

## 02 MACROPHAGE ACTIVATION SYNDROME IN SLE

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Macrophage activation syndrome (MAS) is a life-threatening hyper-inflammatory syndrome characterised by excessive activation and proliferation of T lymphocytes and macrophages and a consequent massive production of cytokines, or 'cytokine storm'. MAS is considered a secondary or acquired form of haemophagocytic lymphohistiocytosis (HLH) and is usually associated with infection (systemic Epstein-Barr virus or cytomegalovirus infections or tuberculosis), malignancy, or rheumatic diseases like systemic lupus erythematosus (SLE).

SLE-MAS can occur both in adult and childhood-onset,<sup>1 2</sup> at the time of diagnosis of SLE and frequently relapses in adults. There are no validated diagnostic or classification criteria for HLH/MAS in adults. HLH-2004 criteria developed for children are often used but are not sensitive enough to allow early diagnosis. These criteria include fever, splenomegaly, cytopenia affecting at least two lineages (hemoglobin <10 g/dL, platelets <100,000/mm<sup>3</sup>, neutrophils <1000/mm<sup>3</sup>), hypertriglyceridaemia (fasting >265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL), haemophagocytosis, hyperferritinemia (N: 500 mg/dL), impaired natural killer cell function and elevated soluble CD25. According to those, the diagnosis of HLH requires the presence of five out of eight criteria. Other biological features of MAS include significant increases of the levels of AST, LDH, CRP, and PCT

In SLE, MAS can mimic a flare of the underlying disease because both entities share some common features, such as fever, lymphadenopathy, and 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. MAS can lead to a multiple organ dysfunction syndrome requiring hospitalization in Intensive Care Unit. Therapeutic regimen is based on high-dose steroids (IV methylprednisolone pulses) often associated with IV cyclophosphamide or etoposide.<sup>3 4</sup> Other therapies have included ciclosporin, methotrexate, tacrolimus, intravenous immunoglobulin and biologics (rituximab, tocilizumab and anti-interferon gamma) in a very limited number of patients.

#### Learning objectives

- Diagnose MAS in SLE
- Make differential diagnosis between SLE flare and MAS
- Treat SLE-associated MAS

#### REFERENCES

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## 03 EVIDENCE-BASED TREATMENT OF SLE COMORBIDITIES

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Patients with systemic lupus erythematosus (SLE) manifest increased frequency of several comorbidities, particularly cardiovascular diseases, infections, osteoporosis and fragility fractures, and also, malignant disorders such as lymphoma.<sup>1</sup> Comorbid diseases may develop both early and later during the course of the disease due to complex interaction between lupus inflammation and administered treatments, especially glucocorticoids. Their prevention, early diagnosis and management is of great importance to ensure favourable long-term patient outcomes, as highlighted in the 2019 Update of the EULAR recommendations for the management of SLE.<sup>2</sup> Despite extensive research, there is paucity of controlled studies to guide the treatment of comorbidities in SLE patients, and it remains elusive whether therapeutic goals (e.g. target levels of serum LDL-cholesterol) in SLE should be different than those in the general population.

The increased cardiovascular disease (CVD) burden seen in SLE patients emphasizes the need for primary prevention strategies cardiovascular disease. This includes the use of validated CVD risk prediction tools (e.g. Framingham Risk Score, Systematic COronary Risk Evaluation (SCORE), QRISK2), which however tend to underestimate the actual risk in patients with SLE.<sup>3</sup> The role and indications in clinical practice for non-invasive modalities for assessing subclinical atherosclerosis (e.g. coronary artery assessment, carotid intima media thickness) is less clear.<sup>4</sup> General non-pharmacological interventions include smoking cessation, avoidance of sedentary lifestyle and maintenance of ideal body mass index. High blood pressure should be adequately controlled preferentially with renin-angiotensin-aldosterone axis blockade, and dyslipidemia be treated with statins. Aspirin may be considered in SLE patients with high-risk antiphospholipid antibodies profile and/or high estimated CVD risk after careful evaluation of the bleeding risk.<sup>5</sup> At the chronic maintenance stage, the dose of glucocorticoids should be minimized to less than 7.5 mg/day of prednisone equivalent. Importantly, hydroxychloroquine should be considered – unless contraindicated – in all cases due to its putative atheroprotective role.<sup>6</sup>

Infections and sepsis represent another important comorbidity associated with increased risk for hospitalization and death in patients with SLE.<sup>7</sup> Application of general preventative strategies such as hygiene measures and immunizations cannot be overemphasized.<sup>8</sup> Modification of SLE-related risk factors such as reduction of exposure to glucocorticoids and avoidance of treatment-related leukopenia/neutropenia are important.<sup>9</sup> High-intensity immunosuppressive (high-dose azathioprine, mycophenolate, cyclophosphamide) or biologic (rituximab) therapies have also been associated with increased risk for infections, especially when used in combination with