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Macrophage activation syndrome in children with systemic juvenile idiopathic arthritis and systemic lupus erythematosus

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Abstract Macrophage activation syndrome (MAS) is a hyper-inflammatory disorder secondary to a rheumatic disease such as systemic juvenile idiopathic arthritis (SJIA) and systemic lupus erythematosus (SLE). We aimed to present the characteristics of our pediatric MAS patients. Clinical features, laboratory parameters, treatment, and outcome of 34 patients (28 SJIA; six SLE; 37 MAS episodes) followed at a tertiary health center between 2009 and 2015 were retrospectively reviewed. The median age at MAS onset was 11 years. More SJIA patients had MAS at disease onset than SLE patients (53.6 vs. 16.7 %). Fever, high C-reactive protein and hyperferritinemia were present in all MAS episodes. Rash was less ($p = 0.03$), and fatigue was more frequent ($p = 0.042$) in SLE than SJIA patients. All received corticosteroids. Cyclosporine was given in 74.2 % of SJIA-MAS; 66.7 % of SLE-MAS episodes. Intravenous immunoglobulin, anakinra, or etoposide was administered during 67.7; 41.9; 32.3 % of SJIA-MAS and 33.3; 33.3; 50 % of SLE-MAS episodes, respectively. Plasmapheresis was performed during 41.9 % of SJIA-MAS and 33.3 % of SLE-MAS episodes. The mortality rate was 11.8 % ($n = 4$;3 SJIA, 1 SLE). Hepatosplenomegaly was more frequent ($p = 0.005$), and plasmapheresis was performed more frequently ($p = 0.021$) in the patients who died compared to the cured patients. The median duration between symptom onset and admission to our hospital was longer among the patients who died (16.5 vs. 7 days; $p = 0.049$). Our patients' characteristics were similar to the reported cases, but our mortality rate is slightly higher probably due to late referral to our center. Early diagnosis and effective treatment are crucial to prevent mortality.

Keywords Macrophage activation syndrome · Systemic juvenile idiopathic arthritis · Systemic lupus erythematosus · Child

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a severe, potentially life threatening, hyper-inflammatory disorder [1]. There are mainly two forms of HLH: primary (hereditary) and secondary (reactive, acquired). Primary HLH usually presents in early childhood while acquired form can present at any age and is usually seen in the background of different disorders such as infections, malignancies, and rheumatologic disorders [2, 3]. Acquired HLH is usually called as macrophage activation syndrome (MAS) when it is secondary to a rheumatic disease [4, 5]. MAS reflects an exaggerated and dysregulated immune response of the host and can be triggered by various events such as exacerbation of the underlying disorder, viral infections, and drugs [6]. It occurs with the continual activation and expansion of T lymphocytes and macrophages which results in increased proinflammatory cytokines [7, 8].

Studies on animal models have provided information about the role of cytokines in MAS. Repeated stimulation

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of Toll-like receptor 9 (TLR9) in mice caused HLH-like syndrome with elevated serum levels of interleukin 6 (IL-6), IL-10, IL-12, IL-18 and interferon gamma (IFN-γ) [9]. However, fulminant MAS did not develop unless IL-10 signaling was blocked. In another study, TLR4 stimulation resulted in cardinal features of HLH with elevated IL-1β, IL-18, IFN-γ, and tumor necrosis factor alpha (TNF-α) in a transgenic mice producing high levels of IL-6 [10, 11]. Previous experiments pointed at a central role for IFN-γ in HLH; however, recently they have shown that IFN-$\gamma^{-/-}$ mice with IL-10 blockade displayed HLH with the exception of anemia [12]. In the same lines, they demonstrated that HLH could develop in the absence of IL-12, TNF-α, IFN-α, and IFN-β, suggesting a complex cytokine interaction in pathogenesis [12]. Decreased perforin expression and reduced natural killer (NK) cytotoxicity have been reported in a few MAS patients [13].

Blockade of different cytokines such as IL-1, IL-6, IL-18, TNF-α, or IFN-γ could be good strategy for MAS treatment. Anti-IL-1 or anti-IL6 therapies are used in clinical practice; however, we know that MAS can occur in patients who are already on these drugs [14–18]. Administration of natural inhibitor of IL-18 was found beneficial in mouse models of HLH [19]. Therapeutic use of IL-10 has also been proposed in TLR9-triggered MAS models [9, 20]. In addition, there is an ongoing pilot study with an anti-IFN-γ monoclonal antibody treatment in primary HLH patients [21].

The highest prevalence of MAS is seen in systemic juvenile idiopathic arthritis (SJIA), adult-onset Still's disease, and systemic lupus erythematosus (SLE) [22]. MAS frequency has been reported as 7–13 % in SJIA; however, as high as one-third of SJIA patients show signs of subclinical MAS during disease course [23–26]. The reported incidence of MAS in SLE ranges from 0.9 to 4.6 % [27].

Recognition of MAS in patients with SJIA and SLE is often challenging because MAS may mimic all signs and symptoms even laboratory features of the underlying disease. SJIA may be associated with anemia and hyperferritinemia in the absence of MAS [28]. In addition, cytopenias may present in the course of SLE without MAS [29]. Early diagnosis of MAS is crucial to prevent morbidity and mortality. Currently, there is no pathognomonic clinical or laboratory parameter for MAS diagnosis. It is not appropriate to rely solely on histopathological findings since hemophagocytosis may not appear in the biopsy at early phases of MAS [30]. Furthermore, there are other conditions causing hemophagocytosis in the reticuloendothelial system such as blood transfusion and severe sepsis [31–33].

It is also difficult to distinguish MAS form other diseases such as sepsis, rheumatic diseases, and malignancies. The HLH-2004 criteria are considered more suitable for primary (hereditary) conditions; these criteria are based on several laboratory tests which are not routinely performed such as soluble CD25 level and NK cell activity [34]. Parodi et al. [35] reported preliminary diagnostic criteria for MAS as a complication of juvenile SLE. Kostik et al. [36] have recently reported diagnostic criteria for early recognition of MAS in active SJIA. Most recently, Ravelli et al. [37] have reported new criteria for MAS in SJIA patients. According to these new pediatric MAS classification criteria, a febrile patient with known or suspected SJIA is classified as having MAS when he has ferritin level >700 ng/mL and two of the following four criteria: platelet count <180,000/mm^3; aspartate aminotransferase (AST) >50 IU/L; triglyceride >160 mg/dL; and fibrinogen ≤360 mg/dL [37].

In this study, our aim was to present all our patients diagnosed with MAS and discuss the clinical and laboratory characteristics of MAS in children.

Patients and methods

A total of 34 patients with 37 episodes considered as having MAS (associated with SJIA or SLE) and followed at Pediatric Rheumatology and Hematology Departments, Hacettepe University, Ankara, Turkey, between 2009 and 2015 were retrospectively reviewed. Clinical features, laboratory parameters, treatment, and outcome were retrieved from medical charts of the patients. Two cases with SJIA experienced more than one episode of MAS (one with two episodes; other with three episodes). The diagnosis for MAS was mainly based on expert opinion. However, we checked whether our patients were fulfilling HLH-2004 criteria [34] (all patients), criteria by Parodi et al. [35] (only SLE patients), criteria by Kostik et al. [36] (only SJIA patients), and criteria by Ravelli et al. [37] (only SJIA patients). The items of these different criteria sets are presented in Supplementary Table 1. Indications for plasmapheresis mainly depended on the severity of thrombocytopenia and organ failure.

Statistical analysis

Statistical analyses were performed using the SPSS software version 15. Descriptive analyses were presented using proportions, medians, minimum, and maximum values as appropriate. The Chi-square test or Fischer's exact test, where appropriate, was used to compare the proportions in different groups. The Mann–Whitney *U* test was performed to compare non-normally distributed continuous variables. A p value of <0.05 was considered to show a statistically significant result.

Results

The study group (28 SJIA and six SLE) included 14 girls and 20 boys, and the median (min–max) age at MAS onset was 11 (1–16) years. The characteristics of MAS patients are summarized in Tables 1 and 2 according to the underlying rheumatologic disease; SLE or SJIA. More patients with SJIA presented with MAS at disease onset when compared to SLE patients; however, this difference did not reach a statistical significance (53.6 vs. 16.7 %; $p = 0.18$). None of the patients had underlying infection at the time of MAS. MAS is thought to be triggered by the activation of the underlying disease in all patients. In one patient with SJIA, MAS occurred immediately after the first dose of canakinumab (anti-IL-1 drug); however, the disease was active as well at that time. The median (min–max) time to admission to our hospital from the onset of MAS-related features was 10 (1–30) days. In 12 out of 37 MAS episodes (32.4 %), patients were admitted ≥15 days later since they were initially followed in their regional health unit.

Table 1 Clinical and laboratory characteristics of systemic juvenile idiopathic arthritis (SJIA) and systemic lupus erythematosus (SLE) patients at the time of macrophage activation syndrome (MAS)

Characteristics [*n* (%) or median (min–max)]	SJIA (28 patients; 31 MAS episode)	SLE (6 patients; 6 MAS episode)	*p* value
Age at initial diagnosis (years)	7 (1–16)	13 (4–13.5)	0.13
Age at MAS diagnosis (years)	9 (1–16)	14 (5–15)	0.28
Gender (female)	9 (32.1)	5 (83.3)	0.061
Time interval between initial diagnosis and MAS [month (s)]	0 (0–102)	13 (0–24)	0.28
Initial diagnosis with MAS	15 (53.1)	1 (16.7)	0.18
Fever	31 (100)	6 (100)	–
Rash	21 (67.7)	1 (16.7)	0.03
Arthralgia/arthritis	17 (54.8)	1 (16.7)	0.18
Fatigue	3 (9.7)	3 (50)	0.042
Dyspnea	2 (6.5)	0 (0)	1
Pleural effusion	3 (9.7)	0 (0)	1
Pericardial effusion	2 (6.5)	0 (0)	1
Hb (g/dL)	9.2 (5.1–15)	9.05 (7–11.3)	0.81
WBC (10^3/mm^3)	8 (2–70)	2.45 (0.8–11.3)	0.20
Platelet (10^3/mm^3)	121 (23–590)	140.5 (63–390)	0.70
Hepatosplenomegaly	10 (32.3)	1 (16.7)	0.64
Ferritin (ng/mL)	7838 (360–150,099)	4158 (1300–15,456)	0.28
Fibrinogen (mg/dL)	254 (50–834)	313.5 (226–507)	0.59
TG (mg/dL)	245 (55–931)	235 (65–430)	0.65
LDH (U/L)	1457 (197–14,623)	836 (321–1852)	0.71
Vit B12 (pg/mL)	370.5 (87–1381)	317 (155–503)	1
aPTT (s)	29 (21.5–61)	32 (30–37)	0.57
ALT (U/L)	60 (5–623)	63 (26–107)	0.94
AST (U/L)	71 (5–2007)	53 (22–756)	0.36
Albumin (mEq/L)	2.97 (1.29–4.59)	3.41 (2.29–4.2)	0.59
Na (mEq/L)	136 (124–141)	135.5 (132–144)	0.95
ESR (mm/h)	14 (2–120)	29 (4–70)	0.33
CRP (mg/dL)	9.76 (1.35–56.2)	8.8 (1.9–15.8)	1
Symptom onset to hospital admission (days)	10 (1–20)	8.5 (4–30)	1
Symptom onset to hospital admission ≥15 days	10 (32.3)	2 (33.3)	1
Exitus	3 (10.7)	1 (16.7)	0.55

ALT alanine aminotransferase, *aPTT* activated partial thromboplastin time, *AST* aspartate aminotransferase, *CRP* C-reactive protein (normal range 0–0.5), *ESR* erythrocyte sedimentation rate (normal range 0–20), *Hb* hemoglobin, *IVIG* intravenous immunoglobulin, *LDH* lactate dehydrogenase, *MAS* macrophage activation syndrome, *SJIA* systemic juvenile idiopathic arthritis, *SLE* systemic lupus erythematosus, *vit B12* vitamin B12, *TG* triglyceride, *WBC* white blood cell

Table 2 Characteristics of macrophage activation syndrome (MAS) patients according to the final outcome (cured or exitus)

Characteristics [*n* (%) or median (min–max)]	Cured (30 patients; 33 MAS episodes)	Exitus (4 patients; 4 MAS episodes)	*p* value
Age at MAS diagnosis (years)	9 (1–15.5)	15 (7–16)	0.59
Gender (female)	12 (40)	2 (50)	1
Diagnosis (SJIA)	28 (84.8)	3 (75)	0.52
Initial diagnosis with MAS	15 (45.5)	1 (25)	0.60
Fever	33 (100)	4 (100)	–
Rash	20 (60.6)	2 (50)	1
Arthralgia/arthritis	15 (45.5)	3 (75)	0.34
Fatigue	5 (15.2)	1 (25)	0.52
Dyspnea	1 (3)	1 (25)	0.20
Pleural effusion	3 (9.1)	0 (0)	1
Pericardial effusion	2 (6.1)	0 (0)	1
Hb (g/dL)	9.2 (5.1–12.2)	9.6 (7.1–15)	0.72
WBC (10^3/mm^3)	7.3 (0.8–40.1)	8.1 (1.6–70)	0.90
Platelet (10^3/mm^3)	139 (23–590)	48.5 (27–79)	0.12
Hepatosplenomegaly	7 (21.2)	4 (100)	0.005
Ferritin (ng/mL)	6952 (360–150 099)	53,822 (7682–97,767)	0.55
Fibrinogen (mg/dL)	254 (50–834)	299 (238–780)	0.55
TG (mg/dL)	233.5 (55–722)	389.5 (220–931)	0.59
LDH (U/L)	1116 (197–14 623)	2574.5 (1852–11,133)	0.09
Vit B12 (pg/mL)	317 (87–1381)	445.5 (388–503)	0.19
aPTT (s)	29.5 (21.5–61)	31 (22.4–39)	0.79
ALT (U/L)	59 (5–623)	167 (34–251)	0.55
AST (U/L)	56 (5–2007)	390.5 (38–756)	0.55
Albumin (mg/dL)	3.32 (1.8–4.59)	2.29 (1.29–2.3)	0.12
Na (mEq/L)	136 (124–144)	128.5 (128–134)	0.22
ESR (mm/h)	18.5 (2–120)	4 (2–14)	0.11
CRP (mg/dL)	8.7 (1.35–29.8)	11.6 (8.8–56.2)	1
Etoposide	10 (30.3)	3 (75)	0.11
Cyclosporine A	23 (69.7)	4 (100)	0.55
IVIG	19 (57.6)	4 (100)	0.27
Plasmapheresis	11 (33.3)	4 (100)	0.021
Anakinra	13 (39.4)	2 (50)	1
Symptom onset to hospital admission (days)	7 (1–20)	16.5 (15–30)	0.049
Symptom onset to hospital admission ≥15 days	8 (24.2)	4 (100)	0.008

ALT alanine aminotransferase, *aPTT* activated partial thromboplastin time, *AST* aspartate aminotransferase, *CRP* C-reactive protein (normal range 0–0.5), *ESR* erythrocyte sedimentation rate (normal range 0–20), *Hb* hemoglobin, *IVIG* intravenous immunoglobulin *LDH* lactate dehydrogenase, *MAS* macrophage activation syndrome, *SJIA* systemic juvenile idiopathic arthritis, *vit B12* vitamin B12 *TG* triglyceride, *WBC* white blood cell

Fever (≥38 °C), elevated C-reactive protein, and hyperferritinemia (over 600 ng/mL in all but one) were observed in all patients at the time of MAS diagnosis. An extremely elevated lactate dehydrogenase level was displayed in all MAS episodes except one (96 %). When we compared the characteristics of SLE and SJIA patients, we have seen that rash was less frequent and fatigue was more frequent in SLE patients ($p = 0.03$; $p = 0.042$, respectively) (Table 1). The median white blood cell count was also lower in SLE patients than ones with SJIA; however, this difference did not reach a statistical significance (2.4 vs. 8×10^3/mm^3, respectively; $p = 0.2$). Other characteristics did not differ significantly between two groups.

All patients received pulse methylprednisolone for 3–5 days (30 mg/kg/day; max 1000 mg/day) IV and then oral prednisolone (1–2 mg/kg/day) treatment. Cyclosporine A was

given in 23 out of 31 MAS episodes (74.2 %) in SJIA patients and four out of six MAS episodes (66.7 %) in SLE patients, in combination with corticosteroid therapy. Intravenous immunoglobulin (IVIG) treatment was given during 21 (67.7 %) MAS episodes in SJIA and 2 (33.3 %) episodes in SLE patients. Only one patient with SJIA received etanercept (anti-TNF treatment), while anakinra (anti-IL-1 treatment) was given during 13 (41.9 %) SJIA-MAS and 2 (33.3 %) SLE-MAS episodes. All SJIA patients diagnosed after 2011 received anakinra. Etoposide treatment was given in 10 (32.3 %) SJIA-MAS and 3 (50 %) SLE-MAS episodes. Plasmapheresis was performed during 13 (41.9 %) SJIA-MAS and 2 (33.3 %) SLE-MAS episodes at a median of 3 (1–8) times.

The overall mortality rate was 11.8 % ($n = 4$; 3 with SJIA and 1 with SLE) in our group. The median (min–max) time from onset of MAS-related symptoms to the admission to our hospital was 16.5 (15–30) days for these four patients. When we compared the cured patients with the patients who died (Table 2), we have seen that hepatosplenomegaly was more frequent (100 vs. 21.2 %, respectively; $p = 0.005$) and plasmapheresis was performed more frequently (100 vs. 33.3 %, respectively; $p = 0.021$) in exitus group than cured patients. The median duration between symptom onset and admission to our hospital was longer in the patients who died (16.5 vs. 7 days, respectively; $p = 0.049$) and more patients admitted to our hospital $\geq$15 days later than the onset of MAS-related symptoms in the exitus group than cured ones (100 vs. 24.2 %, respectively; $p = 0.008$).

We checked whether our patients met different diagnostic criteria sets: HLH-2004 criteria [34] (all patients), criteria by Parodi et al. [35] (only SLE patients), criteria by Kostik et al. [36] (only SJIA patients), and criteria by Ravelli et al. [37] (only SJIA patients). All SJIA patients were fulfilling the diagnostic criteria by Ravelli et al. [37], and all but one SLE patients met the criteria by Parodi et al. [35]. HLH-2004 criteria were met in only 14 out of 37 (37.8 %) MAS episodes. However, we cannot test CD25 level and NK cell activity in our hospital; thus, we could not evaluate two items of the HLH-2004 criteria set [34]. When we compared the patients fulfilling HLH-2004 patients with the rest of the patients (Supplementary Table 2), we have seen that more patients had initial diagnosis of the rheumatologic disease with MAS (64.3 vs. 30.4 %, respectively; $p = 0.01$). The median platelet count was lower (69.5 vs. 186 $\times$ 10^3/mm^3, respectively; $p < 0.001$), the median ferritin, triglyceride, and alanine aminotransferase levels were higher (17447 vs. 5760 ng/mL, 358 vs. 196 mg/dL, and 168 vs. 40 U/L, respectively; $p = 0.01$ for all), IVIG was administered more frequently (85.7 vs. 47.8 %, respectively; $p = 0.021$) and plasmapheresis was performed more frequently (71.4 vs. 21.7 %, respectively; $p = 0.003$) in patients who fulfilled HLH-2004 criteria.

When we applied the criteria by Kostik et al. [36] to the patients with SJIA-MAS, 26 out of 37 (70.2 %) MAS episodes fulfilled the criteria. When we compared the SJIA-MAS patients fulfilling criteria by Kostik et al. [36] with the rest of the SJIA-MAS patients (Supplementary Table 3), we have seen that the median platelet count, fibrinogen level, and erythrocyte sedimentation rate were lower (107 vs. 536 $\times$ 10^3/mm^3, 238 vs. 604.5 mg/dL, and 11 vs. 80 mm/h, respectively; $p = 0.04$ for all) in the ones who met the criteria. From these parameters, platelet count and fibrinogen level were already the components of the criteria set by Kostik et al. [36].

Discussion

Macrophage activation syndrome, a major cause of morbidity and mortality in pediatric rheumatology, is most strongly associated with SJIA. There are no validated diagnostic criteria, and early diagnosis is difficult [7]. Moreover, it is sometimes difficult to distinguish rheumatic disease flare from MAS [8]. MAS is overt in 10 % of children with SJIA but occurs subclinically in another 30–40 % [23, 26]. The results from the registry of the Turkish Paediatric Rheumatology Association showed that the frequency of MAS was 15.2 % among SJIA patients [38]. In our hospital, we were following 110 SJIA patients in this time period and we observed MAS in 28 (25.4 %) of them. This high rate may be due to the fact that we are the referral center, and we receive more severe cases.

MAS is becoming increasingly recognized in SLE and reported incidence of MAS in SLE ranges from 0.9 to 4.6 % [27]. In our hospital, we followed 85 SLE patients between 2009 and 2015 and we observed MAS in six of them (7 %). In some cases, SLE-associated MAS may not be recognized because of similar laboratory features with the disease itself.

Single parameters are nonspecific, and only a set of clinical and laboratory features may lead to the diagnosis of MAS. Therefore, certain diagnostic criteria sets were developed for early and true diagnosis of RHS [34–37]. None of these criteria have been validated prospectively, and some items of these criteria sets are difficult to test in routine clinical practice. In our study, almost all SJIA and SLE patients were fulfilling the MAS diagnostic criteria by Ravelli et al. [37] and Parodi et al. [35], respectively. Of SJIA patients, 70.2 % met the criteria by Kostik et al. [36]. However, only 37.8 % of all patients met the HLH-2004 criteria [34]. One of the reasons for this low frequency could be that we cannot test CD25 and NK cell activity in our center. When we compared the patients fulfilling HLH-2004 patients with the rest of the patients, we have seen that the patients who met the HLH-2004 criteria had a more severe MAS with lower

platelet count, higher ferritin, triglyceride levels, and more frequent treatment with IVIG and plasmapheresis.

Early suspicion of MAS is usually possible by the detection of subtle changes in laboratory values even before the onset of symptoms. Since the laboratory characteristics of the underlying disease differ, the change in these values over time is thought to be more relevant than evaluating according to a certain threshold [39]. For example, cytopenia may be a feature of SLE without MAS; however, in the case of SJIA, thrombocytosis is present in the active disease and one should suspect MAS before platelet values decrease below the threshold for thrombocytopenia. Thrombocytopenia below 100,000/mm^3 was not present in 45.2 % of SJIA-associated MAS episodes in our study but none had thrombocytosis. In recent years, hyperferritinemia has been recognized as an important laboratory hallmark of MAS. A sharp rise in ferritin level is usually observed in the acute phase of MAS, and it was high in all of our patients. Hyperferritinemia was reputed the best parameter to discriminate between MAS-associated SLE as well and active SLE with a sensitivity and specificity of almost 100 % [27]. Ravelli et al. [39] demonstrated that platelet count, ferritin level, and AST were the laboratory tests in which the experts found change over time to be most important for the early diagnosis of MAS in SJIA. AST was elevated in almost 60 % of MAS episodes in our study. Increased LDH levels were also present in almost all MAS episodes which points at the probability of LDH being a potential biomarker for MAS diagnosis.

MAS could be the initial manifestation of SJIA or SLE [6, 40]. In our group, more than half of the patients (13/22) with SJIA were diagnosed after having an initial MAS episode, while only one SLE patient presented with MAS. In the study by Minoia et al. ($n = 362$), 22.2 % of patients had MAS at SJIA onset [6]. One may think that the prognosis for patients presenting with MAS is worse than that of patients who developed MAS in the course of the disease. In our group, two of these patients ($n = 16$) who presented with MAS died. One of them was diagnosed in another center and received inappropriate treatment for the first 15 days and was referred to our center for the further evaluation at the late stage of MAS. She died within the first admission day because of multiorgan failure. The other patient was misdiagnosed as having septic arthritis and received antibiotics for 2 weeks. After that she suddenly developed splenomegaly and thrombocytopenia and progressed to multiorgan failure with overt MAS and died shortly after admitting to our hospital. We cannot draw an exact conclusion because of the small number of patients. Minoia et al. demonstrated that patients in whom MAS occurred at the onset of SJIA were younger and had a lower central nervous system involvement, intensive care unit admission, and death rate [6].

In the current literature, there are no consensus- or evidence-based guidelines on how to treat MAS in rheumatologic diseases. In the study by Minoia et al., almost all patients received corticosteroids and 61 % received cyclosporine [6]. High dose pulse methylprednisolone seems to be more effective than oral corticosteroid in MAS treatment [41]. Cyclosporine is also a safe and effective choice in MAS treatment [6]. IVIG is another treatment option. In a study by Singh et al. [42], none of the patients with SJIA-associated MAS achieved remission with IVIG monotherapy; however, one responded to combination therapy of IVIG and corticosteroids. When the patient is resistant to first-line therapies, next-line immunosuppressive treatments such as etoposide and cyclophosphamide can be added to the main treatment protocol. Etoposide is regularly used in the first-line treatment of especially primary HLH [34]. In different studies, etoposide treatment was also given to the patients with MAS secondary to SJIA or SLE [40, 43–45]. It induced rapid recovery in these cyclosporine or steroid resistant cases. However, since it may have possible harmful side effects such as neutropenia and secondary infections, it is considered as a last resort especially by pediatric rheumatologists [41]. In our study, etoposide treatment was given in one-third of the MAS episodes.

Biologic drugs are increasingly used for the treatment of MAS, especially when it is secondary to SJIA, since these drugs are less immunosuppressive, more target directed, and they are effective to suppress the underlying disease activity. There are unsatisfactory results with anti-TNF treatment [44, 46]; however, anakinra seems to be an effective option. Miettunen et al. [44] reported eight SJIA-associated MAS patients who responded to anakinra after insufficient response to steroid, IVIG, and cyclosporine treatment. However, one should keep in mind that MAS may occur in patients who are already on biologic drugs such as anti-IL-1 or anti-IL-6 drugs [16–18, 47–49]. Furthermore, in some cases, MAS occurred immediately after the biologic dose [48]. In our study, MAS was seen in one case immediately after the canakinumab dose. Our results consistent with the literature imply that IL-1 or IL-6 blockage does not always protect from MAS. In the current era, combination therapy with high dose corticosteroids, cyclosporine, and anakinra is likely to become the treatment of choice in SJIA-associated MAS. In our study, anakinra was the biologic of choice in MAS treatment. And high dose corticosteroid–cyclosporine A-anakinra combination was given during 11 (35.4 %) out of 31 MAS episodes secondary to SJIA, especially for the patients diagnosed after 2011. All SJIA patients who received corticosteroid, cyclosporine A, and anakinra at the onset of first symptom reached remission. In SLE-associated MAS, corticosteroid and cyclosporine A therapies form the cornerstone of treatment [50]. Bennett et al. reported that pediatric MAS patients with SLE and SJIA received cyclosporine A at similar rates, but more children with SLE received

cyclophosphamide and mycophenolate mofetil and more children with SJIA received anti-IL-1 agents [15].

Supportive treatments such as plasmapheresis may be beneficial in MAS possibly by decreasing circulatory inflammatory cytokines. In some reports, plasmapheresis was reported as an effective supportive treatment in MAS [14, 51]. In our group, plasmapheresis was performed during 15 (40.5 %) out of 37 MAS episodes.

The mortality rate for children hospitalized with SJIA and MAS is estimated to be around 6 % [15, 24, 52]. In the largest population of patients with SJIA-associated MAS ($n = 362$), the mortality rate was 8.1 % [6]. Overall mortality was almost 12 % in our study. Hepatosplenomegaly was more common, plasmapheresis was performed more frequently, and the duration between symptom onset and admission to our hospital was longer in patients who died than the cured patients. The reason for higher mortality rate among these patients is probably the late ($\geq$15 days) admission to our hospital after the onset of MAS-related symptoms. Thus, these patients were already at the advanced stage of MAS when they admitted to our hospital and it was too late to rescue these late-referrals.

In conclusion, our study provides information on the clinical spectrum, laboratory features, treatment, and outcome of MAS patients with SJIA and SLE. The clinical features, laboratory values, and outcomes of our patients seem to be very similar to the reported cases. The higher mortality is due to the group of patients who were referred $\geq$15 days after the onset of MAS symptoms which suggests that early treatment is critical in MAS. Early diagnosis is possible through recognizing subtle dynamic changes in laboratory values before the clinical features settle. Biologic therapies especially anakinra may be a good option for SJIA-associated MAS; however, further studies are needed to draw a firm conclusion. Early and effective treatment is crucial to prevent morbidity and mortality.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval The study was approved by the ethics committee of Hacettepe University and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki (1964). All these patient files were evaluated retrospectively, and all patients were anonymous. When the patients admitted to the hospital, the parents gave a general consent approving anonymous data use for academic purpose.

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