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Review

Clinical spectrum and therapeutic management of systemic lupus erythematosus-associated macrophage activation syndrome: A study of 103 episodes in 89 adult patients☆

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ABSTRACT

Objectives: Macrophage activation syndrome (MAS) is a life-threatening hyperinflammatory syndrome that can occur during systemic lupus erythematosus (SLE). Data on MAS in adult SLE patients are very limited. The aim of this study is to describe the clinical characteristics, laboratory findings, treatments, and outcomes of a large series of SLE-associated MAS.
Methods: We conducted a retrospective study that included 103 episodes of MAS in 89 adult patients with SLE.
Results: 103 episodes in 89 adult patients were analyzed. Median age at first MAS episode was 32 (18–80) years. MAS was inaugural in 41 patients (46%).Thirteen patients relapsed. Patients had the following features: fever (100% episodes), increased serum levels of AST (94.7%), LDH (92.3%), CRP (84.5%), ferritin (96%), procalcitonin (41/49 cases). Complications included myocarditis (n = 22), acute lung injury (n = 15) and seizures (n = 11). In 33 episodes, patients required hospitalization in an ICU and 5 died. Thrombocytopenia and high CRP levels were associated independently with an increased risk for ICU admission. High dose steroids alone as first line therapy induced remission in 37/57 cases (65%). Additional medications as first or second line therapies included

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IV immunoglobulins (n = 22), cyclophosphamide (n = 23), etoposide (n = 11), rituximab (n = 3). Etoposide and cyclophosphamide-based regimens had the best efficacy.
Conclusion: MAS is a severe complication and is often inaugural. High fever and high levels of AST, LDH, CRP, ferritin and PCT should be considered as red flags for early diagnosis. High dose steroids lead to remission in two third of cases. Cyclophosphamide or etoposide should be considered for uncontrolled/severe forms.

Contents

1. Introduction

The hemophagocytic syndrome, also referred to as hemophagocytic lymphohistiocytosis (HLH) is a potentially life-threatening hyperinflammatory syndrome characterized by a set of non-specific clinical and laboratory features with inconstant histiocyte proliferation and hemophagocytosis. The classical presenting symptoms are high-grade fever, hepatosplenomegaly, lymphadenopathy, and skin rash [1–3].The most typical laboratory abnormalities are cytopenias, elevated levels of ferritin, triglycerides, transaminases, bilirubin and lactate dehydrogenase (LDH), and low fibrinogen. The current diagnostic criteria for HLH have been proposed in 2004 by the HLH Study Group of the Histiocyte Society [4] but are only validated for children. HLH is categorized as primary or familial HLH (FHLH), when there is a familial history of HLH or a known underlying genetic defects [5] such as perforin gene mutations [6]. Secondary HLH can occur during systemic infections (in particular with Epstein-Barr virus [EBV] or cytomegalovirus [CMV]), [7] malignancy, [8] and rheumatic disorders such as Still disease or systemic lupus erythematosus (SLE) [9–14]. When associated with rheumatic disorder, it is also called the macrophage activation syndrome (MAS).

In SLE, MAS can mimic an acute exacerbation of the underlying disease because both entities share some common features, such as fever, lymphadenopathy, splenomegaly and blood cytopenias. This overlap in clinical presentations can hinder the recognition of incipient MAS and delay the selection of the most appropriate therapeutic approach. Additionally, a differential diagnosis between MAS, infections, and adverse effects of medications should also be considered in SLE. Up to now, there is only limited information on MAS in SLE, particularly in adults. Available data originate mostly from a systematic review of heterogeneous case reports and a small case-series [10,12].The largest series thathas been published was a monocentric report of 15 episodes (3 of them were juvenile lupus) described by Lambotte et al [13]. We undertook this study with the primary aim of describing *in depth* the clinical, laboratory and pathological features as well as treatment strategies and prognosis of this rare association in a large multicentric cohort of adult SLE patients.

2. Patients and methods

2.1. Patients

This multicenter retrospective study included patients with SLE complicated by MAS seen from January 1990 to February 2016 in 20 French departments of internal medicine, rheumatology and clinical immunology. Most of these departments are reference and/or tertiary-care centers for systemic autoimmune diseases, and all are members of the CRI (Club Rheumatism and Inflammation) and FAI^{2}Rnetworks. The CRI is a clinical research infrastructure enabling multicentric clinical research in immune-mediated inflammatory diseases, while the FAI^{2}R health network emerged from the 2011–2014 French National Rare Diseases Plan and is dedicated to patients affected by rare autoimmune and autoinflammatory diseases.

To be included in the study, patients had to fulfill at least 4 of the 1997 American college of Rheumatology criteria for SLE [15] and to have had at least one episode of MAS diagnosed and treated as such by the attending physician. Since there are no validated diagnostic or classification criteria for HLH/MAS in adults, we determined the number of MAS episodes that fulfilled the HLH-2004 criteria [4], that have been designed as eligibility criteria for HLH- 2004. They are used de facto as diagnostic criteria in children. These criteria include fever, splenomegaly, cytopenia affecting at least 2 lineages (hemoglobin < 10 g/dL, platelets < 100,000/mm^3, neutrophils < 1000/mm^3), hypertriglyceridemia (fasting > 265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL), hemophagocytosis, hyperferritinemia (>500 mg/dL), impaired natural killer cell function and elevated soluble CD25. According to those, the diagnosis of HLH requires the presence of 5 out of 8 criteria. These criteria are thought not to be sensitive enough to allow early diagnosis. Diagnostic criteria for MAS as a complication of juvenile SLE have been