02 MACROPHAGE ACTIVATION SYNDROME IN SLE

Zahir Amoura. *French National Reference Centre for SLE and APS, IE3M institute, Hôpital Pitié-Salpétrière, Sorbonne Université, Paris, France*

10.1136/lupus-2019-la.5

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,[1 2] 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^3, neutrophils <1000/mm^3), 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.[3 4] 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

1. Borgia RE, Gerstein M, Levy DM, *et al*. Features, Treatment, and Outcomes of Macrophage Activation Syndrome in Childhood-Onset Systemic Lupus Erythematosus. *Arthritis & Rheumatology* 2018;**70**(4):616–24.
2. Gavand P-E, Serio I, Arnaud L, *et al*. Clinical spectrum and therapeutic management of systemic lupus erythematosus-associated macrophage activation syndrome: A study of 103 episodes in 89 adult patients. *Autoimmunity Reviews* 2017;**16**(7):743–49.
3. Grom AA, Horne A, De Benedetti F. Macrophage activation syndrome in the era of biologic therapy. *Nature Reviews Rheumatology* 2016;**12**(5):259–68.
4. La Rosée P, Horne A, Hines M, *et al*. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood* 2019;**133**(23):2465–77.

03 EVIDENCE-BASED TREATMENT OF SLE COMORBIDITIES

George Bertsias. *Rheumatology, Clinical Immunology and Allergy, University of Crete Medical School, Greece and Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas (FORTH), Greece*

10.1136/lupus-2019-la.6

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.[1] 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.[2] 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.[3] 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.[4] 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.[5] 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.[6]

Infections and sepsis represent another important comorbidity associated with increased risk for hospitalization and death in patients with SLE.[7] Application of general preventative strategies such as hygiene measures and immunizations cannot be overemphasized.[8] Modification of SLE-related risk factors such as reduction of exposure to glucocorticoids and avoidance of treatment-related leukopenia/neutropenia are important.[9] 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

moderate or high doses of glucocorticoids[10 11]. Pre-emptive use of antibiotics is not recommended, nevertheless a low index of suspicion to diagnose an infection – including possible Pneumocystis pneumonia[12] – and commence antibiotics promptly is warranted in high-risk groups including elderly or neutropenic patients, those with comorbidities (e.g. diabetes) or who are receiving glucocorticoids.

Osteoporosis and fragility fractures are potentially avoidable and readily treated comorbidities in patients with SLE.[13 14] Factors impacting adversely on bone mass density, particularly chronic use of glucocorticoids, should be corrected.[15] Osteoprotective and/or anti-osteoporotic interventions should be similar to those in the general population or patients with other chronic inflammatory disorders, yet caution is recommended in cases of kidney disease and reduced glomerular filtration rate. To this end, SLE patients should also be screened for vitamin D insufficiency, which should be corrected considering its presumed multifaceted effects on the disease.[16]

Learning objectives

- Describe primary prevention strategies for SLE comorbidities including cardiovascular disease, infection and osteoporosis
- Explain screening and treatment options for key comorbid diseases in patients with SLE

REFERENCES

1. Gonzalez LA, Alarcon GS. The evolving concept of SLE comorbidities. *Expert review of clinical immunology* 2017;**13**(8):753–68.
2. Fanouriakis A, Kostopoulou M, Alunno A, *et al*. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Annals of the rheumatic diseases* 2019;**78**(6):736–45.
3. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ* **2017**;357:j2099.
4. Wu GC, Liu HR, Leng RX, *et al*. Subclinical atherosclerosis in patients with systemic lupus erythematosus: A systemic review and meta-analysis. *Autoimmunity reviews* 2016;**15**(1):22–37.
5. Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A Systematic Review and Meta-analysis. *JAMA* 2019;**321**(3):277–87.
6. Fasano S, Pierro L, Pantano I, *et al*. Longterm Hydroxychloroquine Therapy and Low-dose Aspirin May Have an Additive Effectiveness in the Primary Prevention of Cardiovascular Events in Patients with Systemic Lupus Erythematosus. *The Journal of rheumatology* 2017;**44**(7):1032–38.
7. Tektonidou MG, Wang Z, Dasgupta A, *et al*. Burden of Serious Infections in Adults With Systemic Lupus Erythematosus: A National Population-Based Study, 1996–2011. *Arthritis care & research* 2015;**67**(8):1078–85.
8. van Assen S, Agmon-Levin N, Elkayam O, *et al*. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Annals of the rheumatic diseases* 2011;**70**(3):414–22.
9. Danza A, Ruiz-Irastorza G. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. *Lupus* 2013;**22**(12):1286–94.
10. Jung JY, Yoon D, Choi Y, *et al*. Associated clinical factors for serious infections in patients with systemic lupus erythematosus. *Sci Rep* 2019;**9**(1):9704.
11. Teh CL, Wan SA, Ling GR. Severe infections in systemic lupus erythematosus: disease pattern and predictors of infection-related mortality. *Clinical rheumatology* 2018;**37**(8):2081–86.
12. Weng CT, Liu MF, Weng MY, *et al*. Pneumocystis jirovecii pneumonia in systemic lupus erythematosus from southern Taiwan. *J Clin Rheumatol* 2013;**19**(5):252–8.
13. Garcia-Carrasco M, Mendoza-Pinto C, Leon-Vazquez ML, *et al*. Incidence of Vertebral Fractures in Women with Systemic Lupus Erythematosus After 8 Years of Follow-Up. *Calcif Tissue Int* 2017;**101**(3):291–99.
14.. Mendoza-Pinto C, Rojas-Villarraga A, Molano-Gonzalez N, *et al*. Bone mineral density and vertebral fractures in patients with systemic lupus erythematosus: A systematic review and meta-regression. *PloS one* 2018;**13**(6):e0196113.
15.. Carli L, Tani C, Spera V, *et al*. Risk factors for osteoporosis and fragility fractures in patients with systemic lupus erythematosus. *Lupus science & medicine* 2016;**3**(1):e000098.
16. Mak A. The Impact of Vitamin D on the Immunopathophysiology, Disease Activity, and Extra-Musculoskeletal Manifestations of Systemic Lupus Erythematosus. *Int J Mol Sci* 2018;**19**(8).

Hot Topic Lecture

01 APS IN SLE PATIENTS: BEST TREATMENT PRACTICE

Munther Khamashta. *London Bridge Hospital, London, UK*

10.1136/lupus-2019-la.7

Recently, recommendations for the management of antiphospholipid syndrome (APS) in adults were published by the European League Against Rheumatism based on evidence from a systematic literature review and expert opinion.[1] The antiphospholipid antibody (aPL) type, the presence of multiple (double or triple) *versus* single aPL type, their titre (moderate-high titre *versus* low titre) and the persistence of aPL positivity in repeated measurements are defined as the ' aPL profile'. The aPL profile is an important factor determining the risk of thrombotic and obstetric events, and consequently the intensity of treatment. The presence of aPL in asymptomatic individuals or patients with systemic lupus erythematosus (SLE) does not confirm the diagnosis of APS but can be associated with increased risk of thrombosis or pregnancy morbidity, depending on aPL characteristics and coexistence of other risk factors.[2] Low dose aspirin (LDA) is recommended for asymptomatic aPL carriers, patients with SLE without prior thrombotic or obstetric APS, and non-pregnant women with a history of obstetric APS only, all with high- risk aPL profile. Immunosuppressive drugs plus steroids do not protect against recurrent thrombosis in APS. Patients with APS and first unprovoked venous thrombosis should receive long-term treatment with vitamin k antagonists (VKA) with a target international normalized ratio (INR) of 2.0–3.0. In patients with APS, with first arterial thrombosis, treatment with VKA with INR 2.0–3.0 or 3.0–4.0 is recommended, considering the individual's bleeding/thrombosis risk. In all cases treatment should be continued even if the patient becomes aPL negative. Direct oral anticoagulants (DOACs) could be considered in APS patients with venous thrombosis who are not able to achieve a target INR despite good adherence to VKA or those in whom VKA is contraindicated (e.g. allergy or intolerance to VKA).[3] Rivaroxaban should not be used in patients with APS with triple aPL positivity.[4] Based on the current evidence, the use of DOACs in patients with APS and arterial events is not recommended due to the high risk of recurrent thrombosis. For patients with recurrent arterial or venous thrombosis despite adequate treatment, addition of LDA, increase of INR target to 3.0–4.0 or switch to low molecular weight heparin may be considered. Other potential strategies for refractory APS cases include rituximab and hematopoietic stem cell transplantation. Thrombocytopenia is not rare in APS and is mostly mild, not requiring intervention. Bleeding is uncommon in these patients and it is important not to stop VKA therapy because low platelet counts do not protect against thrombosis. Careful monitoring is advocated for mild-moderate thrombocytopenia, and corticosteroids are recommended for severe cases. In women with prior obstetric APS, combination treatment with LDA and prophylactic dosage heparin during pregnancy is recommended. In patients with recurrent pregnancy complications, increased heparin to therapeutic dose, addition of hydroxychloroquine or addition of low dose prednisolone in the first trimester may be considered. Use of intravenous immunoglobulin might be considered in highly selected cases.