Haemophagocytic syndrome in Systemic Lupus Erythematosus – clues to an early diagnosis

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Hemophagocytic lymphohisticytosis (HLH), also called Macrophage Activation Syndrome (MAS) when associated with autoimmune diseases, is a rare and potentially life-threatening disorder charaterized by ativation of T-cells and macrophages, responsible for an overwhelming secretion of cytokines[1, 2].

The diagnosis of HLH requires 5/8 of the following criteria: fever, splenomegaly, cytopenias affecting at least 2 lineages, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow, spleen and lymphnodes, low or absent natural killer cell activity, ferritin ≥500ng/ml and soluble CD25 ≥2400U/mL[3].

With overlap of clinical features, distinguishing MAS from lupus flare, sepsis or even medication side effects can represent a major challenge. Therefore, a high degree of suspicion is necessary for timely diagnosis and immediate treatment[4]. Following the occurrence of recent cases in our department, the authors intend to highlight important clinical aspects for an early differential recognition and management of MAS, particularly in Systemic lupus erythematosus (SLE) adult population (Table I).

Despite the nonspecific symptoms and signs of the syndrome, certain laboratory parameters, and even more their trend over time, should be carefully investigated as they can be helpful in differential diagnosis[5]. As suggested by Sawhney *et al*, a relative change in blood cell counts, even if not under the normal ranges, could represent an early abnormality[6]. Also, in opposite to typical response in the most inflammatory condition, a paradoxical falling of erythrocyte sedimentation rate can be seen in MAS, as consequence of fibrinogen consumption[4, 5]. Soluble CD25 measurement must be attempted as Hayden *et al* confirmed that it is a good sensitive diagnostic test, suggesting that threshold of ≤2400U/ml is a reasonable rule out value and when >10000U/ml confers a specificity of 93%[7]. Nevertheless, elevation of ferritin and lactate dehydrogenase seems to be the best laboratory parameter to discriminate between secondary HLH from SLE activity[1,5,8].

Hemophagocytosis is the pathologic hallmark of HLH. Although, its absence does not exclude the diagnosis and should not delay treatment in cases with supportive clinical findings. Concurrently, if suspicion remains high, repeated biopsies are justified[2, 9].

As MAS's occurrence has been linked to numerous triggers including malignancy, exacerbation of underlying disease and infection agents such virus and bacterias, which can determine a therapeutic decision, additional screening is strongly recommended in the initial approach. It must include blood and urine cultures, chest x-ray and specific surveillance of mycobacteria, especially in patients under anti-TNF therapy. Evaluation of viral titers and serologies for Epstein-Barr Virus (EBV), Citomegalovirus (CMV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV), Herpes Simplex Virus (HSV), Varicella-zoster Virus (VZV), parvovirus, adenovirus, measles virus and Human Herpes Virus 8 (HHV8) is also suggested. Investigation for a malignant trigger should be considered, especially when no other cause is identified[9, 10].

Corticosteroid remain the cornerstone of treatment. As second-line option, cyclosporine has been the most frequently used. For refractory disease, anakinra should be considered as a therapeutic option. Etoposide or rituximab can be proposed especially in EBV-triggered HLH due to its properties in reducing EBV viral load. Use of intravenous immunoglobulin has been described in individual case reports. Its comparative safety profile in infectious situations make it an acceptable choice[1, 2, 5, 8]. Although a safety profile of biological therapies has been acceptable, occasional reports described patient with rheumatic disease that developed MAS while on treatment with those immunossupressive

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TABLE I. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE CASE SERIES

	Case 1	Case 2	Case 3
Age	54 years	38 years	43 years
Gender	Female	Female	Male
Previous personal history	SLE	SLE	Psoriatic arthritis with 12 years of evolution
Duration of SLE at MAS onset	16 years	22 years	–
MAS as onset of SLE	No	No	Yes (drug-induced Lupus)
Treatment for underlying disease	Azathioprine 150mg/id, PDN 5mg/id, HCQ 400mg*	PDN 5mg id	Etanercept 50mg/week, naproxen 500mg/2id, PDN 7.5mg/id
Likely trigger factor	EBV	Kingella Kingae	VZV
Clinical features			
Fever	Yes	Yes	Yes
Lympadenopathy	Yes	No	No
Hepatomegaly	Yes	No	Yes
Splenomegaly	Yes	No	Yes
Laboratory testing			
Cytopenias			
Anemia	Yes	No	Yes
Leukopenia	Yes	Yes	Yes
Thrombocytopenia	Yes	Yes	No
Liver dysfuntion	Yes	Yes	Yes
Hypofibrinogenemia	No	No	No
Maximum values for:			
Ferritin (ng/mL)	22 170	3025	910
Triglycerides (mg/dL)	200	669	192
Lactate dehydrogenase (U/L)	363	973	406
ESR (mm/h)	125	16	98
CRP (mg/L)	162	12	181
Low C3c or C4	Yes	Yes	No
Elevated anti-ds DNA	No	No	Yes
Hemophagocytosis	Yes (just found in the 2nd BM biopsy)	Yes (BM)	Yes (BM)
Hospitalization	1st admission: 57 days 2nd admission: 18 days 3rd admission: 25 days	16 days	21 days
Treatment			
1st option	GC	GC	GC
2nd option	CSP	CSP	CSP
3rd option	IVIG		

EBV: Epstein Barr Vírus; VZV: Varicella zoster Vírus; GC: Glucocorticoids; IVIG: Intravenous immunoglobulin; CSP: cyclosporin; RTX: Rituximab; SLE: Systemic lupus erythematosus; HCQ: Hydroxychloroquine; PDN: prednisolone; MAS: Macrophage Activation Syndrome; BM: Bone marrow; ESR: erythrocyte sedimentation rate; CRP: C- reactive protein; *poor therapeutic adherence in the previous 9 months

drugs, leading to its withdrawal in most of the cases. However, in that specific population attention for a concomitant infection is extremely important, since biologic agent-induced infections are more likely to be the cause of MAS, rather than the drug itself[9].

Promptly anti-microbial therapy should be instituted to treat an identified infectious trigger, as they can influence the vital prognosis, and if there is ongoing diagnostic uncertainty between sepsis and HLH[4,10].

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