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Review

Prognostic factors of macrophage activation syndrome, at the time of diagnosis, in adult patients affected by autoimmune disease: Analysis of 41 cases collected in 2 rheumatologic centers

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ABSTRACT

Macrophage activation syndrome (MAS) is a rare, life-threatening disease in which early diagnosis and aggressive therapeutic strategy may improve the outcome. Due to its rarity, epidemiologic data are still lacking. Hyperferritinemia is frequently associated with MAS and might modulate the cytokine storm, which is involved in the development of multiple organ failure.

In this paper, we investigated clinical data, treatments, and outcome of a homogeneous cohort of 41 adult MAS patients, complicating autoimmune rheumatic diseases. MAS-related death occurred in 17 patients (42.5%) during the follow-up, and older age and increased serum ferritin levels, at the time of diagnosis, were significantly associated with mortality.

In conclusion, adult MAS is associated with high mortality rate. Some clinical features at diagnosis may be predictive of MAS-associated death.

Contents

1. Introduction

Adult macrophage activation syndrome (MAS), is a life-threatening complication, developing during the clinical course of several inflammatory diseases such as adult onset Still's disease (AOSD) and systemic

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lupus erythematosus (SLE) [1]. MAS refers to reactive hemophagocytic lymphohistiocytosis (HLH), which may be classified into primary, the genetic forms, and secondary, the reactive forms, which are associated with infective, autoimmune, or neoplasia-related diseases [1]. Continuous high fever, adenopathies with hepatosplenomegaly, pancytopenias, intravascular coagulation, and hyperferritinemia, are the typical clinical features associated with the histopathological evidence of hemophagocytosis by activated macrophages, in bone marrow as well as in reticuloendothelial organs, generally leading to multiple organ failure and unfavorable outcome [2,3].

Although MAS may occur at any age, it must be pointed out that multiple lines of evidence derived from pediatric patients; in fact MAS may be the most severe complication during the course of systemic onset juvenile idiopathic arthritis (SOJIA) with frequency ranging from 10% to 40% of all cases [4,5].

On the contrary, the adult epidemiological profile of MAS is still not fully defined [3]. Available literature suggests that MAS may affect from 10 to 25% of AOSD patients and from 0.9 to 4.6% of SLE patients, directly occurring from the beginning, during the course of the disease as well as triggered by infective agents [6,7] and its high mortality rate may be dramatically influenced by an early diagnosis with consequent aggressive treatments, which have been shown to improve the survival of these patients [1–3,8].

The combination therapy of MAS usually includes the elimination of possible triggers leading to abnormal immune system activation, the suppression of the inflammatory response by immunosuppressive drugs and supportive cares [3]. However, due to its low frequency, it has always been impossible to plan controlled clinical trials to investigate the best therapeutic options for adult MAS patients. At present, information regarding the treatment of this disease is derived from small case series, uncontrolled study and retrospective analyses. High dosage steroids, cyclosporine A, intravenous immunoglobulin therapy, and more recently, biologic drugs, have been reported to have some effectiveness in these patients [1–8].

MAS pathogenesis seems to be related to a defect in granule mediated cytotoxicity, which may be associated with an enhanced antigen presentation and with repeated interferon γ-dependent stimulation of Toll-like receptors [9–12]. This abnormal activation of immune response results in a massive hypersecretion of pro-inflammatory cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6, finally evolving to a very severe condition, the cytokine storm, in which an enhanced proliferation and activation of macrophages may be observed leading to hemophagocytosis [9–13].

Hyperferritinemia is a typical laboratory marker of MAS patients, and recently, it has been suggested that these exceptionally high levels of serum ferritin might contribute to the development of the cytokine storm [14]. In fact, in the last years, ferritin has been considered not only a serological biomarker, but also an immunomodulatory molecule, with probably binding and activating specific cell surface receptors, involved in the regulation of immune responses, and recently MAS, AOSD, catastrophic anti-phospholipid syndrome and septic shock have been included in a common family named 'hyperferritinemic syndrome' [14].

In the current study, we aimed to investigate clinical data, including laboratory findings, treatments, and outcomes of adult MAS patients associated with autoimmune rheumatic disease, in order to identify the clinical factors, at diagnosis, which may be predictive of the unfavorable outcome.

2. Patients and methods

In this study, we retrospectively reviewed the medical records of 41 adult MAS patients associated with autoimmune diseases, referred to the Rheumatology Clinic of L'Aquila University and to the Rheumatology Clinic of Palermo University, over the last 10 years. All patients fulfilled the diagnostic guidelines criteria for HLH proposed by the Histiocyte Society in 1991 and updated in 2004 [15,16]. We recorded, in all patients, at the time of diagnosis of MAS, the following clinical characteristics: age, gender, values of white blood cell count (WBC), red blood cells (RBC), hemoglobin (HB), platelet count (PLT), serum ferritin, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT), treatments, concomitant comorbidities, defined and scored by Charlson Comorbidity Index [17,18], time of observation and outcome. The latter has been defined as favorable in the case of complete disappearance of systemic symptoms associated with normalization of laboratory tests, during the follow-up.

The local ethics committee approved the procedure. It has been performed according to the Good Clinical Practice guidelines, according to the Declaration of Helsinki.

2.1. Statistical analysis

IBM-SPSS version 13.0 (IBM, Armonk, NY) was used for statistical analysis. The statistical analysis provided descriptive statistics for the sample. Continuous variables were expressed as the mean ± SD unless otherwise indicated. To compare the clinical characteristics of patients with favorable outcome and MAS-related death, the T-test was used for all the continuous variables and the Chi squared test was used for the categorical variables. Furthermore, binary logistic regression was used to identify the possible predictor factors between clinical and serological features, supposed to be involved in the outcome. Statistical significance was expressed by a p value <0.05.

3. Results

3.1. Clinical characteristics

Clinical characteristics and laboratory features of our patients are shown in Tables 1 and 2. In our cohort, 24 patients had a favorable outcome (57.5%), and 17 patients died of MAS-related death (42.5%). The 41 patients consisted of 15 men (37.5%) and 26 women (62.5%), and we did not observe any statistical difference between gender and outcome. The mean age of our patients, at the time of diagnosis, was 48.20 ± 14.10 and MAS-related death was significantly associated with older age ($p = 0.0001$). As far as the underlying disease is

Table 1
Clinical characteristics of enrolled MAS patients.

Clinical data	Patients
Women (men)	26 (15)
Age (years ± SD)	48.20 ± 14.10
Underlying disease, number (%)	41 (100%)
AOSD	30 (75%)
SLE	9 (20%)
SSc	1 (2.5%)
AS	1 (2.5%)
Trigger factor, number (%)	35 (87.5%)
Flare of the disease	17 (60%)
Severe infection	11 (27.5%)
Comorbidities, number (%)	16 (40%)
Severe infection	11 (27.5%)
Systemic arterial hypertension	4 (10%)
Kidney failure	2 (5%)
Kidney transplant	1 (2.5%)
Heart failure	1 (2.5%)
Lymphoma	1 (2.5%)
Time of follow-up, months ± SD	6.96 ± 2.82
MAS-related death, number (%)	17 (42.5%)

Abbreviations: AOSD: adult onset Still's disease; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; AS: ankylosing spondylitis; MAS: macrophage activation syndrome.

Table 2
Laboratory features at the time of diagnosis of enrolled patients.

Laboratory parameters	Mean ± SD
WBC (10^3/mL)	3.23 ± 1.44
RBC (10^3/mL)	3.22 ± 0.70
HB (gr/dL)	8.79 ± 1.55
PLT (10^3/mL)	45.52 ± 26.60
Serum ferritin (ng/mL)	6842.70 ± 7569.70
ESR (mm/h)	63.87 ± 30.19
CRP (mg/L)	51.59 ± 46.92
Triglycerides (mg/dL)	220.02 ± 71.25
ASAT (IU/L)	84.23 ± 51.97
ALAT (IU/L)	145.28 ± 94.23

Abbreviations: mL: milliliter; ng: nanogram; g: gram; L: liter; mm: millimeter, h: hour; mg: milligram; IU: international unit; WBC: white blood cell count; RBC: red blood cells; HB: hemoglobin; PLT: platelet count; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase.

concerned, 30 out of 41 enrolled patients were affected by AOSD (75%), 9 patients by SLE (20%), 1 patient by systemic sclerosis (SSc) (2.5%), and 1 by ankylosing spondylitis (AS) (2.5%). Twenty-four out of enrolled patients (60%) did not show any comorbidity, and MAS was diagnosed in the context of flare of AOSD. Sixteen patients (40%) reported at least one comorbidity, and severe infections, defined as life-threatening, requiring hospitalization and/or intravenous antibiotic therapy, were largely the more frequent. Eight out of 9 SLE patients developed MAS triggered by a severe infection. Four AOSD patients were affected by essential hypertension, 1 AS patient was affected by lymphoma, 1 AOSD patient was affected by kidney failure and underwent kidney transplant, and 1 SSc patient was affected by both kidney and heart failure and severe infection. Interestingly, MAS-related death was significantly associated with a higher value of Charlson Comorbidity Index ($p = 0.009$). The analysis of laboratory tests showed a reduction of WBC, RBC and PLT, as typically observed in MAS patients. Furthermore, the patients with MAS-related death showed significant lower levels of WBC, RBC and PLT ($p = 0.001$, $p = 0.001$, $p = 0.0002$, respectively) when compared with patients with favorable outcome. All the patients displayed a strong increase of inflammatory markers, such as serum ferritin, ESR and CRP levels. We found a significant association among the highest levels of both serum ferritin and CRP levels and MAS-related death ($p < 0.0001$, $p = 0.0002$, respectively), on the contrary, no association was observed for ESR levels (Table 3).

3.2. Treatments

The therapeutic strategies, at the time of diagnosis, of all the enrolled patients were recorded (Table 4). All patients received high dosages of methylprednisolone pulses (500–1000 mg/daily for a maximum of 6 cycles). As far as the immunosuppressive drugs associated with steroids are concerned, 17 patients were treated with associated immunosuppressive drugs (40%). Fourteen patients were treated with cyclosporine A (32.5%), 6 patients with methotrexate (MTX) (15%), and 3 patients with intravenous immunoglobulin therapy (7.5%). Three patients were treated with combination therapy cyclosporine A + MTX and 3 patients were treated with combination therapy cyclosporine A + intravenous immunoglobulin therapy. A small percentage of our patients were treated with biologic drugs. Specifically, 4 patients were treated with biologic agents (10%), 3 patients with anakinra, an IL-1 receptor antagonist, and 1 patient with tocilizumab, an anti-IL-6 receptor antibody.

Table 4
Treatments of MAS patients at the time of diagnosis.

Treatment	
High dosage steroids pulses, number (%)	41 (100%)
Methylprednisolone pulses 1000 mg/die	31 (75%)
Methylprednisolone pulses 500 mg/die	10 (25%)
Immunosuppressive drugs, number (%)	17 (40%)
Cyclosporine A	14 (32.5%)
Methotrexate	6 (15%)
Intravenous immunoglobulin therapy	3 (7.5%)
Biologic drugs, number (%)	4 (10%)
Anakinra	3 (7.5%)
Tocilizumab	1 (2.5%)

3.3. Clinical outcome and prognosis

In our cohort, 17 patients died of MAS-related death (42.5%), mainly due to multiple organ failure and disseminated intravascular coagulation, occurring during the follow-up. Therefore, we performed binary logistic regression in order to quantify the strength of the association between MAS-related death and the clinical and serological variables, at the time of diagnosis. In the univariate analysis (Table 5), we observed that older age ($p = 0.017$), serum ferritin levels ($p = 0.001$), CRP levels ($p = 0.029$) and a higher value of Charlson Comorbidity Index ($p = 0.01$) were significantly predictive of MAS-related death. When all these variables were analyzed by multivariate analysis, we observed that older age ($p = 0.039$) and higher serum ferritin levels ($p = 0.008$) were independently predictive of MAS-related death, thereby confirming the increased risk to develop an unfavorable outcome in older patients with higher serum ferritin levels. Table 6 shows these results.

Table 3
Clinical data, at the time of diagnosis, of MAS patients with unfavorable and favorable outcome.

	MAS-related death (17 patients, 42.5%)	Favorable outcome (24 patients, 57.5%)	Statistical value
Women (men)	9 (8)	17 (7)	ns
Age (years ± SD)	58.94 ± 14.91	40.26 ± 9.04	$p = 0.0001$
Charlson Comorbidity Index (mean ± SD)	2.06 ± 0.90	1.21 ± 0.42	$p = 0.009$
WBC (10^3/mL) (mean ± SD)	2.63 ± 1.28	3.52 ± 1.46	$p = 0.001$
RBC (10^3/mL) (mean ± SD)	2.83 ± 0.24	3.41 ± 0.78	$p = 0.001$
HB (mean ± SD)	8.2 ± 1.85	9.07 ± 1.76	$p = 0.01$
PLT (10^3/mL) (mean ± SD)	32.28 ± 18.47	52.14 ± 28.11	$p = 0.0001$
Serum ferritin ± SD (ng/mL)	12,224.23 ± 8600.44	2865.04 ± 2977.18	$p < 0.0001$
ESR ± SD (mm/h)	61.41 ± 28.89	65.69 ± 31.62	ns
CRP (mg/L) ± SD	68.86 ± 48.23	38.82 ± 42.54	$p = 0.0002$
ASAT (IU/L) (mean ± SD)	98.42 ± 50.68	77.14 ± 52.98	$p = 0.002$
ALAT (IU/L) (mean ± SD)	164.71 ± 99.15	135.57 ± 93.91	$p = 0.002$

Abbreviations: mL: milliliter; ng: nanogram; g: gram; L: liter; mm: millimeter, h: hour; mg: milligram; IU: international unit; WBC: white blood cell count; RBC: red blood cells; HB: hemoglobin; PLT: platelet count; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase.

Table 5
Univariate analysis of clinical and laboratory features and MAS-related death in enrolled patients.

Factor	p	OR	95% CI
Gender	p = 0.088	3.187	0.842–12.072
Age	**p = 0.007***	1.181	1.046–1.333
Charlson Comorbidity Index	**p = 0.003***	6.891	1.909–24.873
WBC	p = 0.189	0. 629	0.314–1.257
RBC	p = 0.090	0.049	0.001–1.602
HB	p = 0.147	0.490	0.187–1.284
PLT	p = 0.126	0.963	0.918–1.011
Serum ferritin	**p = 0.002***	1.289	1.021–2.781
ESR	p = 0.654	0.995	0.974–1.017
CRP	**p = 0.049***	1.015	0.999–1.031
ASAT	p = 0.973	1.000	0.982–1.018
ALAT	p = 0.468	0.996	0.984–1.008

Abbreviations: WBC: white blood cell count; RBC: red blood cells; HB: hemoglobin; PLT: platelet count; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase.

4. Discussion

In this study, we show, in a large cohort of adult MAS, that older age and higher serum ferritin levels, at the time of diagnosis, are strongly predictive of MAS-related death, thus identifying a subset of patients with a more severe disease at risk of an unfavorable outcome, and probably needing a strong aggressive immunosuppressive therapy from the beginning of the treatment.

Although MAS may complicate many autoimmune and autoinflammatory diseases, occurring during disease flare or triggered by severe infection [1–3,19–21], however, its frequency is increased in patients with AOSD, suggesting a possible overlap between these 2 forms [22,23]. In fact, recent literature suggests that these 2 diseases may be considered 2 sides of the same disease spectrum, in which AOSD may be the milder form [22]. In our study, we observed that the most common factor triggering MAS, during AOSD, was a new disease flare, followed by severe infections. This finding confirms previous experiences, in which the most common MAS trigger was an active phase of the disease [24–26].

As far as prognostic factors are concerned, we observed that higher serum ferritin levels, at the time of diagnosis, in our cohort, were independently associated to MAS-related death, by multivariate analysis, strongly suggesting its possible role during this disease. In this context, it has been reported that elevated serum ferritin was negatively associated with survival in MAS patients [27,28]. In fact, recently, it has been suggested that MAS should be included under a common umbrella, named 'hyperferritinemic syndrome' [14], in which, ferritin may be considered not only a serological biomarker, but also a molecule with a potential pathogenic role. The hyperferritinemia may be possibly involved in a vicious loop where the inflammatory proprieties of ferritin are exacerbated, leading to a massive over-production of inflammatory mediators characterizing the cytokine storm [14]. In fact, ferritin synthesis is regulated, in addition to iron availability, by different cytokines [29,30], such as IL-1, IL-6, and TNF, which are largely overexpressed in MAS patients, and may induce a further expression of ferritin [29–33].

Table 6
Multivariate analysis of clinical and laboratory features and MAS-related death in enrolled patients.

Factor	p	OR	95% CI
Age	**p = 0.039***	1.347	1.015–1.789
Charlson Comorbidity Index	p = 0.663	1.973	0.093–41.810
Serum ferritin	**p = 0.008***	1.776	1.030–2.028
CRP	p = 0.830	1.005	0.960–1.052

Abbreviations: CRP: C reactive protein.

This overexpressed molecule is able to stimulate, after binding to specific receptors on the surface of immune cells, the production of many pro-inflammatory cytokines via a vicious loop, thus perpetuating the inflammatory state [14,34,35]. Furthermore, a strong correlation of ferritin tissue levels in target organs and the severity of patients, affected by MAS and AOSD, has been shown [36–38].

Of interest, our multivariate analysis shows that older age, at the time of diagnosis, is significantly associated with unfavorable outcome in our adult MAS patients. Recently, the mortality rate of adult MAS has been estimated to be 41%, on the contrary, this mortality is significantly lower in the pediatric form (7–15%), as recently reported in available literature [39,40] and directly confirming the relationship between the age of patients and survival. Furthermore, our data in patients affected by MAS, associated with autoimmune diseases, mirror results observed in MAS following hematologic and infectious diseases, in which older age of patients was one of the most important prognostic factors associated with survival [3,41–43].

Our results showed a significantly higher value of Charlson Comorbidity Index in patient with unfavorable outcome, suggesting that comorbid illness may play a contributing role in these patients as observed in other inflammatory diseases [44,45]. It must be pointed out that the Charlson Comorbidity Index was created to predict death in a sample of hospitalized patients [18] and successively applied in different clinical conditions [17]. To confirm our data a multivariate analysis was performed to assess the independent role of Charlson Comorbidity Index as predictor of mortality in our patients, but the analysis failed to confirm any association with the outcome. This lack of association, in our opinion, may be related to the relatively low number of enrolled patients and suggest the need of larger multi-center studies, specifically designed, to better assess the role played by comorbidities in this setting.

As far as the therapy of MAS is concerned, we have to point out that, due to its rarity, specific guidelines, in adult patients, have not been still established and, anecdotally, the pivotal therapeutic strategy is the administration of high-dosage steroids [46–50]. In our cohort, we reported that all the patients were treated with high dosages of steroids, associated with immunosuppressive drugs, in a large percentage of patients, specifically, cyclosporine A, MTX and intravenous immunoglobulin therapy. In addition, some of our patients received biologic drug therapy, which has been reported to be helpful in adults with refractory MAS [51–54] Recently, small case series report that early treatment with anakinra, an anti-IL-1 molecule, may lead to a better outcome and suggest that inhibition of the IL-1 pathway, blocking the cytokine storm may lead to a rapid clinical improvement [26,55,56]. In this paper, we did not analyze any possible association between the treatments and the outcome. In fact, our study was not specifically designed to analyze this effect and treatment was not randomized. Furthermore, due to lacking international guidelines for adult MAS treatment, it could be possible that physicians decided to prescribe a more intensive treatment to the patients that, in their opinion, were affected by a more aggressive disease, resulting in a "confounding by indication" bias [57,58].

Although the potential limitations of our study, i.e. clinical data collected retrospectively and laboratory data collected from different centers may decrease the strength of our result, we must point out that this paper analyzed data from a large and homogeneous cohort of MAS in adult patients affected by autoimmune rheumatic diseases.

In conclusion, our paper shows that adult MAS is associated with a high mortality, which is significantly associated with the highest levels of circulating ferritin and older age. Given the rarity of the adult MAS and the difficulties to design specific prospective studies, a retrospective analysis of the data of these patients may pragmatically increase our knowledge concerning the clinical management of this disease.

Competing interest

None.

Take-home messages

- MAS is a life-threatening disease in which early diagnosis and treatment may improve the outcome.
- Some clinical features, at the time of diagnosis, may identify a subset of patients with a more severe disease and at risk of an unfavorable outcome.
- Older age and increased serum ferritin seem to be associated with MAS- related death.

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