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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.