Clinical features of anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis with macrophage activation syndrome

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Abstract

Objective

This study aimed to describe the clinical features of patients with anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody-positive dermatomyositis (DM) who had macrophage activation syndrome (MAS).

Methods

We retrospectively examined 44 patients with anti-MDA5-positive DM and compared the clinical features between patients with MAS (n = 11) and those without (n=33). Patients without MAS were selected randomly in the same year as those with MAS at a ratio of 3:1. Among patients with MAS, we compared the features between non-survivors and survivors. We used Fisher's exact test, Student's t test, the Mann-Whitney U test and the log-rank test for the statistical analysis.

Results

Patients complicated with MAS had a significantly higher incidence of infection, heliotrope sign, Gottron's papule, V-neck sign, and higher serum levels of ferritin, aspartate aminotransferase (AST), lactic dehydrogenase (LDH), and creatine kinase (CK) than those without MAS ($p<0.05$). Among the 11 patients with MAS, 4 (36.4%) died after intensive treatment. Deceased patients were older, given more combination therapy with tofacitinib (TOF) and had a higher incidence of rapid progressive interstitial lung disease, infection, heart failure and renal impairment than those who survived ($p<0.05$).

Conclusion

Among anti-MDA5-positive DM, Infection, DM typical rashes, and higher serum levels of ferritin, AST, LDH, and CK were more common in patients complicated with MAS. The mortality of patients with MAS was high, particularly among patients who were older, given more combination therapy with TOF, and had RP-ILD, infection, heart failure and renal impairment.

Key words

anti-melanoma differentiation-associated gene 5 antibody, dermatomyositis, haemophagocytic lymphohistiocytosis, interstitial lung disease, macrophage activation syndrome

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Received on August 24, 2023; accepted in revised form on November 13, 2023.

Funding: this study was funded by The Medical Science and Technology Research Project of Henan Province, China (grant no. LHGJ20220309).

Competing interests: none declared.

Introduction

Dermatomyositis (DM) is an inflammatory myopathy with systemic involvement that usually affects the skin, skeletal muscle, and lungs. Anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody-positive DM, as a special type of DM, is characterised by a high mortality rate and may develop serious complications, including macrophage activation syndrome (MAS) (1, 2). MAS refers to a subset of patients with haemophagocytic lymphohistiocytosis (HLH) arising on a background of systemic autoinflammation/autoimmunity and is commonly associated with systemic juvenile idiopathic arthritis, adult-onset Still's disease, systemic lupus erythematosus, and Kawasaki disease and is rarely seen in DM (3, 4). MAS is a rare complication in DM, but DM is one of the risk factors associated with mortality among MAS underlying autoimmune diseases (3).

MAS is a phenomenon that is characterised by uncontrolled activation of macrophages and production of proinflammatory cytokines, leading to a cytokine storm, haemophagocytosis and multiorgan damage. Macrophages, cytotoxic T cells and NK cells produce several proinflammatory cytokines, including interferon gamma (IFN-γ), through a feed-forward functional loop (5). IFN-γ is a key mediator of MAS development (6). In anti-MDA5-positive DM, IFN-γ also has important effects on key tissues affected during the disease, such as the lungs, skin, and vessels (7, 8).

In addition to pathogenesis, anti-MDA5 antibody-positive DM and MAS have some similar features both in symptoms and laboratory results. It has been reported that most anti-MDA5 antibody-positive DM patients have high serum levels of ferritin, which may be related to severe pulmonary inflammation (9). In rheumatic patients with hyperferritinemia, suspicion for MAS should be raised, and further MAS testing should be initiated. In clinical practice, we sometimes overlook the development of MAS among patients with anti-MDA5-positive DM. Although difficult to identify, distinguishing this condition is significant because early diagnosis and initiation of therapy are key to improving the prognosis of MAS (10, 11). Some studies have reported the characteristics of MAS in rheumatic diseases, but very few cases of MAS in anti-MDA5-positive DM patients have been reported (3). The aim of the present study was to describe the clinical characteristics of MAS in anti-MDA5 antibody-positive DM patients.

Methods

Patients

We conducted a retrospective study of patients who visited the First Affiliated Hospital of Zhengzhou University between January 1, 2019, and February 1, 2023, and were diagnosed with anti-MDA5 antibody-positive DM and MAS at the same time. The titre of anti-MDA5 antibody in the serum of patients was detected by an ELISA kit (MBL, Japan). DM was diagnosed according to the criteria of Bohan and Peter (12). The diagnosis of MAS was based on the HLH-2004 criteria from the Histiocyte Society (five out of the eight criteria below): fever ≥38.5°C, splenomegaly, cytopenia involving at least two lineages of peripheral blood (neutrophil count $<1.0 \times 10^9$/L, haemoglobin <90 g/dl, or platelet $<100 \times 10^9$/L), hypertriglyceridaemia (≥265 mg/dl) and/or hypofibrinogenaemia (<1.5 g/L), haemophagocytosis in the bone marrow, spleen, liver or lymph nodes, low or absent NK cell activity, serum ferritin ≥500 μg/L, and soluble CD25 (soluble interleukin - 2 receptor) ≥2400 IU/ml (13). The exclusion criteria were as follows: 1) an age of onset <18 years old, 2) complications with other connective diseases, 3) DM secondary to tumours, and 4) incomplete clinical or laboratory data necessary for this study. Finally, 11 patients were enrolled in our study.

Control group

The control group included patients with anti-MDA5 antibody-positive DM without MAS. They were stratified by the visit time consistent with the MAS patients and randomly selected from the medical record library at a ratio of 3:1 with a random number table. DM patients younger than 18 years old or who had not been treated were excluded.

Table I. Clinical characteristics of 11 patients with anti-MDA5 antibody-positive DM and MAS.

No.	Age/Sex	Disease duration to MAS onset (months)	DM symptoms	MAS symptoms	Treatment targeting both diseases	Treatment targeting MAS	Infection	Outcomes
1	27/M	7	I, My, H, G	C, P	GC, IVIG, TAC, CYC	VP16	-	Alive
2	55/M	2	Fe, I(RP-ILD), H, G	C	GC, IVIG, CYC	VP16	PCP	Dead
3	57/M	3	Fe, I(RP-ILD), My, MH, G	C, HF	GC, IVIG, TAC, TOF	VP16	Pulmonary aspergillosis	Dead
4	36/F	2	Fe, I, My, H, G	C	GC, IVIG	VP16	-	Alive
5	60/F	1	I, My, H	C	GC, IVIG, TAC, CYC	VP16	-	Alive
6	59/M	2	Fe, I(RP-ILD), My, H, G, V	C, HF, R	GC, IVIG, TAC	VP16	PCP/fungal	Dead
7	46/F	5	Fe, I, My, H, MH	C, P	GC, IVIG, CyA		PCP/bacteria	Alive
8	37/M	1	Fe, I, My, H, G, V	C	GC, IVIG, CyA, TAC		-	Alive
9	59/F	3	Fe, I(RP-ILD), H, G, V	C, HF, R TCZ, CyA, TOF	GC, IVIG, TAC, CYC,	VP16	*Klebsiella pneumoniae* septicaemia	Dead
10	59/F	2	I, My, H, G, V	C, P	GC, IVIG, TAC, TCZ	VP16	-	Alive
11	38/M	8	Fe, My, H, G, V	C	GC, IVIG, CYC, TAC		-	Alive

CyA: cyclosporin A; CYC: cyclophosphamide; C: coagulation dysfunction; F: female; Fe: fever; G: Gottron's papules; GC: glucocorticoids; H: heliotrope sign; HF: heart failure; I: interstitial lung disease; IVIG: intravenous immunoglobulin; M: male; MAS: macrophage activation syndrome; MDA5: melanoma differentiation-associated gene 5; MH: mechanic hands; My: myositis; P: pericardial effusion; PCP: Pneumocystis carinii pneumonia; R: renal impairment; RP-ILD: rapidly progressive interstitial lung disease; TAC: tacrolimus; TCZ: tocilizumab; TOF: tofacitinib; V: V-neck signs; VP16: etoposide.

Data collection

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Review Committee (ERC) of the First Affiliated Hospital of Zhengzhou University (IRB number 2020-KY-194). The following data were collected from the patients' electronic medical records: demographic information, including age and sex, combined infection and therapeutic schedule, and laboratory data such as complete blood cell count (CBC), aspartate aminotransferase (AST), fibrinogen, triglyceride (TG), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and ferritin. We also collected information on the patients' clinical conditions at baseline and during follow-up, including vital signs and neuropsychiatric symptoms. In the retrospective study, all data were anonymous and aggregated.

Statistical analyses

Categorical variables are presented as frequencies with percentages (n, %), and Fisher's exact tests were used for comparisons. Continuous variables are expressed as the means (standard deviations) or medians (interquartile ranges) (IQRs) and were calculated using Student's t-test for parametric data or the

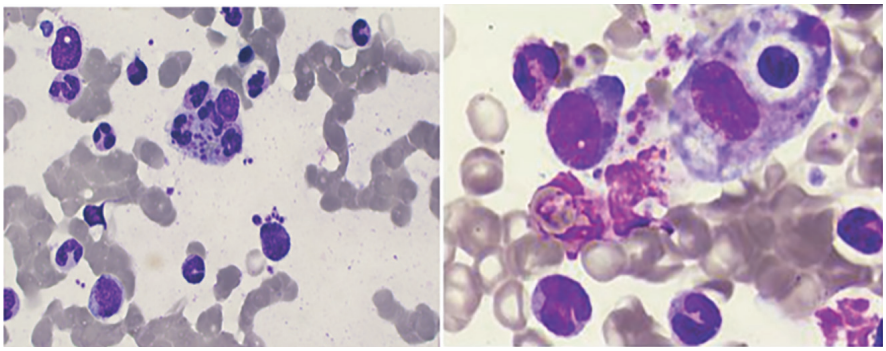

Fig. 1. Bone marrow aspirate smears of two MAS patients showing haemophagocytosis. MAS: macrophage activation syndrome.

Table II. Diagnostic criteria fulfilled by the 44 eligible patients in HLH - 2004.

Diagnostic criteria	MAS (n=11)	Without MAS (n=33)
Fever, n (%)	8 (72.7)	4 (12.1)
Splenomegaly, n (%)	3 (27.3)	1 (3.0)
Cytopenia (2/3 cell lineage), n (%)	10 (90.9)	0 (0)
Hypertriglyceridaemia or hypofibrinogenaemia, n (%)	9 (81.8)	13 (39.4)
Hypertriglyceridaemia ≥265 mg/dl, n (%)	9 (81.8)	13 (39.4)
Hypofibrinogenaemia ≤150 mg/dl, n (%)	6 (54.5)	0 (0)
Haemophagocytosis, n (%)	2 (18.2)	0 (0)
Ferritin ≥500 ng/ml, n (%)	11 (100)	24 (72.7)
Low/absent NK-cell activity, n (%)	6 (54.5)	0 (0)
Soluble CD25 ≥2400 U/ml, n (%)	4 (36.4)	0 (0)
HLH-2004, n (%)	11 (100)	0 (0)
HScore* >169, n (%)	11 (100)	0 (0)
PRINTO criteria, n (%)	11 (100)	8 (24.2)

*HScore calculator (for the percentage probability of secondary HLH) is available at http://sintantoine.aphp.fr/score/.
HLH: haemophagocytic lymphohistiocytosis; MAS: macrophage activation syndrome; NK cell: natural killer cell; PRINTO: Paediatric Rheumatology International Trials Organization.

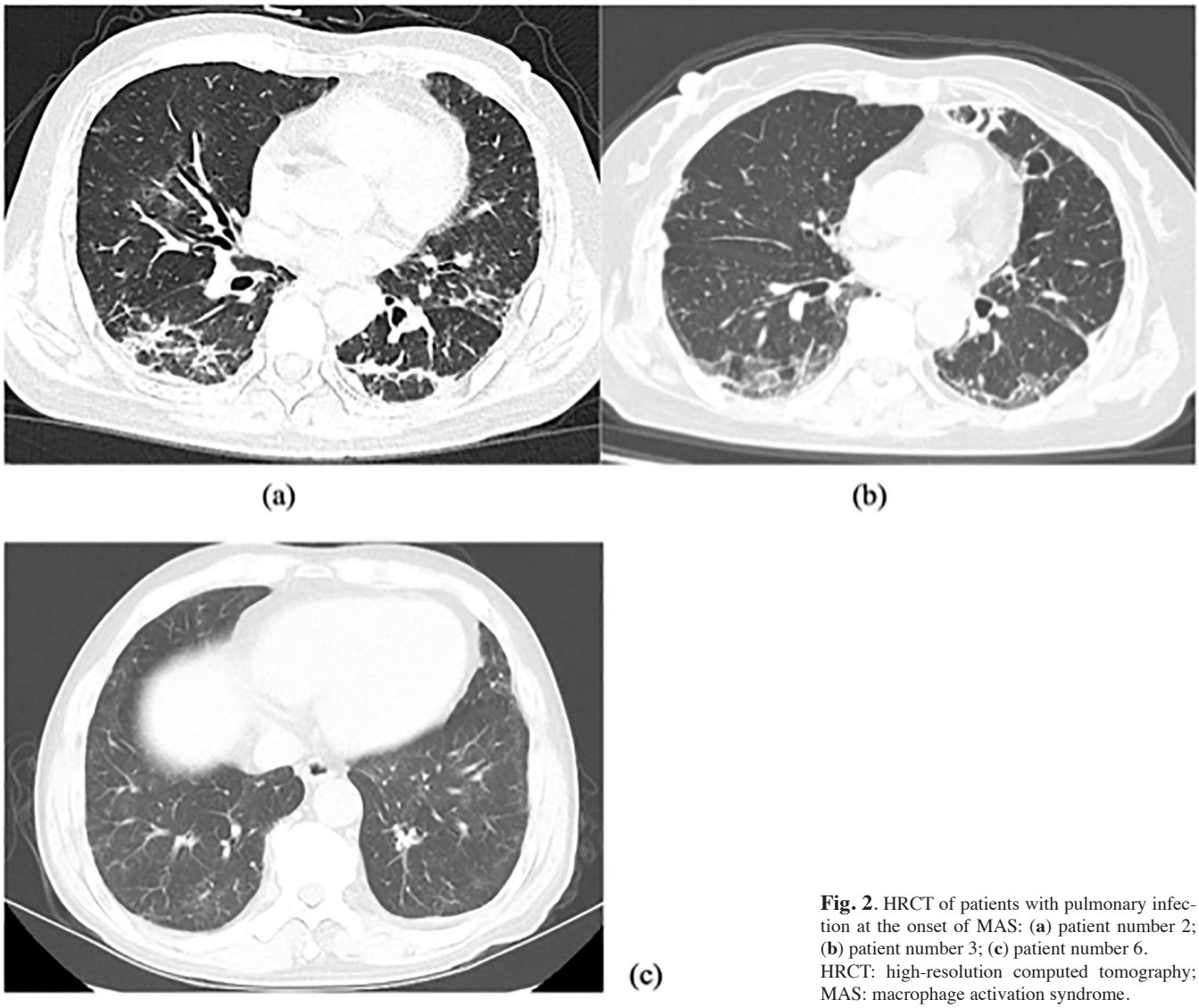

Fig. 2. HRCT of patients with pulmonary infection at the onset of MAS: (**a**) patient number 2; (**b**) patient number 3; (**c**) patient number 6.
HRCT: high-resolution computed tomography; MAS: macrophage activation syndrome.

Mann-Whitney U-test for nonparametric data. Overall survival rates were calculated by the Kaplan-Meier method and compared by log-rank tests stratified by MAS status (with or without). A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (v. 26.0; IBM, Armonk, NY).

Results

Characteristics of patients with MAS

Among the 11 patients with anti-MDA5 antibody-positive DM and MAS, the median duration between the onset of DM and MAS development was 2 months (range, 1–8 months). Eight (72.7%) of the 11 patients developed MAS within 3 months after the onset of DM. All patients with MAS have abnormal coagulation function, and some of them also have abnormalities in other systems. Their characteristics are summarised in Table I. All 11 cases showed hyperferritinaemia (median, 2723 μg/L; IQR, 2155–4228 μg/L) at the onset of MAS and had this characteristic before MAS onset. Considering the clinical features of DM, all of them showed hallmark skin rashes, and only 2 (18.2%) patients met the diagnostic criteria for clinically amyopathic DM (CADM). In addition, anti-Ro52 antibody was positive in 6 (54.5%) patients. Six patients completed bone marrow aspiration, and two of them had haemophagocytosis (Fig. 1). The clinical and laboratory findings of the 11 patients according to the HLH-2004 criteria are presented in Table II. All 11 MAS patients fulfilled the 2016 the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR)/Paediatric Rheumatology International Trials Organization (PRINTO) classification criteria for MAS, and had an HScore higher than 169 (mean, 204.3) (Table II) (11, 14).

Treatment and follow-up of patients with MAS

Once MAS was diagnosed, 10 patients were treated with high-dose corticosteroids (≥prednisolone equivalent 1 mg/kg). However, all 11 patients were refractory to medium- or high-dose corticosteroids and consequently received immunosuppressive agents, biological or targeted synthetic agents and etoposide. After intensive treatment, 4

Table III. Baseline characteristics of anti-MDA5 antibody-positive DM patients with MAS and without MAS.

		DM with MAS (n=11)	DM without MAS (n=33)	*p* value
Clinical features				
Sex, female, n (%)		5 (45.4)	20 (60.6)	0.489
Age, years, mean (SD)		48.4 (12.1)	48.6 (12.6)	0.961
Fever, n (%)		8 (72.7)	13 (39.4)	0.083
CADM, n (%)		2 (18.2)	15 (45.5)	0.211
Infection, n (%)		5 (45.5)	4 (12.1)	0.030*
RP-ILD, n (%)		4 (36.4)	7 (21.2)	0.425
Extent of ILD	<10%	6 (54.5)	17 (51.5%)	0.586
, n (%)	10-20%	1 (9.1)	7 (21.2%)	
	>20%	4 (36.4%)	9 (27.3%)	
Muscle force	level 5	4 (36.4%)	16 (48.5%)	0.765
, n (%)	level 4	7 (63.6%)	15 (45.5%)	
	level 3	0 (0)	2 (6.0%)	
Heliotrope sign, n (%)		10 (90.9)	6 (18.2)	<0.005*
Gottron's papule, n (%)		9 (81.8)	9 (27.3)	0.005*
V-neck sign, n (%)		6 (54.5)	3 (9.1)	0.005*
Mechanic hand, n (%)		2 (18.2)	3 (9.1)	0.784
Laboratory findings at DM diagnosis				
ANC, × 10^9/L, median (IQR)		3.4 (2.4, 10.9)	3.8 (2.6, 5.6)	0.655
Hb, g/L, mean (SD)		122.5 (15.7)	121.1 (16.2)	0.799
PLT, × 10^9/L, mean (SD)		168.6 (67.8)	181.6 (62.9)	0.562
TG, mg/dl, median (IQR)		381 (301, 461)	159 (124, 283)	0.881
Fibrinogen, g/L, median (IQR)		3.2 (2.4, 4.4)	3.0 (2.4, 3.6)	0.684
Ferritin, μg/L, median (IQR)		2723.0 (2155.0, 4228.0)	813.0 (371.0, 1396.0)	<0.005*
AST, U/L, median (IQR)		78.0 (36.0, 98.0)	35.0 (23.0, 52.0)	<0.005*
LDH, U/L, median (IQR)		431.0 (289.0, 654.0)	308.0 (241.0, 351.0)	0.012*
CK, U/L, median (IQR)		152.0 (91.0, 213.0)	43 (25.0, 84.0)	0.009*
ESR, mm/h, median (IQR)		50.0 (16.0, 78.0)	23.0 (13.0, 46.0)	0.103
CRP, mg/L, median (IQR)		4.6 (0.5, 28.5)	1.4 (0.5, 6.3)	0.186

ANC: absolute neutrophil count; AST: aspartate aminotransferase; CADM: clinically amyopathic dermatomyositis; CK: creatine kinase; CRP: C-reactive protein; DM: dermatomyositis; ESR: erythrocyte sedimentation rate; Hb: haemoglobin; ILD: interstitial lung disease; LDH: lactic dehydrogenase; MDA5: melanoma differentiation-associated gene 5; MAS: macrophage activation syndrome; PLT: platelet; RP-ILD: rapidly progressive interstitial lung disease; TG: triglyceride.
*p<0.05.

(36.4%) patients died during the management of DM and MAS, and they were all admitted to the intensive care unit due to anoxia or multiorgan failure. Two of them died during the first 30 days after admission to our centre. All of the patients who died had coinfections. Two of them were diagnosed with Pneumocystis carinii pneumonia by next-generation sequencing of bronchoalveolar lavage fluid before the onset of MAS. Pulmonary imaging showed ILD, as determined by high-resolution computed tomography (HRCT) (Fig. 2 a, b). One of the remaining patients who died had pulmonary aspergillosis before MAS diagnosis (Fig. 2c). The other patient was diagnosed with *Klebsiella pneumoniae* septicaemia after intensive treatment for MAS.

Comparison of patients with and without MAS

Compared with 33 patients with anti-MDA5 antibody-positive DM without MAS at baseline, patients complicated with MAS had a significantly higher incidence of infection (45.5% *vs*. 12.1%, p=0.03), heliotrope sign (90.9% *vs*. 18.2%, p<0.005), Gottron's papule (81.8% *vs*. 27.3%, p=0.005), V-neck sign (54.5% *vs*. 9.1%, p=0.005), and higher serum levels of ferritin (2723 ng/dl *vs*. 813 ng/dl, p<0.005), AST (78 U/L *vs*. 35 U/L, p<0.005), LDH (431 U/L *vs*. 308 U/L, p=0.012), and CK (152 U/L *vs*. 43 U/L, p=0.009) (Table III). Sex, age, the rate of RP-ILD, CADM and mechanic hands, the extent of ILD, the level of muscle force, the serum levels of CBC, TG, fibrinogen, CRP and ESR were not different between the groups (p>0.05).

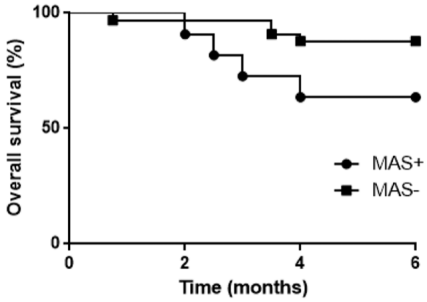

Fig. 3. Overall survival of patients with anti-MDA5 antibody-positive DM with or without MAS within 6 months.
DM: dermatomyositis; MAS: macrophage activation syndrome; MDA5: melanoma differentiation-associated gene 5.

The six-month cumulative survival rate as assessed by the Kaplan-Meier method of anti-MDA5-positive DM patients with MAS appeared to be lower than that of those without MAS, but the difference was not statistically significant (p=0.058; Fig. 3).

Comparison of survivors and non-survivors among MAS patients

Among MAS patients, RP-ILD (100% *vs*. 0%, p=0.003), infection (100% *vs*. 14.3%, p=0.015), heart failure (75% *vs*. 0%, p=0.004), renal impairment (50% *vs*. 0%, p=0.027) and combination therapy regimen with tofacitinib (TOF) (50% *vs*. 0%, p=0.027) were more common in non-survivors (Table IV). Otherwise, more older patients died after treatments were initiated (57.6±2.3 *vs*. 44.8±12.5 years, p=0.022). The ratio of sex, fever, CADM, treatment with calcineurin inhibitor (CNI) alone, combination therapy regimen with tocilizumab, treatment with tacrolimus (TAC) combined with cyclophosphamide (CTX), treatment with etoposide (VP16), the serum levels of CBC, TG, ferritin, creatinase, fibrinogen, CRP and ESR were not significantly different between them (p>0.05).

Discussion

Regarding the temporal relationship with DM onset, most of our present patients developed MAS within 3 months after the diagnosis of anti-MDA5 antibody-positive DM, which is quite different from other rheumatic diseases

Table IV. Comparison of characteristics between survivors and non-survivors in patients with MAS.

	Dead (n=4)	Alive (n=7)	*p*-value
Clinical features			
Sex, female, n (%)	2 (50)	3 (42.9)	0.576
Age, years, mean (SD)	57.6 (2.3)	44.8 (12.5)	0.022*
RP-ILD, n (%)	4 (100)	0 (0)	0.003*
Fever, n (%)	4 (100)	4 (57.1)	0.236
CADM, n (%)	2 (50)	0 (0)	0.109
Opportunistic infection, n (%)	4 (100)	1 (14.3)	0.015*
Heart failure, n (%)	3 (75)	0 (0)	0.004*
Renal impairment, n (%)	2 (50)	0 (0)	0.027*
CNI alone	1 (25)	2 (28.6)	0.898
Combination therapy with TCZ	1 (25)	1 (14.3)	0.662
Combination therapy with TOF	2 (50)	0 (0)	0.027*
TAC combined with CTX	0 (0)	3 (42.9)	0.068
VP16	4 (100)	4 (57.1)	0.068
Laboratory findings at MAS diagnosis			
ANC, × 10^9/L, median (IQR)	3.1 (2.0, 4.3)	1.6 (1.0, 2.2)	0.257
Hb, g/dl, mean (SD)	94.7 (27.5)	91.7 (14.9)	0.814
PLT, × 10^9/L, mean (SD)	92.3 (87.3)	86.0 (32.8)	0.865
TG, mg/dl, median (IQR)	345 (301, 392)	399 (257, 469)	0.426
Fibrinogen, g/L, median (IQR)	1.5 (1.4, 1.5)	1.6 (1.5, 2.2)	0.257
Ferritin, μg/L, median (IQR)	5635.5 (3911.5, 16011.5)	12048.0 (3792.0, 18273.0)	0.571
AST, U/L, median (IQR)	67.0 (64.5, 162.5)	219.0 (87.0, 1107.0)	0.131
LDH, U/L, median (IQR)	360.0 (264.3, 1190.8)	451.0 (393.0, 1298.0)	0.450
CK, U/L, median (IQR)	135.5 (55.8, 162.0)	135.0 (91.0, 214.0)	0.257
ESR, mm/h, median (IQR)	30.0 (7.0, 85.3)	30.0 (9.0, 98.0)	0.507
CRP, mg/L, median (IQR)	4.6 (0.5, 42.9)	0.5 (0.5, 26.5)	0.428

ANC: absolute neutrophil count; AST: aspartate aminotransferase; CADM: clinically amyopathic dermatomyositis; CK: creatine kinase; CNI: calcineurin inhibitor; CRP: C-reactive protein; CTX: cyclophosphamide; DM: dermatomyositis; ESR: erythrocyte sedimentation rate; Hb: haemoglobin; LDH: lactic dehydrogenase; MAS: macrophage activation syndrome; PLT: platelet; RP-ILD: rapidly progressive interstitial lung disease; TG: triglyceride; TOF: tofacitinib; TCZ: tocilizumab; VP16: etoposide. *$p<0.05$.

complicated with MAS. Before the onset of MAS, patients had higher serum levels of ferritin, CK, LDH and AST than patients without MAS. In addition, the frequencies of the heliotrope sign, Gottron's papule, and V-neck sign were higher in patients who developed MAS. Ding *et al*. collected case data and reviewed literatures for cases with anti-MDA5 antibody-positive DM complicated with MAS (15). They found that DM patients with anti-MDA5 antibody and MAS had higher levels of AST, LDH, and ferritin than patients without MAS, consistent with our results. These results suggest that if the patient has high serum levels of ferritin, creatinase, accompanied by typical DM rashes, we need to be alert to the occurrence of MAS, especially in the early stage of anti-MDA5 antibody-positive DM. For RP-ILD, the incidence was not different between patients with and without MAS. However, among MAS patients the non-survivors had a higher rate of RP-ILD than the surviving group.

In our study, high incidence of infection is another feature of anti-MDA5 antibody-positive DM patients complicated with MAS. Most episodes of infection preceded the diagnosis of MAS and were opportunistic infections after anti-inflammatory and immunosuppressive therapy. The role of infection in the pathogenesis and prognosis of MAS has received much attention recently. MAS is most prevalent and well described in sJIA, where infection is identified as a trigger in approximately one-third of patients (16). Infection is not only associated with the onset of MAS. In anti-MDA5 antibody-positive DM patients with MAS, we also found that dead patients had a higher rate of infection than the surviving. Recent trials of tocilizumab and canakinumab in MAS have indicated that controlling underlying inflammation alone is not sufficient to manage MAS, especially MAS triggered by infection (17, 18). These results suggest that we need to be alert to the occurrence of infection, and give appropriate immunosuppressive and antibiotic therapy, which may be useful to improve the prognosis.

Regarding MAS mortality in other rheumatic diseases, 9.5% of AOSD and 4.9% of SLE patients had fatal conditions (19, 20). Kishida *et al*. reviewed 18 adult DM patients complicated with MAS, and 7 (38.9%) patients died after treated with high doses of glucocorticoids and immunosuppressants (ISAs) (21). In the present study, the mortality of patients without MAS was 12.1% within six months after DM onset. Similar survival rates were reported by Tiniako *et al*. (22). In comparison, 4 (36%) anti-MDA5 antibody-positive DM patients had fatal conditions after complicated with MAS. These results support the findings of higher mortality in DM patients with MAS than in patients with other rheumatic diseases, including anti-MDA5 antibody-positive patients.

Given the importance of the early diagnosis of MAS, new classification criteria may be helpful. Therefore, in the present study, we used the HLH-2004 criteria and checked the EULAR/ACR/PRINTO criteria and HScore for MAS diagnosis. We confirmed that all of our MAS patients met above criteria. Among patients without MAS, no patients met HLH-2004 and EULAR/ACR/PRINTO criteria, and few patients had Hscore greater than 169 (Table II). One large retrospective study applied these criteria for MAS to patients with SLE and fever when admitted to the hospital, and one-third of these patients were classified as having MAS. Finally, 35% of these patients who fulfilled the MAS criteria died, compared with 3% without (23). The above results indicate that these classification criteria and tools may be useful in patients with rheumatic disease to identify MAS, which needs more data for validation.

Several studies have reported high levels of IFN-γ in the serum of patients with anti-MDA5-positive DM (7, 24). High IFN-γ levels in sera are associated with a higher rate of a severe clinical course (25). IFN-γ is also strongly affected during MAS as a key mediator

of disease development (5). Major biological functions of IFN-γ include the modulation of immune and inflammatory responses mainly via Janus kinases (JAKs) (26). Based on their essential roles in transmitting cytokine-induced signals, JAKs have become a target for pharmacologic manipulation in inflammatory diseases (27). Recently, a prospective clinical trial of ruxolitinib (JAK1/JAK2 inhibitor) showed positive results in adults with secondary HLH. Honda *et al*. reported that an AOSD patient complicated with MAS was successfully treated with aggressive immunosuppressive therapy and tofacitinib (28). In addition to MAS, Ye *et al*. also reported the effectiveness of tofacitinib for RP-ILD in anti-MDA5-positive CADM in a prospective study (29). Among our 11 MAS patients, two were given TOF and died. Importantly, both of them were cotreated with the other immunosuppressive agents, biological agents and etoposide. Although the combination treatment regimen with TOF showed a higher mortality rate in our study, we still expect that JAK inhibitors are emerging as a promising treatment strategy for patients with anti-MDA5 antibody-positive DM and MAS.

While it is clear that MAS is a possible complication of anti-MDA5 antibody-positive DM, the similarities and differences between MAS caused by DM and other rheumatic diseases need to be further studied. This study has several limitations. Because the coexistence of anti-MDA5 antibody-positive DM and MAS is low, only 11 patients with anti-MDA5-positive DM and MAS were included, which made it challenging to speculate risk factors for MAS. Furthermore, due to the small number of cases, it is difficult to find the effective treatment.

In conclusion, MAS tends to occur in the early phase of anti-MDA5 antibody-positive DM. Before the onset of MAS, patients had a higher rate of infection, DM typical rashes, and abnormal serological indicators than patients without MAS. Its mortality was high, particularly in elderly, infected, heart failure, renal impairment, receiving combination therapy with TOF and RP-ILD patients.

Acknowledgements

We would like to thank the participants in this study.

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