Rheumatology International (2019) 39:97–104
https://doi.org/10.1007/s00296-018-4114-1

Rheumatology
INTERNATIONAL

CLASSIFICATION CRITERIA

Are the 2016 EULAR/ACR/PRINTO classification criteria for macrophage activation syndrome applicable to patients with adult-onset Still's disease?

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Received: 14 June 2018 / Accepted: 21 July 2018 / Published online: 26 July 2018

Abstract

The objectives of this study are to determine whether the 2016 European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organization classification criteria for macrophage activation syndrome (MAS) complicating systemic juvenile idiopathic arthritis (SJIA) can be used to identify MAS in patients with adult-onset Still's disease (AOSD). Using laboratory data from 76 AOSD patients with and without MAS, we analyzed the ability of the collective and individual constitutive elements of the 2016 MAS in SJIA criteria and additional laboratory measures to discriminate between AOSD patients with ($n=16$) and without ($n=60$) MAS. Cutoff values to determine the sensitivity, specificity, and predictive values were calculated from receiver operating characteristic curves, and modified classification criteria for MAS in AOSD were evaluated. The 2016 MAS in SJIA classification criteria had an overall sensitivity of 100%, specificity of 70.0%, positive predictive value of 47.1%, and negative predictive value of 100% to discriminate between AOSD patients with and without MAS based on laboratory data. Among the individual criteria, the sensitivity of triglycerides (46.7%) and the specificity of ferritin (15.0%) for MAS in AOSD were particularly low. The sensitivity and specificity for classifying MAS in AOSD patients were increased to 100 and 93%, respectively, by excluding triglycerides and changing the cutoff values for other criteria in the 2016 MAS in SJIA classification. The 2016 classification criteria for MAS in SJIA had higher sensitivity but lower specificity to identify MAS in AOSD patients compared with SJIA patients.

Keywords Adult-onset Still's disease · Macrophage activation syndrome · Classification criteria · Ferritin · Fibrinogen · Platelet

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00296-018-4114-1) contains supplementary material, which is available to authorized users.

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Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disease with spiking fever, arthritis, and evanescent rash as its three main symptoms. Typical laboratory data for AOSD patients include leukocytosis with neutrophilia, elevated transaminase and C-reactive protein levels, no autoantibodies, and hyperferritinemia [1, 2]. The etiology and pathogenesis of the inflammatory response in AOSD are still unclear, but it is thought to derive mainly from the excessive production of cytokines, including interleukin (IL)-1, IL-6, IL-18, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), predominantly produced by macrophages and T cells [3].

Macrophage activation syndrome (MAS) is one of the most important and severe complications of AOSD and systemic juvenile idiopathic arthritis (SJIA) [4, 5]. Patients with MAS develop reactive hemophagocytosis (RH) that leads to leukocytopenia and thrombocytopenia. The incidence of MAS and RH in AOSD patients is thought to be around 12–20% [6–10]. The mortality rate from MAS in patients with rheumatic diseases is high, underscoring the importance of early diagnosis and prompt treatment [10–15]. However, MAS is sometimes difficult to diagnose. Typical symptoms and laboratory findings of MAS, such as high fever and high serum ferritin or lactate dehydrogenase (LDH) levels, are also seen in highly active AOSD and SJIA or in complications of infection. Although a demonstration of hemophagocytosis in the bone marrow or lymph nodes is an important factor for diagnosing MAS, several studies have shown that it is generally detected at low rates (39–60%) especially at the early stages of MAS [14, 16–18]. According to the current criteria, hemophagocytic lymphohistiocytosis (HLH)-2004 [19], the presence of hemophagocytosis is only one of eight criteria, and it is not specific when compared with other criteria.

Recently, a collaborative initiative group from the European League Against Rheumatism (EULAR), American College of Rheumatology (ACR), and Paediatric Rheumatology International Trials Organization (PRINTO) published new classification criteria for MAS complicating SJIA, which showed a sensitivity of 73% and a specificity of 99% [20]. Because AOSD is an adult counterpart of SJIA and its basic pathology, clinical features, and complications are similar to those of SJIA, we speculated that the new classification criteria might also be applicable to the diagnosis of MAS in patients with AOSD. To address this, we evaluated the sensitivity and specificity of the 2016 criteria to detect MAS in AOSD patients by applying the criteria to laboratory data from AOSD patients with MAS [referred to as MAS (+)] and without MAS [hereafter MAS (−)].

Our aim was to evaluate the 2016 MAS in SJIA criteria for the diagnosis of MAS complicating AOSD and propose modified criteria that might be more appropriate for a diagnosis of MAS in patients with AOSD.

Patients and methods

Patients

We performed a retrospective review of the medical records of two independent cohorts of patients with AOSD; one cohort [44 patients, including 7 MAS (+) patients] was from Saga University Hospital from January 1996 to March 2017, and the second cohort [32 patients, including 9 MAS (+) patients] was from Kyushu University Hospital from January 2007 to March 2017. All 76 patients were hospitalized and newly diagnosed with AOSD according to Yamaguchi's classification criteria [21]. This study was approved by the institutional ethics committees (Saga University Hospital ethics committee #2017-07-R-01 and Kyushu University Hospital ethics committee #29-521) and was performed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained with opt-out. For disease controls, patients with rheumatic diseases, including systemic lupus erythematosus (SLE, 26 patients, including three patients with MAS), anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV, 25 patients), polymyositis, and dermatomyositis (PM/DM, 24 patients) were included, and their laboratory data were collected. All patients were diagnosed at Saga University Hospital from April 2013 to December 2016 and were at the active stage of disease.

Definition of MAS

The diagnosis of MAS was reviewed by two authors (YT and SI) using the criteria for MAS published by Kumakura [5] and the HLH-2004 guidelines [19]. Prerequisites were: cytopenia of at least one lineage, proof of hemophagocytosis in the bone marrow, and exclusion of other reasons for MAS, such as drug-induced cytopenia. For inconclusive cases, such as negative bone marrow biopsy findings, three authors (YT, SI, NO) discussed the cases and made a consensus diagnosis of MAS (+) or MAS (−).

Clinical and laboratory data

From patient records, we extracted clinical findings, including age, sex, Yamaguchi's AOSD classification criteria [21], complications (pleuritis, pericarditis, interstitial pneumonitis, disseminated intravascular coagulation), laboratory data, treatment, and outcomes. The laboratory data were collected at the time of AOSD diagnosis [for the 60

MAS (−) patients] or the time of MAS diagnosis [for the 16 MAS (+) patients]. The data included complete blood count, and levels of C-reactive protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH, triglyceride (TG), fibrinogen, fibrin/fibrinogen degradation products (FDP), soluble interleukin-2 receptor (sIL-2R), and ferritin. The normal range for ferritin differed between males and females and between the two hospitals; however, the upper limits of normal were similar in both hospitals (males 273–345 ng/mL, females 100–140 ng/mL). Therefore, we used the raw data for analysis. We excluded D-dimer levels because only small numbers of MAS (−) patients were available.

Sensitivity and specificity determination

We analyzed the sensitivity and specificity of the overall 2016 classification criteria for MAS in SJIA and those of each constitutive criterion [ferritin, platelet count (PLT), AST, TG, and fibrinogen].

Statistical analysis

Laboratory data were compared by the nonparametric Mann–Whitney *U* test. $P < 0.05$ was considered statistically significant. The cutoff values were determined by receiver operating characteristic curve analysis. Odds ratios were calculated by univariate analysis. All statistical analyses were performed using Prism version 6 software (GraphPad, San Diego, CA, USA).

Results

The 76 patients with AOSD comprised 16 (21%) MAS (+) and 50 (79%) MAS (−) patients. One MAS (+) patient did not undergo a bone marrow biopsy but displayed bicytopenia (white blood cell count (WBCs) 4.26×10^9/L and PLT 64×10^9/L), decreased fibrinogen (50 mg/dL), and elevated AST and LDH (936 and 2742 U/L, respectively) at diagnosis. The patient entered remission after treatment with methylprednisolone pulse therapy, oral prednisolone, and cyclosporin A. A second MAS (+) patient was negative for hemophagocytosis by bone marrow biopsy; however, a diagnosis of MAS was made based on marked changes in laboratory data occurring post-diagnosis, including neutropenia (from 17.9×10^9/L at AOSD diagnosis to 4.1×10^9/L at MAS diagnosis), elevated LDH (from 336 to 1027 U/L), and decreased fibrinogen (from 1003 to 252 mg/mL). The remaining 14 MAS (+) patients showed hemophagocytosis in bone marrow aspirates. Among these MAS (+) patients, AOSD and MAS were simultaneously diagnosed in ten patients, and MAS developed 1 month to 2 years after the diagnosis of AOSD in six patients. All MAS patients were treated with steroids and 11 patients (68.8%) received intravenous methylprednisolone pulse therapy. In addition, cyclosporine was administered to ten (62.5%) patients and methotrexate was administered to two patients (12.5%). Among the 60 AOSD MAS (−) patients, bone marrow biopsies were performed in 15 and minimal hemophagocytosis was noted in three patients. In these patients, bone marrow examinations were performed for the differential diagnosis of hematological diseases, such as lymphoma and tuberculosis. However, these patients did not develop cytopenia and showed no significant changes in TG and fibrinogen with reference to the HLH-2004 criteria. Therefore, we did not diagnose them as MAS (+).

Sensitivity and specificity of classification criteria for MAS

Patient laboratory data were screened against the 2016 classification criteria for MAS in SJIA. All 16 MAS (+) patients in our cohort were classified as MAS, as were an additional 18 patients (18/60, 30%) in our MAS (−) group (Table 1). Thus, the sensitivity of the 2016 MAS in SJIA

Table 1 Sensitivities and specificities of individual classification criteria for the diagnosis of MAS in patients with AOSD

	MAS (+) ($n = 16$)	MAS (−) ($n = 60$)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Fulfilling criteria	16/16 (100%)	18/60 (30.0%)	100.0	70.0	47.1	100.0
Criteria items						
Ferritin > 684 ng/ml	16/16 (100%)	51/60 (85.0%)	100.0	15.0	23.9	100.0
PLT ≤ 181×10^9/L	15/16 (93.8%)	10/60 (16.7%)	93.8	83.3	60.0	98.0
AST > 48 U/L	16/16 (100%)	28/60 (46.7%)	100.0	53.3	36.4	100.0
TG > 156 mg/dL	7/15 (46.7%)	14/57 (24.6%)	46.7	75.4	33.3	84.3
Fibrinogen ≤ 360 mg/dL	14/15 (93.3%)	9/48 (18.8%)	93.3	81.3	60.9	97.5

Data are presented as *n* (%)

MAS macrophage activation syndrome, *PLT* platelets, *AST* aspartate transaminase, *TG* triglycerides, *PPV* positive predictive value, *NPV* negative predictive value

criteria for MAS in AOSD patients was 100%, the specificity was 70.0%, the positive predictive value was 47.1%, and the negative predictive value was 100%. We also analyzed the sensitivities and specificities of the individual constituent criteria (Table 1). PLT counts and fibrinogen levels showed high sensitivities (93.8% and 93.3%, respectively) and specificities (83.3 and 81.3%, respectively). In contrast, the sensitivity of TG (46.7%) and the specificities of AST and ferritin (53.3 and 15.0%, respectively) were low. Among the 60 MAS (−) patients, 28 (46.7%) and 51 patients (85.0%) fulfilled the AST (> 48 U/L) and ferritin (> 684 ng/mL) criteria, respectively.

Comparison of laboratory data between MAS (+) and MAS (−) AOSD patients

Next, we compared the laboratory data of MAS (+) ($n = 60$) and MAS (−) ($n = 16$) patients (Table 2). The two groups showed marked and significant differences in ferritin ($P = 0.0001$), PLT ($P < 0.0001$), AST ($P < 0.0001$), fibrinogen ($P < 0.0001$), WBCs ($P < 0.0001$), neutrophils ($P < 0.0001$), and LDH ($P < 0.0001$), whereas TG levels were similar ($P = 0.0396$). To determine the utility of the laboratory data to distinguish between the MAS (−) and MAS (+) groups, we performed receiver operating characteristic curve analysis (Table 3). The largest area under the curve (AUC) was obtained for PLT (0.960), followed by fibrinogen (0.914), LDH (0.884), AST (0.851), WBCs (0.826), neutrophils (0.816), and ferritin (0.803).

Table 3 Receiver operating characteristic curve analysis of the predictive value of laboratory data for discriminating between AOSD patients with and without MAS

	No. with available data	AUC	95% CI	*P* value
Criteria				
Ferritin	76	0.8026	0.6937–0.9115	0.0002
PLT	76	0.9604	0.9111–1.010	< 0.0001
AST	76	0.8505	0.7630–0.9381	< 0.0001
TG	72	0.6731	0.5331–0.8131	0.0402
Fibrinogen	63	0.9139	0.8440–0.9838	< 0.0001
Other laboratory data				
WBC	76	0.8255	0.7040–0.9471	< 0.0001
Neutrophil	76	0.8156	0.6859–0.9454	0.0001
Hemoglobin	76	0.5417	0.3919–0.6915	0.6103
ALT	76	0.7625	0.6451–0.8799	0.0013
LDH	76	0.8840	0.8082–0.9598	< 0.0001
Albumin	76	0.6474	0.5071–0.7877	0.0715
sIL-2R	50	0.7127	0.5351–0.8904	0.0276
FDP	34	0.8220	0.6777–0.9662	0.0022

MAS macrophage activation syndrome, *AUC*, area under the curve, CI confidence interval, PLT platelets, *AST* aspartate transaminase, *TG* triglycerides, *WBC* white blood cell count, *ALT* alanine transaminase, *LDH* lactate dehydrogenase, *sIL-2R* soluble interleukin-2 receptor, *FDP* fibrin/fibrinogen degradation products

Table 2 Comparison of laboratory data between patients with and without MAS

	MAS (+)		MAS (−)		*P* value
	No. with available data	Median (IQR)	No. with available data	Median (IQR)	
Criteria					
Ferritin (ng/mL)	16	19,450 (7890–42,736)	60	5028 (1158–13,552)	0.0001
PLT ($\times 10^9$/L)	16	80.0 (74–92)	60	295.0 (214–413)	< 0.0001
AST (U/L)	16	146 (102–242)	60	44 (30–99)	< 0.0001
TG (mg/dL)	15	153 (125–176)	57	116 (86–158)	0.0396
Fibrinogen (mg/dL)	15	259 (140–348)	48	518 (383–665)	< 0.0001
Other laboratory data					
WBC ($\times 10^9$/L)	16	7.4 (4.1–10.2)	60	13.0 (10.4–18.0)	< 0.0001
Neutrophil ($\times 10^9$/L)	16	4.7 (3.0–9.2)	60	11.2 (8.6–16.1)	< 0.0001
Hemoglobin (g/dL)	16	11.5 (10.4–12.5)	60	11.0 (10.0–12.4)	0.6175
ALT (U/L)	16	142 (46–196)	60	41 (20–80)	0.001
LDH (U/L)	16	1019 (692–1446)	60	411 (279–613)	< 0.0001
Albumin (g/dL)	16	2.65 (2.2-3.0)	60	2.90 (2.5–3.3)	0.0712
sIL-2R (U/mL)	12	2580 (1505–4302)	38	1433 (889–2420)	0.0270
FDP (mg/dL)	12	66.9 (19.7–143.4)	22	12.55 (8.0–28.0)	0.0016

MAS macrophage activation syndrome, *IQR*, interquartile range, *PLT* platelet count, *AST* aspartate transaminase, *TG* triglycerides *WBC* white blood cell count, *ALT* alanine transaminase, *LDH* lactate dehydrogenase, *sIL-2R* soluble interleukin-2 receptor, *FDP* fibrin/fibrinogen degradation products

From these analyses, TG levels appeared to be less useful for the classification of MAS in AOSD patients than in SJIA patients. We then determined the optimal cutoff values for the individual laboratory measures (excluding TGs) to determine their relative utility to identify MAS in AOSD patients. We obtained new cutoff values of ferritin 2810 mg/mL, PLT 137×10^9/L, AST 95 U/L, fibrinogen 365 mg/dL, WBCs 10.25×10^9/L, neutrophils 7.86×10^9/L, ALT 81 U/L, and LDH 580 U/L (Table 4). Notably, the cutoff value for PLT was lower (original criterion $\leq 181 \times 10^9$/L) and those for AST and ferritin were higher (original criteria > 48 U/L and > 684 ng/mL, respectively) for classifying MAS complicating AOSD compared with MAS complicating SJIA [20]. Univariate analysis showed that each factor was significantly associated with MAS (Table 4).

Modification of the classification criteria for MAS complicating SJIA for utilization in patients with AOSD

From these analyses, we modified the classification criteria for MAS in SJIA to determine their utility for classifying MAS in AOSD. We excluded TG from the original criteria and used the newly identified cutoff values for the remaining four original criteria (ferritin, PLTs, AST, fibrinogen). The tentative modified classification criteria were (i) ferritin > 2810 mg/mL and (ii) any two of the following: PLT $\leq 137 \times 10^9$/L, AST > 95 U/L, and fibrinogen ≤ 365 mg/dL. When this model was applied to our patient cohort, all 16 MAS (+) patients but only 4 of the 60 MAS (−) patients (6.7%) were classified as MAS. Thus, the modified criteria had a sensitivity of 100%, specificity of 93%, positive predictive value of 80%, and negative predictive value of 100%.

Application of MAS classification criteria to patients with rheumatic disease controls

We evaluated the specificity of the criteria in active rheumatic diseases, including SLE, AAV, and PM/DM (Supplementary Tables 1 and 2). All 3 SLE patients complicated with MAS and only 2 out of 72 MAS (−) controls (2.8%) fulfilled the original MAS classification criteria (sensitivity of 100% and specificity of 97.2%). By the modified criteria, two patients out of three MAS (+) SLE and no MAS (−) control patients fulfilled the criteria (sensitivity of 66.7% and specificity of 100%). In either case, the specificity was markedly high in these populations.

Discussion

MAS/RH is a critical complication of many autoimmune diseases, including AOSD and SLE, and can sometimes be fatal. The previously established criteria for a diagnosis of MAS/RH, known as the HLH-2004 criteria [19], are problematic for diagnosing MAS in patients with autoimmune diseases. For example, MAS markers such as lymphadenopathy and hyperferritinemia are also common features of active SJIA and AOSD, making it difficult to distinguish the symptoms of MAS from those of the active disease. In addition, MAS-associated neutrophil and PLT counts and fibrinogen levels may vary depending on the disease context. These factors are increased to a much greater extent during the active phase of inflammatory diseases, including AOSD, compared with non-inflammatory diseases, such as malignant lymphoma or systemic lupus erythematosus; thus, a

Table 4 Univariate analysis of the ability of laboratory data to discriminate between AOSD patients with and without MAS

	No. with available data	Odds ratio (95% CI)	*P* value	Sensitivity (%)	Specificity (%)
Criteria (excluding TG)					
Ferritin > 2810 ng/mL	76	25.35 (1.45–442.3)	0.0007	100.0	45.0
PLT $\leq 137 \times 10^9$/L	76	285.00 (27.6–2941)	< 0.0001	93.8	95.0
AST > 95 U/L	76	21.00 (4.27–103.3)	< 0.0001	87.5	75.0
Fibrinogen ≤ 365 mg/dL	63	82.00 (9.25–726.8)	< 0.0001	93.3	85.4
Other laboratory data					
WBC < 10.25×10^9/L	76	14.24 (3.54–57.22)	< 0.0001	81.3	76.7
Neutrophil < 7.86×10^9/L	76	12.00 (3.28–43.89)	< 0.0001	75.0	80.0
ALT > 81 U/L	76	5.48 (1.69–17.75)	0.0053	62.5	76.7
LDH > 580 U/L	76	44.00 (5.35–362.2)	< 0.0001	93.8	74.6

MAS macrophage activation syndrome, *CI* confidence interval, *PLT* platelets, *AST* aspartate transaminase, *WBC* white blood cell count, *ALT* alanine transaminase, *LDH* lactate dehydrogenase

decrease in these factors—even to the normal range—could indicate the onset of MAS in patients with AOSD. The 2016 classification criteria for MAS complicating SJIA are simple and easy to apply to any patient population [20] because the data are collected in standard laboratory tests without the need for special procedures, such as natural killer cell assays or bone marrow biopsies. Although we found that these criteria could be applied for diagnosing MAS in AOSD patients, several potential problems were identified.

First, the difference in TG levels between patients with and without MAS was smaller than that of other criteria, suggesting this is a less useful factor for AOSD than SJIA patients. Hypertriglyceridemia is frequently observed in primary MAS/HLH [22, 23] and is included in the classification criteria for this disease [19]. However, it was shown that TG levels of patients with MAS in SJIA were significantly lower than in those with primary HLH [24] and that the incidence of hypertriglyceridemia was lower in adult patients with secondary HLH compared with primary HLH [25, 26]. In our cohort, TG levels in MAS (+) patients were lower than previously reported [14, 16, 27]. We cannot explain the reason for these differences, and therefore we should be careful in interpreting this result because the number of samples is small. We consider TG levels may vary based on comorbidities or the age of adult patients, and we should be aware of this point in interpreting TG values. Indeed, TGs have been excluded from several previously proposed diagnostic criteria for hemophagocytic syndrome [5, 28]. Second, although ferritin, AST, and PLT were good markers to discriminate between AOSD patients with and without MAS, adjustments to their cutoff values may be necessary for application in AOSD. In general, serum ferritin levels in the absence of MAS were higher in AOSD patients (3000–11,000 ng/mL) [9, 16] than in SJIA patients (200–2500 ng/mL) [17, 20, 29]. Similarly, AST levels were higher in AOSD patients than in SJIA patients [16, 20, 29]. In contrast, we found that PLT and fibrinogen levels were similar in patients with AOSD and SJIA. Consequently, the PLT and fibrinogen cutoff values derived in this study were similar to those of the 2016 criteria.

By excluding TGs and using the new cutoff values for ferritin, AST, PLT, and fibrinogen, our modified criteria showed an excellent ability to differentiate between AOSD patients with and without MAS (100% sensitivity and 93% specificity). This indicates that, except for TGs, the same criteria are applicable for classifying MAS in both AOSD and SJIA. Of the four patients who fulfilled our modified criteria for MAS but were not originally diagnosed as MAS (+), three had low PLT ($43–110 \times 10^9$/L) and elevated AST levels (111–134 U/L) and were diagnosed as having disseminated intravascular coagulation. Two also had low fibrinogen levels (242 and 245 mg/dL), and one had normal bone marrow findings. The remaining patient had high AST (344 U/L) and low fibrinogen (247 mg/dL) levels without blood count abnormalities.

In our analyses, we found that LDH, WBCs, and neutrophils were potential additional candidate criteria to PLT, fibrinogen, AST, and ferritin for the diagnosis of MAS in AOSD. To test this, we explored multiple sets of criteria, including elevated ferritin plus any two of PLT, LDH, and fibrinogen, or elevated ferritin plus any three of PLT, AST, fibrinogen, and neutrophils. However, these candidate criteria showed similar sensitivities and specificities to those of the final modified criteria selected (ferritin > 2810 mg/mL and any two of PLT 137×10^9/L, AST > 95 U/L, and fibrinogen 365 mg/dL) in discriminating between MAS (+) and MAS (−) patients in our AOSD cohort.

A recent study showed that AOSD patients who fulfilled the 2016 EULAR/ACR/PRINTO classification criteria for MAS had more severe disease and a poorer prognosis than patients without MAS [30]. In that study, the frequency of patients fulfilling the MAS criteria (36/64, 56%) was higher than in our study (34/76, 45%). However, both frequencies were markedly higher than those previously reported for MAS associated with AOSD (12–20%) [6–10]. Although there is no doubt that patients who fulfill the MAS criteria display a severe phenotype, they may also contain patients with MAS and "pre-MAS" conditions. In an earlier study [30], the mortality rate was higher for MAS (+) compared with MAS (−) patients (33.3% vs 0%). We did not analyze prognosis in our study because only two patients died [both MAS (−)].

Our study had several limitations. The retrospective study design may reduce the external validity, and some confounding factors, such as misclassification or information biases, might be present in these series. For example, MAS is thought to be triggered by the activation of underlying disease in our patients, but it is sometimes difficult to discriminate MAS caused by infection from the medical records alone. In addition, because of the rarity of the disease and low number of patients, these results might be misinterpreted. Further studies with a prospective and multicentered design might produce more valuable data.

In summary, the 2016 EULAR/ACR/PRINTO classification criteria for MAS complicating SJIA can be applied to patients with AOSD; however, we propose that some minor modifications may provide a more accurate system for classifying MAS in AOSD patients. Further studies will be necessary to validate these criteria.

Acknowledgements The authors thank Ms. Eguchi and Ms. Ibe for secretarial assistance and Atsushi Kawaguchi for statistical analysis. We thank Edanz Group (http://www.edanzediting.com/ac) for editing a draft of this manuscript.

Author contributions YT was responsible for the design of the study, acquisition, analysis and evaluation of the data, and manuscript

preparation. SI, NO, and SK were responsible for acquisition and evaluation of the data, and discussion; AM, RS, MS, YS, and YM were responsible for the acquisition and interpretation of the data. All the authors have read, revised, and approved the content of the manuscript. All the authors agreed to be accountable for the accuracy or integrity of the work.

Compliance with ethical standards

Conflict of interest Author Tada Y has received research grants and personal fees from Mitsubishi-Tanabe, Chugai, Astellas, Takeda, Teijin, and Eisai, personal fees from Novartis, Sanofi, Actelion, Daiichi Sankyo, Ayumi, Abbvie, Bristol-Myers Squibb, Janssen, Asahikasei, Nippon Kayaku, and Pfizer, outside the submitted work. Author Maruyama A has received a speaker honorarium from Janssen, Mitsubishi-Tanabe, Chugai, Astellas, and Bristol-Myers Squibb, outside the submitted work. Author Ono N has received personal fees from Mitsubishi-Tanabe, Chugai, Astellas, Takeda, Teijin, Abbvie, and Bristol-Myers Squibb, outside the submitted work. Author Arinobu Y has received personal fees from Mitsubishi-Tanabe, Chugai, Astellas, Takeda, Eisai, Actelion, Abbvie, Bristol-Myers Squibb, Daiichi-Sankyo, Ayumi, Asahikasei, and Nihon Shinyaku, outside the submitted work. Author Koarada S has received personal fees from Mitsubishi-Tanabe, Chugai, Astellas, Takeda, Eisai, Novartis, Abbvie, Bristol-Myers Squibb, Sanofi, Janssen, Pfizer, and Asahikasei, outside the submitted work. The authors Inokuchi S, Suematsu R, Sakai M, and Sadanaga Y declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. This study was approved by the Saga University Hospital Ethics Committee (#2017-07-R-01) and the Kyushu University Hospital Ethics Committee (#29–521).

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