DE GRUYTER OPEN

Macrophage activation syndrome associated with systemic lupus erythematosus treated successfully with the combination of steroid pulse, immunoglobulin and tacrolimus

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Macrophage activation syndrome (MAS), a variant of secondary hemophagocyticlymphohistiocytosis, is a potentially life-threatening complication of inflammatory and autoimmune diseases. We present a case of MAS as a rare manifestation of systemic lupus erythematosus. Although initial treatment with corticosteroid, *with* or *without* cyclosporine A, is justified in patients with MAS, evidence regarding the effectiveness of this treatment protocol remains to be clarified. Our patient was successfully treated with a combination of intravenous immunoglobulin therapy and intravenous methyl predonisolone pulse therapy, which was followed by a course of oral prednisolone and oral tacrolimus. Based on our experience, we propose tacrolimus to provide a more useful adjuvant treatment to corticosteroid therapy than cyclosporine A.

Key words: hemophagocyticlymphohistiocytosis (HLH), intravenous immunoglobulin (IVIG), macrophage activation syndrome (MAS), systemic lupus erythematosus (SLE), tacrolimus (Tac).

INTRODUCTION

Hemophagocyticlymphohistiocytosis (HLH) is a potentially fatal condition resulting from excessive immune activation and it can occur either as a familial primary form or as a secondary response to a variety of events that disrupt immune homeostasis, such as infections, medications, neoplasms, and rheumatologic diseases [1]. Macrophage activation syndrome (MAS) is classified as a variant of HLH that is associated with autoimmune diseases.

CASE REPORT

A 36-year-old female presented with fever, cervical lymphadenopathy and polyarthralgia. Seven months prior to admission, her symptoms first presented as a facial erythema. Two months prior, she developed a high fever and subsequently cervical lymphadenopathy, polyarthralgia, and gingivitis, initially suspected a viral infection. Six weeks prior, she visited our hospital. Laboratory data revealed persistent elevation of ANA (1: 640), dsDNA-Ab (86.0 IU/mL) and anti-RNP antibody (5.5 U/mL, < 5.0). She was diagnosed with systemic lupus erythematosus (SLE) based on the classification criteria for SLE [2], and oral prednisolone (PSL) 20 mg daily was started, with a temporary resolution of her fever. One week prior, high fever and polyarthralgia recurred and progressed. She was admitted to our hospital.

Her symptoms at physical examination at admission were as follows: body temperature, 40.2°C, and unremarkable respiratory and heart auscultation. A malar rash, oral ulcers, alopecia, lymphadenopathy, splenomegaly and polyarthralgia with tenderness were evident. Laboratory examination revealed elevated levels of C-reactive protein, lactate dehydrogenase and ferritin, thrombocytopenia, lymphocytepenia, liver dysfunction, and proteinuria (Table 1). All tests for possible infection (including hepatitis B virus, hepatitis C virus, EB virus, cytomegalovirus, human herpes virus and fungus) were negative. Hepatosplenomegaly was the only positive finding on computed tomography. Bone marrow aspiration was performed at one week post-admission, confirming hemophagocytosis (Figure 1). Based on the HLH diagnostic criteria, a diagnosis of HLH was

DOI: 10.1515/rjim-2017-0043

made, with MAS secondary to HLH considered based on the clinical course (Figure 2). Initial treatment consisted of intravenous methyl prednisolone (1 g/day for 3 days), followed by oral PSL (1 mg/kg body weight, daily). Intravenous immunoglobulin (IVIG) therapy (20 mg/day for 5 days) was added for persistent fever, transitioned, subsequently, to oral tacrolimus (Tac) 1 mg daily. Symptoms resolved after 3 weeks of treatment, with laboratory findings within normal range. Six weeks after treatment initiation, oral PSL was tapered to 25 mg daily and the patient was discharged without symptoms, with monthly follow-up. The patient remains symptom free at one year post-treatment.

Table 1
Laboratory data at first visit, admission and discharge

		Reference range	First visit	Admission	Discharge
White blood cell count	(/μL)	3,300-8,600	1380	4,400	6,200
Lymphocyte	(/μL)	990-2,990	455	1,020	2,730
Hemoglobin	(g/dL)	11.6-14.8	12.0	12.3	12.0
Hematocrit	(%)	35.1-44.4	36.8	34.9	36.8
Platelet count	($\times10^4$/μL)	15.8-34.8	16.8	9.2	20.3
Na	(mmol/L)	138-145	140	130	141
K	(mmol/L)	3.6-4.8	4.1	3.8	3.1
CL	(mmol/L)	101-108	107	96	107
Creatinine	(mg/dL)	0.46-0.79	0.58	0.70	0.79
Blood uremic nitrogen	(mg/dL)	8.0-20.0	15	13	11
Uric acid	(mg/dL)	2.6-5.5	4.7	3.5	
Glucose	(mg/dL)	73-109	109	115	65
HbA1c	(%)	4.6-6.2	5.8		
Total cholesterol	(mg/dL)	142-248	234	269	240
Triglyceride	(mg/dL)	40-234	126		
ALT	(U/L)	7.0-23.0	47	29	10
AST	(U/L)	13.0-30.0	24	46	10
LDH	(U/L)	124-222	234	866	178
Total protein	(g/dL)	6.6-8.1	7.0	7.2	6.3
Albumin	(g/dL)	4.1-5.1	4.0	3.7	4
IgG	(mg/dL)	861-1747	1870		
IgA	(mg/dL)	93-393	184		
IgM	(mg/dL)	50-269	35		
CRP	(mg/dL)	<0.14	0.01	9.34	0.01
Ferritin	(ng/mL)	6.2-138		1212	127.2
Antinuclear antibody		<40x	640x (speckled)	320x (speckled)	
Anti-dsDNA antibody	(IU/mL)	<10.0	86	13.3	5.0
Rheumatoid factor	(IU/mL)	<15.0	<3.0		
Anti-Sm antibody	(U/mL)	<7.0	101.0		
Anti-RNP antibody	(U/mL)	<5.0	5.5		
Anti-Scl70 antibody	(U/mL)	<10.0	<1.0		
Anti-SSA antibody	(U/mL)	<7.0	>240		
Anti-SSB antibody	(U/mL)	<7.0	2.4		
Anti-ARS antibody		<25.0	5.4		
Anti-cardiolipinβ2GPI antibody	(U/mL)	<3.5	<1.3		
Lupus anticoagulant		<1.3	0.99		
CH50	(U/mL)	25-48	36.5	>60.0	55.5
C3	(mg/dL)	73-138	35.5	85.8	56.6
C4	(mg/dL)	11-31	10	44.9	17.8
Immunocomplex (C1q)	(μg/dL)	<3.0	6.9	4.6	
Urinary protein excretion	(mg/gCr)	0.0-300.0	56.5	339.6	88.5

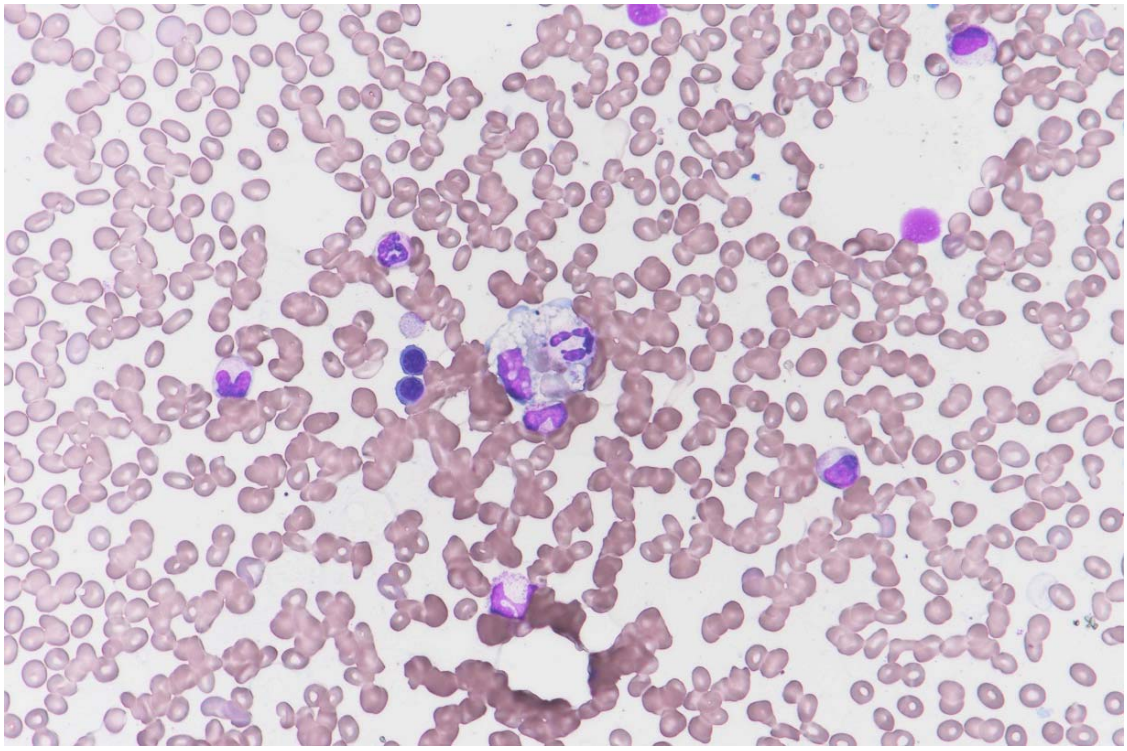
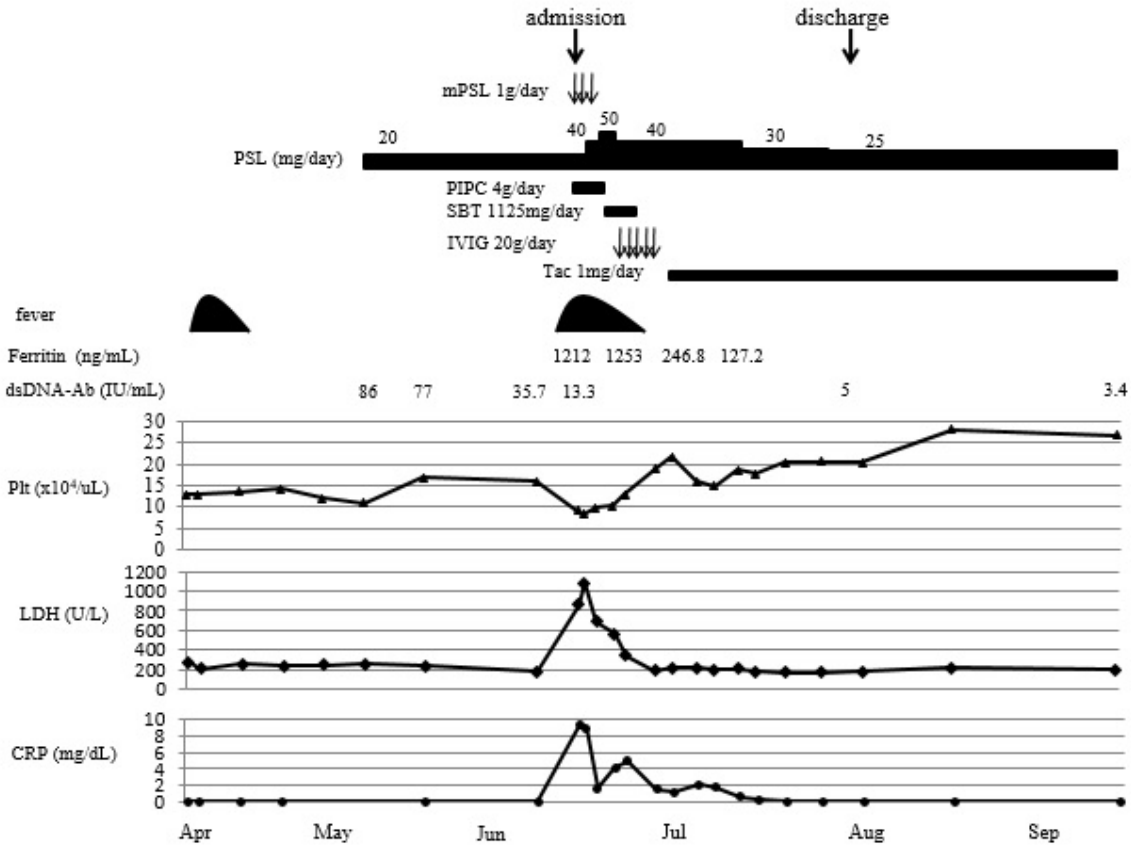


Figure 1. Histopathological examination of bone marrow aspirate showing hemophagocytic macrophage.



mPSL – methyl prednisolone, PSL – prednisolone, PIPC – piperacillin, SBT – sulbactam, IVIG – intravenous immunoglobulin, Tac – tacrolimus, dsDNA-Ab – anti-dsDNA antibody, Plt – platelet, LDH – lactate dehydrogenase, CRP – C-reactive protein.

Figure 2. Clinical course of the present case.

DISCUSSION

MAS, secondary to HLH associated with autoinflammatory and autoimmune diseases, is thought to be caused by excessive activation and proliferation of T lymphocytes and macrophages. HLH occurs more frequently in children than in adults [3]. In patients with SLE, the incidence of MAS is estimated to be between 0.9% and 4.6% [4]. The true incidence, however, is likely to be underestimated, with cases being diagnosed as a flare-up or complication of SLE [5]. The diagnosis of MAS is challenging, with the clinical features of MAS-associated SLE and active SLE being very similar. Certain laboratory parameters inform the differentiation between these two diagnoses. Although severe leukopenia is commonly used as a marker of MAS, thrombocytopenia may provide a more responsive indicator of MAS than leukopenia or anaemia [1]. Hyperferritinemia is acknowledged to be the most appropriate parameter to discriminate between MAS-associated SLE and active SLE, with a sensitivity and specificity of almost 100% [5]. The patient in our case showed progressive thrombocytopenia and hyperferritinemia, with the diagnosis of SLE-associated MAS being made according to the HLH-2004 criteria [1].

In secondary HLH, and MAS in particular, an optimal treatment strategy has not been fully established. Current evidence supports the use of corticosteroid monotherapy, *with* or *without* cyclosporin A (CyA), with the resulting immunosuppression typically providing dramatic improvement of the disease status within days, with a sustained dose providing possible benefits in controlling the underlying autoimmune disease [3]. Use of CyA as the additional immunosuppressant for steroid-resistant MAS is typically recommended, with IVIG also being of benefit [6, 7]. Other researchers have supported the use of Tac for the treatment of CyA-resistant MAS [4]. The use of Tac has recently been supported by a meta-analysis providing evidence of the higher effectiveness of Tac in inducing complete remission of lupus nephritis than intravenous cyclophosphamide [8]. For our patient, we used IVIG therapy and oral tacrolimus with the goal of controlling the disease activity of SLE in addition to treating MAS.

CONCLUSIONS

MAS is a fatal complication of SLE, which is often difficult to distinguish from a flare-up of the disease status of SLE. For prompt diagnosis and early treatment intervention of MAS associated with SLE, it is essential to positively confirm the presence of MAS by bone marrow examination. Aggressive treatment is necessary in the early stages of the disease to gain control over the MAS status. Based on our experience, we propose IVIG therapy and oralTac to provide a better option to CyA to enhance treatment effectiveness.

Declaration of interest: The authors declare that there are no conflicts of interest.

Sindromul de activare macrofagică (MAS), variantă a limfohistiocitozei hemofagocitare, este o complicaţie ameninţătoare de viaţă a bolilor autoimune şi inflamatorii. Prezentăm un caz de MAS ca manifestare rară în cadrul lupusului eritematos sistemic. Deşi tratamentul sugerat este iniţial cu corticosteroid la care se poate adăuga ciclosporina A, eficienţa acestei abordări terapeutice rămâne să fie clarificată. Pacientul nostru a fost tratat cu succes folosind imunoglobulină injectabilă, pulsterapie cu metilprednisolon urmat de o cură de prednison asociat cu tacrolimus oral. Bazat pe experienţa noastră, propunem tacrolimusul ca tratament adjuvant terapiei cu glucocorticoizi în locul ciclosporinei A.

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Received October 8, 2017