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RESEARCH ARTICLE

Clinical Spectrum and Therapeutic Management of Systemic Lupus Erythematosus-Associated Macrophage Activation Syndrome

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ABSTRACT

Macrophage activation syndrome can be primary with a genetic etiology, or secondary, associated with malignancies, infections or systemic diseases. Its a severe and potentially life-threatening complication of autoimmune diseases. The incidence of MAS among patients with systemic lupus erythematosus is not well known, as most of the previous studies were limited to a small number of case series or case reports. In recent years it has been suggested that macrophage activation syndrome in systemic lupus erythemaosus may be underrecognized because it can mimic the clinical features of the underlying disease or be confused with an infectious complication. The diagnosis of macrophage activation sydrome in adults is supported by hyperferritinemia (higher than 2000 ng/ml), and/or splenomegaly, pronounced cytopenias, hypofibrinogenemia, characteristic cytokine profile and hypertriglyceridemia. In the case of systemic lupus erythematosus flare, hyerferritinemia is the strongest indicator to differentiate them from MAS. So far, no validated and universally embraced diagnostic criteria for macrophage activation syndrome in adult secondary to systemic lupus erythematosus are available. It is important to know the parameters that can guide the clinician towards the diagnosis of macrophage activation syndrome in adult with systemic lupus. Early diagnosis and intensive therapy are essential in improving clinical outcomes. Hence, we decided to write this mini-review to focus on the demographic data, on the pathophysiological mechanisms, clinical and laboratory manifestations, treatments, and outcomes of patients with systemic lupus erythematosus associated macrophage activation syndrome.

Keywords: Lupus erythematosus systemic, Macrophage activation syndrome, Ferritin-Treatment-Prognosis.

1. Introduction

Macrophage activation syndrome (MAS) is a severe and potentially fatal complication of autoimmune diseases. It is most often described in systemic Juvenile Idiopathic Arthritis (sJIA), but may also occur, infrequently, in systemic Lupus Erythematosus (SLE) and Kawasaki disease [1-3]. Clinical and laboratory manifestations of MAS include non-remitting high fever, pancytopenia, lymphadenopathy, hepatosplenomegaly, liver dysfunction, coagulopathy with hypofibrinogenemia, high blood triglyceride levels, and increased levels of serum ferritin [4]. Other manifestations were also described, like central nervous system, kidney involvement, or multiple organ failure.

MAS is characterized by an uncontrolled activation and proliferation of T lymphocytes and macrophages with prominent hemophagocytic activity in the bone marrow and other reticuloendothelial systems[4]. These abnormalities lead to a hyperinflammatory state caused by an over production of cytokines.

MAS is currently classified among the secondary or acquired forms of haemophagocytic lymphohistiocytosis (HLHs). The primary (familial) fHLH is a heterogeneous autosomal recessive disease most frequently described in infants and caused by mutation in genes that code for proteins that are involved in "perforin-mediated" cytolytic function [5-6].

Secondary HLH, however, can occur at any age triggered by a heterogeneous group of disorders including autoimmune, autoinflammatory diseases, infection or malignancies [7,10].

MAS associated to autoimmune diseases was reported in 7.0–15.3 % of secondary HLH [6–8] and the prevalence of this complication in SLE ranged from 0.9 to 4.6% [11-12,15-18]. MAS occuring in patients with SLE or other autoimmune diseases represents a diagnostic challenge for the clinician, because, it can be associated with infection, or associated with the activity of the disease (disease flare). Also, the prognosis depends on the diagnostic and early therapeutic management of the disease.

Based on current literature, we performed this recent review to update the demographic data, advances in immunopathogenesis, clinical and laboratory features, therapeutic stratregies, and outcomes of patients with SLE associated MAS.

2. The epidemiology of MAS in SLE patients:

MAS is classified among the secondary forms of haemophagocytic lymphohistiocytosis (sHLH), as a sHLH occurring in the context of a rheumatic disease. MAS is much more common than fHLH and occurs in children and adult. The incidence of MAS in rheumatic diseases is still unknown. Although, MAS is by far most common in sJIA among pediatric rheumatic diseases, in recent years, it has been reported with increasing frequency in childhood and adult-onset SLE. The incidence of MAS among patients with SLE is not well known, as most of the previous studies were limited to a small number of case series or case reports. The prevalence of MAS was reported between 1 to 35% in the literature in adult SLE patients (Table 1). MAS tends to occur in young, female patients. As noted in previous studies of either juvenile or adult patients with SLE. MAS occured after the diagnosis of SLE in two third of the cases. However, it has been suggested that MAS associated with SLE may be more common than previously recognized and probably MAS in SLE may be under-recognized[12-15,17,23]. The mortality rate varied depending on the centers. Previous reports showed that the mortality rate in SLE was ~5%–35% [14,15-17].

Table 1: The frequency and outcomes of adults SLE patients with macrophage activation syndrome in selected studies

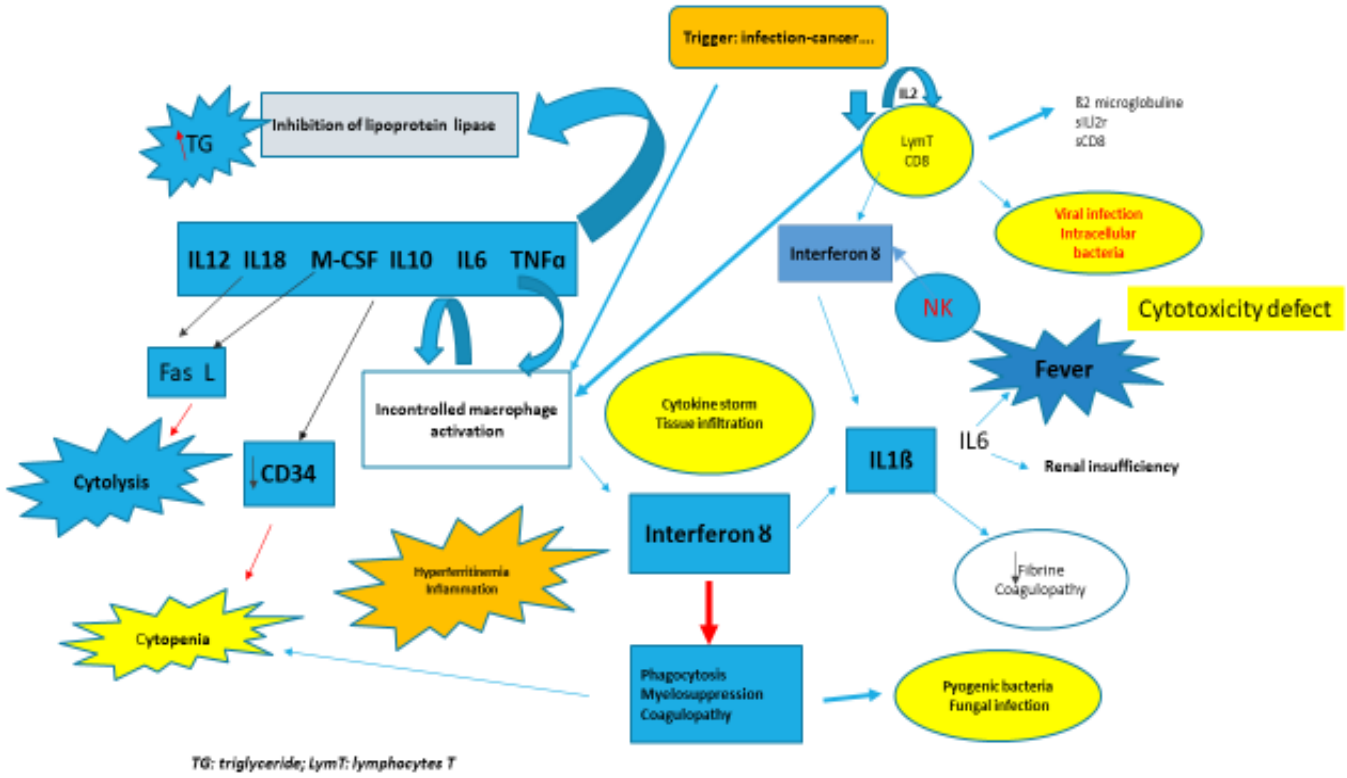
Authors	countries	cases of SLE cohort	cases of SLE with MAS	frequency of SLE with MAS (%)	mortality
Dall'Ara F et al [18]	Italy	511	7	1,4%	No death
Gavand PE et al [17]	France	-	89 (103 episodes)	-	5(4,9%)
Ahn SS et al [19]	South Korea	157	54	34,3%	19(35,1%)
Liu AC et al [20]	China	-	32	-	4(12,5%)
Cohen EM et al [21]	USA	2094	23	1,09%	4 (19%)
Fukaya S et al [7]	Japan	350	18	4,6%	2 (11%)
Ammouri W et al [22]	Morocco	208	20	9,6%	No death

SLE: systemic lupus erythematosus, MAS: macrophage activation syndrome

3. Pathogenic mechanisms of MAS (Figure 1)

The pathogenesis of MAS associated with SLE remains unclear. But some of the pathogenic mechanisms of pHLH may be involved also in MAS. Primary HLH (genetic) is caused by mutation in genes that code for proteins that are involved in "perforin-mediated" cytolytic function, is most common in children. They are either proteins such as perforin, directly involved in cytotoxicity, or proteins involved in vesicle transport and fusion with the plasma membrane. The secondary HLH (acquired such MAS) form is most frequent in adults. Interestingly, heterozygous mutations in fHLH genes may be found in upwards of 40% of individuals with secondary HLH and MAS [24-25]. These gene mutations (e.g., PRF1, UNC13D) alter cytolytic function in NK cells, and presumably CD8 T cells as well. Also, genetics may impact on the recurrence of the disease and there are multiple pathways that can lead to the end common pathology and clinical presentation of MAS, including those that do not require genetic defects in cytolytic pathway genes. MAS is often developing as a 'cytokine storm' and can be associated with infectious, rheumatologic (autoinflammatory/autoimmune disorders) and oncologic triggers leading to a severe hyperinflammatory hyperferritinemic immune response syndrome induced by aberrantly activated macrophages and cytotoxic T cells. However, a massive release of proinflammatory cytokines is associated with its pathogenesis and correlates with a worse prognosis [2]. Nevertheless, the inflammatory state may also contribute to decreased lytic capacity of NK cells and CD8 T cells. The proinflammatory cytokines (Figure 1) associated with MAS include interferon-gamma, IL-1, IL-6, IL-18, IL-10, macrophage-colony-stimulating factor (GM-CSF) and TNF depending on the context. This cytokine storm triggers a cascade of inflammatory pathways that, if untreated, leads to tissue damage and death. Thus, these cytokines are responsible for different symptoms such as fever, lymphadenopathy, cytopenia, hepatic cytolysis, high levels of ferritin and triglycerides, coagulation disorders, increased CRP and histologic hemophagocytosis. The hemophagocytic macrophages induce pathogenesis and as well as multi-organ dysfunction. The cause of red blood cell destruction in hemophagocytic syndromes is largely attributed to activated macrophages [26-28].

Figure 1 : The pathogenesis of MAS



The mechanism of the all cytokines in the pathogenesis of MAS remains controversial. IL-6 in combination with GM-CSF drives the differentiation of suppressive monocytic myeloid derived suppressor cells in bone marrow. IL 10 is associated with cytopenia and interferon gamma with liver dysfunction and coagulation disorders. Recent studies, showed the presence of high levels of IFNγ and of IFN-γ-induced chemokines in patients with secondary HLH [29].

A recent study has also found that increased serum levels of CXCL9 and sTNFR-II were common in MAS associated with SLE [30-31]. It is important to understand the mechanism behind the uncontrolled cytokine storm seen in MAS to target specific cytokines upstream and prevent further stimulation of the activated macrophages. In addition to broadly immunosuppressive medications, such as corticosteroids and cyclosporine, cytokine specific therapy (e.g., IL-1 or IL-6 pathway blockade) may prove more effective in dampening the overly active immune system. Further studies and clinical trials are needed to better assess the role of pro-inflammatory cytokines in the pathogenesis of MAS and determine their clinical relevance.

4. Triggers factors of MAS in SLE:

MAS can be triggered by a variety of infections and malignancies, medications, pregnancy, or during flares of autoinflammatory or autoimmune diseases like SLE. Among infectious diseases, MAS is commonly associated with viral infections, such as the herpes virus family (e.g., epstein-barr virus, cytomegalovirus and human herpesvirus 6), HIV-1 and influenza [17,20, 32, 36]. In addition, hepatitis A, B and C are documented viral triggers of MAS [32]. In the literature of SLE patients with MAS, Epstein-Barr virus (EBV) was the top causative of the patients with identifiable infectious episodes [14,16,18,20,22]. Immunosuppressive therapy in patients with SLE probably increases the risk of EBV infection, which may trigger the occurrence of MAS in SLE. Z

Also, hemorrhagic fever viruses, including dengue and CrimeanCongo, are being recognized as frequently fatal triggers of MAS/secondary HLH, often on an epidemic scale [32].

Bacterial triggers such as Staphylococcus and Salmonella have been shown to trigger MAS. More unusual bacterial species, ranging from Legionella to Mycoplasma to Ehrlichia, have also been frequently documented in patients who develop MAS. Tuberculosis, are also reported to be

associated with MAS on endemic countries [34-36]. Infections, such as Histoplasma and Crytpococcus, can lead to MAS, and globally, parasitic infections, including Leishmania and Toxoplasma, are common MAS triggering organisms.

In addition to infectious triggers of MAS, several malignancies have been associated with MAS development and was associated with a higher mortality rate than other MAS associations. MAS was reported with a strong link with hematopoietic tumors such as T-cell leukemia/lymphoma and both Hodgkin and non-Hodgkin lymphoma [17]. Also, Solid tumors, as hepatocellular carcinoma and lung cancer have been linked to MAS too [32]. Workup for infections (including active viral replications) and malignancies is crucial, because infections can mimic a lupus flare and need prompt and appropriate treatment to prevent of morbidity and mortality.

5. Diagnosis of MAS in SLE patients:

The diagnosis of MAS in SLE is a challenge for clinician, because it could mimic a SLE flare up or be confused with infections. It is essential to differentiate MAS from these medical situations in order to choose the appropriate treatement. Sepsis may lead to cytopenias, fever and hepatic dysfunction, serum ferritin levels do not increase to the same degree as in MAS, and leukocytosis, rather than leukopenia is more commonly seen in sepsis. Also, distinguishing MAS from sepsis may be difficult in some cases, particularly when MAS is complicated by sepsis [37]. Histopathological findings including hemophagocytosis may be absent in the initial phases of MAS and are neither sensitive nor specific for this purpose [38]. The diagnosis of MAS in adults is supported by hyperferritinemia (higher than 2000 ng/ml), and/or splenomegaly, pronounced cytopenias, hypofibrinogenemia, characteristic cytokine profile and hypertriglyceridemia. In the case of SLE flare, hyerferritinemia is the strongest indicator to differentiate them from MAS [16]. Clinical and laboratory manifestations may overlap between SLE and MAS. Fever was the most frequent symptom. This is in accordance with other studies, in which fever is the mainstay manifestation of MAS [17, 20, 22]. Persistent fever with a temperature above 38 ° can guide the diagnosis of a possible MAS, in the absence of symptoms of intercurrent infection. However, Cohen EM et al, reported in a case-control study of 23 SLE patients, that arthritis and hydroxychloroquine used at hospital admission were associated with decreased of MAS risk [21]. The authors, reported the hypothesis that the presence of a musculoskeletal manifestation such as arthritis may be associated with an SLE phenotype with lower risk of hematologic manifestations.

Other abnormal findings that are known to occur in MAS are severe cytopenia and hepatic dysfunction. However, other clinical and biological manifestations are reported by other studies such as neurologic symptoms, neutropenia as well as significant increases of LDH and procalcitonin [16-17, 39-40]. These laboratory features are not commonly raised during lupus flare. Parodi et al[16], described 38 patients with a juvenile SLE complicated by MAS and analyzed the biological variables that may distinguish MAS from lupus flares. In their study, 30 of 38 patients (78.9%) had an hyperferritinemia. Among all laboratory variables, hyperferritinemia using the threshold of >500 µg/L had the best sensitivity (96.2%), and represented the strongest marker to distinguish MAS from active SLE. In the litterature, a high SLEDAI score was also reported to be associated with increased risk of MAS in SLE patients [21-22].

In the sudy of Gavand PE et al [17], an increase of procalcitonin level was found in 41 of 49 MAS episodes, while a bacterial infection was documented only in 15 of these cases. Furthermore, PCT levels are generally not increased during SLE flares without concomitant infection [39- 41]. The PRC, clinical signs and other biological parameters, could be an interesting biomarker for diagnosis of infection in SLE patient with MAS. Also, corticosteroid therapy does not seem to affect PCT values. A significant elevation of CRP levels has also been found in SLE during serositis and polyarthritis. So, the use of this marker alone, does not differentiate between an infection and SLE flare. In addition, elevation of CRP levels is described in the elderly, and although not significant, increases are also seen with gender (male), Body Mass Index, oral contraceptives and renal failure. Treatment with statins, antimalarials and steroids has been linked to reduction of CRP levels [41-43].

So far, no validated and universally embraced diagnostic criteria for MAS are available. The recognition that MAS is clinically similar to HLH has led some to recommend the use of the HLH-2004 diagnostic guidelines, which were developed primarily for homozygous genetic disorders leading to fHLH and validated in pediatric cohorts. Validated diagnostic criteria for MAS in adults secondary to SLE are therefore urgently needed.

The HLH-2004 classification criteria [3] (Table 2) are stringent and many patients are underdiagnosed until the late stage of the disease. The H-score was developed to calculate the individual risk of adult patients having reactive

MAS [44]. The majority of the patients in their study population had haematological malignancy and/or infection and only 4.8% of the patients had rheumatic disorders (3.5% with SLE) and the best cut-off value for the H-Score was 169 (sensitivity 93%; specificity 86%). Recently, Batu ED et al, analysed the performance of the H Score in a series of 30 patients with rheumatic diseases including 6 cases of SLE [45]. In this study, a cut-off value for the H-Score (190.5; sensitivity 96.7%; specificity 97.6%) performed better. However, Further studies may be warranted to determine optimum cut-off values in different patient's populations [20, 45].

Table 2 : The 2004-classification criteria Henter [3]

1. Molecular diagnosis consistent with HLH : pathologic mutations of PRF1, UNC13D, Munc 18-2,Rab27s , STX11,SH2D1A or BIRC4

2. Clinical and laboratory criteria (5/8 criteria should be fulfilled)
Fever
Splenomegaly
Cytopenia ≥2 cell lines
Hemoglobin <90 g/l (below 4 weeks of age <120 g/l)
Platelets $<100 \times 10^9$/l
Neutrophils $<1 \times 10^9$/l
Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides ≥3 mmol/l
Fibrinogen <1.5 g/l
Ferritin ≥500 µg/l
sCD 25 ≥2,400 U/ml
Decreased or absent NK cell activity
Hemophagocytosis in bone marrow, CSF, or lymph nodes

CSF : cerebrospinal fluid ; NK : natural Killer ;

Parodi A et al [16], reported in a study of 38 juvenile SLE patients with MAS (20 with definite MAS and 18 with probable MAS) that clinical manifestations had better specificity than sensitivity, except for fever, which was highly sensitive but had low specificity. Among laboratory variables, the best sensitivity and specificity was hyperferritinemia, followed by increased levels of lactate dehydrogenase, hypertriglyceridemia, and hypofibrinogenemia. Therefore, Parodi et al, developed preliminary diagnostic guidelines for MAS in juvenile SLE. Patients were considered to have MAS if they had one clinical criterion (fever, splenomegaly, hepatomegaly, hemorrhagic manifestations or Central nervous system dysfunction and) and at least 2 laboratory criteria (ferritin level of ≥500 µg/liter, cytopenia affecting 2 or more cell lineages, aspartate aminotransferase (AST) level >40 units/L, TG level >178 mg/dL, and fibrinogen level ≤1,50 gm/liter), increased LDH (≥567 units/liter). However, these guidelines may not be powerful enough to differentiate MAS from infections.

Recently, the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR)/Paediatric Rheumatology International Trials Organization (PRINTO) Collaborative Initiative group proposed new classification criteria for MAS in patients with systemic Juvenile Idiopathic Arthritis [46-47]. According to the 2016 EULAR/ACR/PRINTO classification criteria for MAS, patients were considered to have

MAS if they had fever, had a ferritin level of ≥684 ng/mL, and fulfilled more than 2 of the following 4 criterias: platelet count ≤181,000/µL, AST level >48 units/L, TG level >156 mg/dL, and fibrinogen level ≤360 mg/dL. These 2016 classification criterias have not been validated for SLE, but seems to be simply applicable, and allow early detection in febrile lupus patients than the HLH 2004 criteria as quite often CD25 levels and NK cell function cannot be performed in developing countries. Sung Soo Ahn et al [19], compare the incidence of MAS using HLH 2004 criteria. Among 54 lupus patients with MAS according to the 2016 classification criterias, only 5 patients fulfilled the HLH-2004 criteria because it was difficult to demonstrate hemophagocytosis on bone marrow study, NK cell activity, or soluble CD25 results. Thus, the availability of suitable classification criteria for SLE associated MAS is a necessity for an early diagnosis and specific therapeutic management.

6. Treatment:

The therapeutic strategy for SLE with MAS is not standardized and the HLH-2004 therapy protocols may not be suitable for SLE patients. Management by a multidisciplinary team of experts including hemato-oncologists, rheumatologists, and intensivists is needed. An early treatment with high dose of corticosteroids, immunosuppressants and/or intravenous immunoglobulin (IV IG) is recommended. Individualized therapeutic approach is to be considered too [3]. Corticosteroids are the mainstay of initial treatment of adult SLE patients with MAS. In case of moderately severe MAS, daily administration of methylprednisolone (2 mg/kg/day) or pulsed methylprednisolone (15 mg/kg/day, maximum 1 g/day for 3-5 days) can be used. If SLE patients presented with a highly active MAS and/or organ damage, pulsed methylprednisolone may be the best choice as initial treatement associated to immunosuppressive agents [17, 49]. If the response to pulse methylprednisolone is inadequate, switching to dexamethosone is proposed by some authors, due to more efective antiinflammation compared with other corticosteroids [50-51].

IV IG, plasma exchange, immunosuppressive agents (cyclophosphamide, cyclosporine, mycophenolate mofetil, etoposide) and Biologic therapies (Rituximab, Anakinra), may be added in severe or refractory cases of MAS with SLE. CYC and oral cyclosporine were reported to be more effective in SLE associated MAS [52-53].

Also, Kumakura and colleagues, found IV CYC was superior compared to Cyclosporine and IV IG [38]. In emergency situations of MAS with SLE, etoposide can be used and allows rapid control of the cytokine storm. Its clinical benefit is demonstrated and is included in the HLH-2004 protocol [3]. IVIG treatment improved the outcome, especially when there was neurolgic involvement. IVIG was administrated due to both its immunoregulatory properties and its suppressive effects on infection. IVIG may be prescribed in adult SLE with MAS at the beginning of the macrophage activation process [17,54]. Also, for patients who had a suspected infection, in the absence of microbiological documentation, a broad-sepctre antibiotic treatment is used. Systematic screening and treatment for tuberculosis, EBV, VZV, and CMV infection (PCR) should be also performed. However, it is–unclear whether CMV played a significant role in the onset of MAS as almost all patients with CMV replication recovered without any antiviral therapy. EBV infection is a known cause of secondary HLH particularly in pediatric population [52]. The decision to add antituberculosis treatement is made particularly in the presence of clinical, biological or radiological signs in favor of tuberculosis in endemic country. Different infectious and histological samples tests are taken in parallel, but must not delay the start of treatment [22].

About biologic therapies, rituximab (B cell depleting antibody directed to CD20) may be an effective treatment option for MAS either as a monotherapy or an adjunct to the HLH-2004. In the literature review, a few published cases of rituximab successfully used in the treatment of MAS secondary to SLE were reported. It will be an interesting therapeutic strategy (with less toxicity) of refractoy MAS in SLE patients [55-56].

7. Prognosis:

The MAS may be a potentially fatal condition in SLE patients (Table 5) with the overall mortality of 5-30% [17, 21,38]. Also MAS developement led to high intensive care unit (ICU) admissions [14,17]. Different risk factors for mortality are reported in the literature. The age and higher levels of serum ferritin at the time of diagnosis were associated with mortality in the cohort of 41 adult MAS patients reported by Ruscitti P et al [57]. Also, Yao Ke et al, found in a cohort of 61 rheumatic disease patients with MAS (42.8% of SLE cases) that the presence of serum ferritin > 6000 ng/mL, hepatosplenomegaly and low number of platelets was associated with poor outcome [58]. In a cohort of 116 patients with autoimmune diseases (54% of SLE cases), Kumakura S et al, reported male sex and anemia (hemoglobin <8 g/dl) as factors associated with mortality [38]. Identification of all these risk

factors may improve the therapeutic management and reduce mortality rates in SLE patients with MAS.

Conclusions:

The MAS is an underdiagnosed complication of SLE. The diagnosis is a challenge for the clinician given the absence of suitable diagnostic criteria. Flares and high systemic lupus erythematosus disease activity index (SLEDAI) scores are the leading cause of HLH in lupus patients followed by infections. Therapeutic strategies are still not well established either. However, the prognosis of MAS in SLE is better than other secondary HLHs in adults. Litterature data suggests that serum ferritin levels were the best biomarker to predict the diagnosis of MAS in SLE patients. Increase level of ferritin should alert the clinician for early diagnosis of MAS and appropriate therapeutic management. MAS occuring in SLE patients should be treated with high dose corticosteroids as first line therapy and with etoposide or cyclophosphamide as a second line therapy or as first line in severe cases. Infectious causes of hemophagocytic syndrome must be excluded carefully. In cases with concomitant infections, anti-infectious agent (with or without antituberculosis drugs) should be quickly considered. Prospective and multicenter studies are therefore needed to better analyze the risk factors, therapeutic strategies and the overall prognosis of MAS in SLE patients.

Contributorship

All authors were involved in drafting or revising this article, and all authors approved the final version to be published.

Declaration of conflicting interests

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