is a fatal complication, related to a chronic disease course, it warrants a high index of suspicion in AOSD patients for diagnosis followed by aggressive treatment.

There have been no randomised clinical trials assessing treatment regimens due to the rarity of AOSD. Therefore the treatment of Still's disease remains largely empirical. Non-steroidal anti-inflammatory drugs (NSAIDs) are rarely sufficient, with many patients requiring steroids, anti-rheumatic agents and immunosuppressive drugs to control fever, arthritis, and systemic symptoms. Almost all of our patients were treated with steroids for acute control of their disease and the initial dosage of steroids depended on the clinical conditions. A rapid response to treatment is considered an indicator of freedom from disease even after the termination of therapy. However, during follow-up, about 46.3% of our patients relapsed, with most of the relapses occurring during the tapering of corticosteroids. The patients whom had relapsed more than once and whom had difficulties in tapering steroids were then treated with DMARDs and/or biologics. In our study, we found that decreased response rate was associated with an insufficient starting dose of steroids (≤0.5mg/kg prednisolone), resulting in longer durations of steroid treatment ($p<0.001$) and non-remission time ($p=0.02$). Patients with unfavourable outcomes subsequently exhibited a significantly higher total dose of steroids ($p=0.002$) with more disease-modifying anti-rheumatic drugs ($p=0.002$), compared with patients with favourable outcomes. Controlling disease activity of AOSD at the beginning of treatment through the administration of a sufficient dose of steroids to achieve quicker remission may be critical in achieving a favourable disease course.

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