Predictive factors and prognosis of macrophage activation syndrome associated with adult-onset Still's disease

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ABSTRACT

Objective. *To summarise the clinical data of adult-onset Still's disease (AOSD) patients and analyse their clinical manifestations, predictors for the formation and prognosis of macrophage activation syndrome (MAS).*

Methods. *A retrospective analysis was performed on the clinical data of 182 AOSD hospitalised patients from the Department of Rheumatology of the First Affiliated Hospital of Zhengzhou University, China from January 2012 to August 2018, including 11 patients with pathogenesis of MAS.*

Results. *Compared with the patients without MAS, the patients with MAS had a higher incidence of splenomegaly and pericarditis at the initial diagnosis of AOSD. The number of platelets (PLT) and the concentration of fibrinogen (FIB), D-Dimer and ferritin were significantly higher in AOSD-MAS patients. Multivariate regression analysis showed that splenomegaly (OR: 5.748, 95% CI: 1.378–23.984, p=0.016), pericarditis (OR: 6.492, 95% CI: 1.43–29.461, p=0.015), and ferritin >2000 μg/L (OR: 4.715, 95% CI: 1.12–19.86, p=0.035) were risk factors for MAS. Survival analysis indicated that the mortality of AOSD-MAS patients was significantly higher than patients without MAS.*

Conclusion. *Splenomegaly, pericarditis and elevated ferritin concentration are risk factors for MAS formation in AOSD patients. MAS resulted in a significant decrease in the survival rate of the AOSD patients.*

Introduction

Adult-onset Still's disease (AOSD) is a rare auto-inflammatory disease caused by multiple factors and is one of the common causes of fever of unknown origin. Its characteristic manifestations include high fever, sore throat, skin rash, and arthritis. Laboratory features include higher neutrophil count, increased level of ferritin and abnormal liver enzymes. AOSD has a benign course in most cases, while life-threatening situations may occur due to severe complications and adverse effects of treatments (1).

Macrophage activation syndrome (MAS), also referred to as secondary haemophagocytic lymphohistiocytosis (sHLH), is the most severe complication and may develop at any stage of AOSD. It is often triggered by treatments, infections and the primary disease. The pathogenesis of MAS is associated with inflammasomes and cytokine storm with profuse production of IL-1β and IL-18. IL-18 concentration is positively correlated with high activity of inflammasomes, which helps to differentiate MAS from primary HLH (2, 3). Both AOSD and MAS belong to hyperferritinaemic syndromes. In addition to its function as an acute phase reactant, ferritin can also incite a cytokine storm (4). Inappropriate or delayed treatments may cause death from disseminated intravascular coagulation (DIC), haemophagocytosis, and multiple organ dysfunction syndrome (MODS).

Until now, no well-established diagnosis criteria have been available for MAS. The 2004-HLH criteria or HScore are used for diagnosis, but the sensitivity of this is low, especially for patients at early stage. While bone marrow assay is not absolutely necessary, some reports showed haemophagocytosis of granulocytes, nucleated erythrocytes and at least one haemophagocyte containing multiple nucleated cells, which are strongly associated with HLH (5). The early symptoms/signs of MAS and AOSD are similar, and distinctive features often occur at the later stage, making early diagnosis difficult. However, early diagnosis and prompt intervention may prevent disease progress, thus leading to an improved

treatment outcome and prognosis. Very little has been known about predictors of AOSD patients with MAS, and few RCT studies have been made because of its rarity (6-8).

In this work, we analysed the clinical data of 182 AOSD patients at the time of diagnosis by dividing them into two groups: group 1 including 171 patients with AOSD alone, and group 2 including 11 AOSD patients with MAS. Through the evaluation of their clinical features, we aimed to identify the reliable predictors of MAS formation and to explore potential differences in the prognosis between in these two groups of patients.

Materials and methods

Study design and patients

Retrospective analysis of clinical data of 182 AOSD patients initially diagnosed at the First Affiliated Hospital of Zhengzhou University was performed, including 11 patients who developed MAS. The diagnosis of AOSD was based on the Yamaguchi criteria (9), after excluding tumour, infection, autoimmune and endocrine diseases, and other causes. The diagnosis of MAS was established using the 2004-HLH criteria or HScore (10, 11).

Clinical and laboratory examinations

Clinical features of AOSD patients at the time of diagnosis include gender, age at onset, initial symptoms, fever, rash, arthritis, myalgia, sore throat, weight loss, and internal organ involvements. Systemic scores were used to assess disease activity (12) and these include fever, rash, pleuritis, pneumonia, pericarditis, hepatomegaly or liver dysfunction, splenomegaly, lymphadenopathy, white cell counts over 15000/mm^3, myalgia, sore throat and abdominal pain. Each item was designated 1 point with the maximum score being 12 points.

Once the diagnosis was established, laboratory tests were performed in the patients who were not regularly treated with glucocorticoids. These tests included routine blood tests, liver function, triglycerides, fibrinogen, D-dimer, ferritin concentration, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Treatments were roughly divided into 5 groups: adequate glucocorticoid monotherapy (1–2 mg/kg/d), glucocorticoid pulse therapy (0.5–1.0 g/d), glucocorticoids + csDMARDs, glucocorticoids + immunoglobulin + csDMARDs, glucocorticoids + other medications.

Statistics

Continuous variables that were normally distributed were expressed as $x \pm s$ and compared by *t*-test, if they were not, the data were represented as the median (interquartile range, IQR). Discontinuous variables were expressed as composition ratio and compared by Mann-Whitney U-test. The chi-squared test was used for qualitative data. Clinical data at the time of the first diagnosis in the different groups were compared. It was considered statistically significant when $p<0.05$. Univariate regression analysis was used to screen for possible predictors, and then multivariate regression analysis was used to identify statistically significant variables. Finally, Kaplan-Meier curves were utilised to determine the survival outcomes and survival time of the two groups of patients.

The differences between the curves was determined by the log-rank test. The Statistics Package for Social Sciences (SPSS v. 17.0 and Graphpad-Prism v. 5.0) was used for the analyses.

Results

Clinical data at the time of diagnosis

Altogether, 182 eligible AOSD patients were analysed in this study, including 144 females and 38 males, aged from 26 to 37 years old (mean: 32), 11 patients developed MAS. Common symptoms/signs in these patients included high fever (100%), skin rash (72.0%), arthritis (77.6%), sore throat (50.0%), splenomegaly (31.3%), abnormal liver functions (83.5%), and lymphadenopathy (61.0%). The pulmonary involvement was characterised by interstitial pneumonia. The median of the systemic score was 6 points. Major abnormalities in laboratory examinations included increased WBC (9.9-17.7, mean:14.0× 10^9/ L), A liver enzymes and inflammation markers: ALT 36.5 (20.8–77.0) IU, AST 38.5 (24.0–66.3) IU, ESR 69.6 (41.8–90.0) mm/h, CRP 82.2 (50.5–114.8) mg/L, Ferritin (2000 μg/L). In addition, 22 patients had comorbidities: 12 with hypertension, 12 with diabetes, 7 with hyperthyroidism, 2 with hypothyroidism, and 2 with hepatitis B.

All patients were treated with glucocorticoids including 112 patients with adequate glucocorticoids monotherapy, 5 with pulse therapy, 54 with glucocorticoids + csDMARDs, 9 with glucocorticoids + intravenous immunoglobulin (IVIG) with or without csDMARDs, and 2 with glucocorticoids + IVIG + other drugs. Of all the patients treated with csDMARDs, 46 with MTX, 12 with cyclosporine, and 2 with azathioprine. In the AOSD-MAS group, 2 patients were treated with other drugs: one with etoposide, the other with etoposide+ tocilizumab.

In 11 AOSD-MAS patients, 3 developed MAS during their first hospitalisation, and 8 patients developed MAS during the follow-ups. Two AOSD-MAS patients had urticaria-like rash as the initial symptom, and 9 had high fever. All the 11 patients underwent bone marrow aspiration and 6 with haemophagocytosis. The ratios of splenomegaly and pericarditis were significantly higher in the MAS group at the time of the first diagnosis (28.7% *vs*. 72.7%, $p=0.007$; 7.6% *vs*. 36.4%, $p=0.008$). Platelet count [218.00/L (296.00–354.00) *vs*. 213.00/L (157.00-258.00), $p=0.041$], fibrinogen [4.41 g/L (3.82–5.23) *vs*. 3.56 g/L (2.23–4.96), $p=0.027$], D-dimer [1.13 mg / L (0. 59–3.40) *vs*. 2.89 mg/L (1.72–10.32), $p=0.009$] significantly decreased. The proportion of patients with ferritin over 2000 μg/L was also significantly increased (35.8% *vs*. 72.7%, $p=0.023$). AOSD-MAS received combined therapies instead of glucocorticoid alone: IVIG ± csDMARDs (1.8% *vs*. 54.5%, $p<0.001$), and glucocorticoids with other drugs (0% *vs*. 18.2%, $p=0.003$). Glucocorticoid is sufficient for most AOSD patients without MAS (65.5% *vs*. 0%, $p<0.001$) (see Table I-II).

Predictors of MAS formation

Regression analysis was utilised to identify the predictors for MAS. Uni-

Table I. Baseline clinical features and treatment regimens comparison between patients with and without MAS at the time of diagnosis.

Characteristics	AOSD without MAS (n=171)	AOSD with MAS (n=11)	*p*-value
Age, years	33.00 (26.00-47.00)	26.0 (24.0-31.0)	0.055
Start with fever	123 (71.9)	9 (81.8)	0.908
Female	134 (78.4)	10 (90.9)	0.542
Fever	171 (100)	11 (100)	1
Rash	122 (71.3)	9 (81.8)	0.687
Arthritis	115 (67.3)	8 (72.7)	0.965
Myalgia	79 (46.2)	6 (54.5)	0.591
Sore throat	85 (49.7)	6 (54.5)	0.756
Splenomegaly	49 (28.7)	8 (72.7)	*0.007*
Hepatomegaly	6 (3.5)	1 (9.1)	0.359
Liver involvement	141 (82.5)	11 (100)	0.271
Lymphadenopathy	103 (60.2)	8 (72.7)	0.614
Lung involvement	6 (3.5)	0 (0)	1
Pleurisy	27 (15.8)	3 (27.3)	0.565
Pericarditis	13 (7.6)	4 (36.4)	*0.008*
Abdominal pain	2 (1.2)	1 (9.1)	0.171
Weight loss	33 (19.3)	1 (9.1)	0.658
Systemic score, median (IQR)	5.0 (4.0-7.0)	6.0 (5.0-8.0)	0.073
Treatment regimens			
Monotherapy			
Adequate steroid	112 (65.5)	0 (0)	*<0.001*
high-dose Steroid pulse	4 (2.3)	1 (9.1)	0.270
Combination therapy			
steroids + csDMARD	54 (31.6)	2 (18.2)	0.603
steroids + IVIg ±csDMARD	3 (1.8)	6 (54.5)	*<0.001*
steroids +others	0 (0)	2 (18.2)	*0.003*

Statistical significance was expressed by *p* value <0.05.
csDMARD: conventional synthetic disease-modifying anti-rheumatic drugs; IVIg: intravenous immunoglobulin.
Statistical significance was expressed by *p*-value <0.05.
Italic values indicate statistically significant results.

Table II. Comparison of laboratory markers between patients with and without MAS.

Laboratory markers	AOSD without MAS (n=171)	AOSD with MAS (n=11)	*p*-value
Leukocytosis, $\times 10^9$/L,	9.70 (14.10-17.90)	12.70 (10.00-14.10)	0.345
Hemoglobin, g/L	96.0 (108.00-118.00)	105.00 (100.00-112.00)	0.793
Platelet, $\times 10^9$/L	296.00 (218.00-354.00)	213.00 (157.00-258.00)	*0.041*
Triglyceride, mmol/L	1.18 (0.92- 1.57)	1.12 (0.83-1.67)	0.927
Fibrinogen, g/L	4.41 (3.82-5.23)	3.56 (2.23-4.96)	*0.027*
D-Dimer, mg/L	1.13 (0 .59-3.40)	2.89 (1.72-10.32)	*0.009*
ferritin >2000μg/L	58 (35.8)	8 (72.7)	*0.023*
ESR, mm/H	69.50 (41.75-91.25)	50.00 (25.00-80.00)	0.165
CRP, mg/L,	82.25 (51.86-114.84)	50.66 (21.99-154.12)	0.314

ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.
Statistical significance was expressed by *p*-value <0.05.
Italic values indicate statistically significant results.

variate regression analysis revealed the following features were significantly correlated with MAS: splenomegaly (OR 6.64, 95% CI 1.69–26.07, *p*=0.007), pericarditis (OR 6.95, 95% CI 1.80–26.85, *p*=0.005), systemic score (OR 1.61, 95% CI) 1.09–2.37, *p*=0.017), fibrinogen (OR 0.50, 95% CI 0.28–0.87, *p*=0.015), ferritin >2000 μg/L (OR 5.20, 95% CI 1.33–20.33, *p*=0.018) (Table III). Multivariate regression analysis confirmed that splenomegaly (OR 5.75, 95% CI 1.38–23.98, *p*=0.016), pericarditis (OR 6.49, 95% CI 1.43–29.46, *p*=0.015) and ferritin >2000 μg/L (OR 4.72, 95% CI 1.12–19.86, *p*=0.035) are predictors for MAS (Table IV).

Analysis of patient survival

Standard treatments resulted in remission in 67 patients and the death of 15 patients. The follow-up times ranged from 1.5 to 73 months. Among them, 12 patients without MAS and 3 patients with MAS died. The main causes of mortality were severe pulmonary infection in AOSD patients and MAS deterioration. Survival analysis revealed that the occurrence of MAS significantly reduced the survival rate of AOSD patients (χ^2=5.553, *p*=0.018) (Fig. 1).

Discussion

Our study aimed to determine the reliable predictors for the development of MAS in AOSD patients and the effect of MAS formation on their survival rate. Splenomegaly, pericarditis, and higher ferritin concentration (over 2000μg/L) have been demonstrated to be reliable predictors of MAS, and MAS significantly reduces the survival rate of AOSD patients. When these predictors are present, patients should be monitored closely, and aggressive and prompt treatments should be used to prevent MAS formation. An Italian study in which 119 AOSD patients were followed up indicated that lymphadenopathy and abdominal pain were the predictors of MAS (7). A Korean study that followed up 109 AOSD patients suggested that decreased platelet counts, anaemia and hepatomegaly may predict the occurrence of MAS (8). Wakabayashi and colleagues demonstrated that that β_2- microglobulin was related to the occurrence of MAS (6).

We investigated the predictors of MAS in AOSD patients from central China. Our study showed a young female predominance, and that the most common initial manifestations were high fever followed by skin rash and arthralgia, but did not analyse the pattern of fever, while one report showed that higher temperature was associated with wider variations in diurnal temperature, higher risk of developing MAS, warranting more intense and extended time to reach clinical remission (13). The reticuloendothelial system can be activated during the disease course, such as splenomegaly, lymphadenopathy and liver

Table III. Univariate analyses to define factors associated with MAS in patients with AOSD at the time of diagnosis.

Variables	OR	95%CI	*p*-value
Age	0.95	0.90-1.01	0.08
Start with fever	1.47	0.30-7.05	0.63
Sex	2.76	0.34-22.27	0.34
Rash	1.81	0.38-8.67	0.46
Arthritis	1.30	0.33-5.08	0.71
Myalgia	1.40	0.41-4.75	0.59
Sore throat	1.21	0.36-4.13	0.76
Splenomegaly	6.64	1.69-26.07	*0.007*
Liver involvement	-	-	-
Lymphadenopathy	1.76	0.45-6.87	0.42
Lung involvement	-	-	-
Pleurisy	2.00	0.50-8.02	0.33
Pericarditis	6.95	1.80-26.85	*0.005*
Abdominal pain	8.45	0.71-101.28	0.09
Weight loss	0.42	0.05-3.38	0.41
Systemic score	1.61	1.09-2.37	*0.017*
Leukocytosis	0.96	0.87-1.07	0.47
Palate	0.96	0.99-1.00	0.13
Triglyceride	1.06	0.35-3.20	0.93
Fibrinogen	0.50	0.28-0.87	*0.015*
D-Dimer	1.02	0.99-1.06	0.25
ferritin >2000μg/L	5.20	1.33-20.33	*0.018*
ESR	0.99	0.97-1.01	0.18
CRP	1.00	0.99-1.01	0.57

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.
Statistical significance was expressed by *p*-value <0.05.
Italic values indicate statistically significant results.

Table IV. Multivariate analyses to define factors associated with MAS in patients with AOSD at the time of diagnosis.

Variables	OR	95%CI	*p*-value
Splenomegaly	5.748	1.378-23.984	*0.016*
Pericarditis	6.492	1.43-29.461	*0.015*
Serum ferritin >2000μg/L	4.715	1.119-19.862	*0.035*

*Statistical significance was expressed by *p*-value <0.05.
Italic values indicate statistically significant results.

involvement, consistent with the previous observations (14, 15).

The differential diagnosis is difficult in AOSD patients with MAS because they have many common clinical features, suggesting a similar pathogenetic mechanism. They may represent different stages of disease development (16). Ferritin plays an important role in hyperferritinaemic syndrome like MAS (17). We found that the proportion of patients with ferritin over 2000 μg/L at the time of diagnosis was significantly higher in patients with MAS and was a predictor of MAS occurrence, confirming the important role of ferritin in MAS. Ferritin stimulates the production of many cytokines during inflammation and these cytokines in turn increase production of ferritin. This positive feedback leads to an uncontrolled cytokine production (4, 18). The possible MAS pathogenesis should be considered when ferritin is over 500 μg/L and the relevant laboratory test (fibrinogen, triglycerides, AST, LDH, etc.) should be examined. When ferritin concentration is over 10,000 μg/L, MAS can be diagnosed and prompt treatments are warranted (19).

The incidence of splenomegaly and pericarditis were significantly higher in patients with MAS. Platelet count, fibrinogen and D-dimer were significantly lower, indicating the aberrant haemodynamic response. Pericarditis may be a marker of refractory AOSD that may only respond to treatment with biological agents (20). Fluctuation of the platelet counts is valuable for early diagnosis of MAS and can differentiate early MAS from primary disease relapse (21, 22). Systemic score and fibrinogen are also associated with MAS. The former is positively correlated with organ involvement and disease severity. A previous study by Ruscitti *et al*. demonstrated that mortality is significantly increased when the system score is over 7 points (23). In addition, a systemic score over 7 points and serum ferritin concentration over 684 μg/L are the predictors of MAS in paediatric and adult patients with Still's disease (24). Decreased fibrinogen causes a drop in ESR, suggesting that patients are more severe and may complicate MAS. Further, decreased fibrinogen is involved in severe complications such as disseminated intravascular coagulation (DIC) and thrombotic microangiopathy (TMA). Splenomegaly and pericarditis at the time of diagnosis can be predictors of MAS as well. It is noteworthy that splenomegaly and pericarditis are indicators of MAS disease severity but not the causes. In addition, a previous study has demonstrated that AOSD patients complicated by interstitial pneumonia have a higher risk of MAS and disease recurrence. Our own data showed that interstitial pneumonia occurred in 3.5% AOSD patients and in none of the AOSD-MAS patients, with no statistical difference between the two groups (25). Previous reports indicate that lymphadenopathy, hepatomegaly, abdominal pain, decreased platelet count, anaemia, β2-micoglobulin can predict the occurrence of MAS (7-9). The discrepancy between our study and previous observations may be due to population selection and sample size. Large multicentre studies may help in identifying the most relevant predictors for MAS.

Our result showed that the mortality of the MAS patients was about 27%, consistent with a previous report regarding the MAS mortality that ranged from 5% to 39% (19), with a maximum of 76.9% (23). Poor outcome in AOSD patients without MAS is primarily due to infection, warranting a more delicate balance between the intensity of treat-

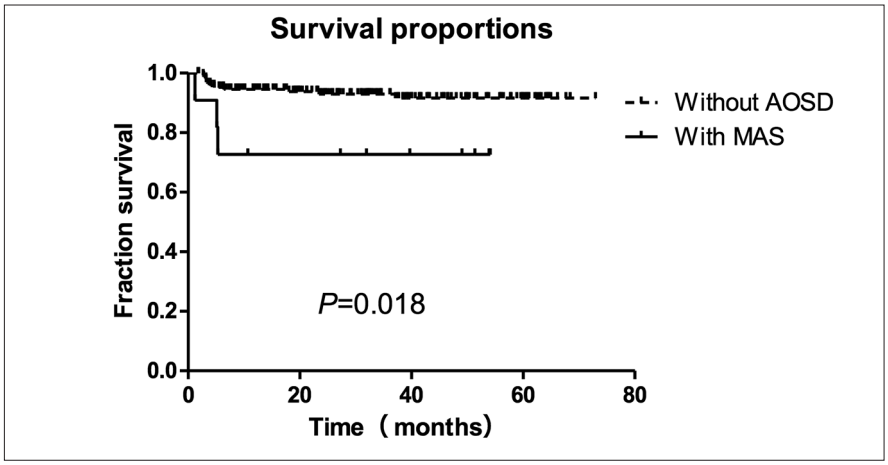

Fig. 1. Kaplan-Meier curves of survival in AOSD patients with or without MAS.

	Chi square	df	Sig.
Log Rank (Mantel-Cox)	5.553	1	*0.018*
Breslow (Generalised Wilcoxon)	6.700	1	*0.010*

*Statistical significance was expressed by p-value <0.05.
Italic values indicate statistically significant results.

ment and the progression of disease. On the other hand, the death of the AOSD-MAS patients is primarily caused by the deterioration of MAS, suggesting the importance of early diagnosis.

Glucocorticoids are the basic drug for AOSD and MAS. Additional treatments of AOSD-MAS patients include IVIG, csDMARDs, etoposide and biological (19). Elucidation of the MAS mechanism may help find new therapeutic targets to improve the outcome and prognosis. Genetic predisposition to macrophage hyper-responsiveness, genetic defect in cytolytic pathway and high levels of inflammatory cytokines (IL-6, IL-1β, IL-18, IFN-γ, etc.) have been demonstrated to contribute to MAS formation. Although little progress has been made in gene therapy, biological agents including inhibitors of TNF-α, IL-1β and IL-6 are effective on AOSD or MAS, however, these inhibitors often cannot completely block the development of MAS (26). A recent study showed that IL-18 inhibition was associated with early signs of efficacy in AOSD (27). Furthermore, JAK inhibitors and monoclonal antibody against IFN-γ may improve the treatment outcomes of these patients (26).

Our retrospective study has several limitations. First, as it is a single center study, the sample size of patients is limited. Secondly, some potential markers such as β2-microglobulin, VLDL, CM, lipoprotein (a) and glycosylated ferritin could not be analysed because of missing data. Lastly, we did not analyse the association of different treatments with the occurrence of MAS, but we will do it when more data are collected.

In conclusion, MAS is a life-threatening complication of AOSD, and significantly reduces the survival rate of patients. Early recognition and timely treatment are pivotal. The levels of platelet count, fibrinogen and D-dimer in patients with MAS are relatively low, and the incidence of splenomegaly, pericarditis and elevated ferritin level are reliable predictors for MAS.

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