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CASE REPORT

Macrophage Activation Syndrome as Initial Presentation of Systemic Lupus Erythematosus

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Macrophage activation syndrome (MAS) is known to be a severe and potentially life-threatening complication of rheumatic disorder, especially systemic juvenile rheumatoid arthritis. It is very rare for MAS to be an initial presentation of systemic lupus erythematosus (SLE). Here, we report a 14-year-old girl in whom MAS developed as an initial presentation of SLE. With early diagnosis and administration of cyclosporine A, she had a fair outcome. Further testing showed positive anti-dsDNA about 8 months later.

1. Case Report

A previously healthy 14-year-old girl was referred to our department with 20 days' history of persistent fever (range, 38.5–40°C), mild dry cough, and bilateral neck pain and weight loss. There was no family history of rheumatic disease. She also had no past history of severe infection or immunodeficiency. She exhibited no butterfly rash, mucous membrane abnormalities, photosensitivity, arthritis, edema, or hepatosplenomegaly.

Physical examination on admission revealed bilateral neck lymphadenopathy (1.5×1.5 cm). Laboratory examination found leukopenia (white blood cell count, 2800/cm^3; absolute neutrophil count, 2251/cm^3), thrombocytopenia (75,000/cm^3), impairment of liver function (alanine aminotransferase, 150 U/L; aspartate aminotransferase, 181 U/L), and positive antinuclear antibody (1:1280) (speckle). Serum antibody test for mycoplasma IgM (equivocal, 16.70 BU/mL) and IgG (positive, 31.58 BU/mL), Epstein-Barr virus anti-VCA IgM (negative) and IgG (1:640), cytomegalovirus IgG (negative, 3.5 AU/mL) and IgM (negative), herpes simplex virus IgM (negative) and IgG (positive, 11.843 RU/mL) all showed no evidence of recent infection. Findings for complement C3 (111 mg%), C4 (19.70 mg%), rheumatic factor (<11 IU/mL), anti-dsDNA (13.1 IU/mL), anti-Sm (3.1 U/mL), anti-SSA (2.4 U/mL), and anti-SSB (1.3 U/mL) were all negative.

Seven days after admission, the patient developed severe epistaxis and status epilepticus. Magnetic resonance imaging and electroencephalography both showed encephalopathy. Under suspicion of autoimmune disease-related encephalopathy, methylprednisolone pulse therapy (1 g/day) was administered for 3 consecutive days. However, the patient's condition did not improve. She then developed profound

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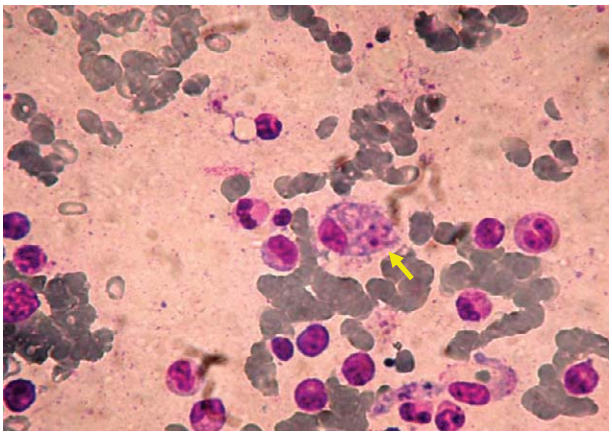

Figure 1 Smear of bone marrow shows stimulated histiocytes phagocytosing platelets and erythroblasts (arrow).

depression of blood cell lines (white blood cell count, 2400/cm^3; absolute neutrophil count, 1080/cm^3; hemoglobin, 8.4 g/dL; platelet count, 46,000/cm^3), prolonged activated partial thromboplastin time (>120 s), hematuria, proteinuria, disseminated intravascular coagulopathy, hyperglycemia, hyperammonemia and renal function impairment. Bone marrow aspiration revealed increased histiocytes with evidence of hemophagocytosis (Figure 1). Diagnosis of systemic lupus erythematosus (SLE) with macrophage activation syndrome (MAS) was supported by high ferritin level (73,968 μg/L), low platelet count (89,000/cm^3), impaired liver function (aspartate aminotransferase, 2534 U/L; alanine aminotransferase, 375 U/L), low fibrinogen (141 g/L), high triglyceride (297 mg/dL), and high lactate dehydrogenase (2675 U/L).

The patient was started on intravenous gamma globulin (IVIG) infusion, followed by intravenous cyclosporine A (5 mg/kg/day). After 7 days of treatment, her condition improved greatly, and oral prednisolone was used as therapy. She has had a fair course since then. Further testing showed positive anti-dsDNA (321.46 IU/mL) about 8 months later.

2. Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome that is composed of different disease entities classified into two groups, genetic and acquired HLH.[1] Genetic HLH includes familial HLH and immunodeficiency-associated HLH. Acquired HLH diseases include infection-associated hemophagocytic syndrome (IAHS), MAS associated with rheumatic diseases, inborn errors of metabolism and malignancy-associated HLH.[2] The pathologic findings of HLH result from the aggressive proliferation of normal histiocytes in various tissues. Hemophagocytosis of red cells (erythrophagocytosis), other white blood cells or platelets in the bone marrow, spleen or lymph nodes is the key diagnostic finding.

The clinical presentations of MAS are sudden onset of non-remitting high fever, hepatosplenomegaly, lymphadenopathy, hemorrhage and central nervous system dysfunction. There is usually profound depression of all three blood cell lines, elevation of serum liver enzymes, abnormal coagulation profile with hypofibrinogenemia and hypertriglyceridemia. The important laboratory hallmark of MAS is hyperferritinemia. Results from the HLH-94 study indicated that a ferritin level ≥ 500 μg/L was 80% specific for the diagnosis. Numerous well-differentiated macrophages actively phagocytosing hematopoietic cells are seen on bone marrow examination.[3]

The widely used criteria for diagnosing MAS are the HLH criteria, which include fever, splenomegaly, cytopenias affecting at least two of three lineages in the peripheral blood, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow, spleen or lymph nodes, low or absent natural killer cell activity, hyperferritinemia, and high levels of sIL-2r (Table 1). Altogether, five of the eight criteria must be fulfilled; patients with a molecular diagnosis consistent with HLH do not necessarily need to fulfill the diagnostic criteria.[4–8]

MAS was first described as a complication of systemic-onset juvenile rheumatoid arthritis in 1985 by Hadchouel et al.[9] MAS has also been observed in a small number of patients with many other rheumatic disorders: polyarticular juvenile rheumatoid arthritis, SLE, rheumatoid arthritis, sarcoidosis, dermatomyositis, and Kawasaki disease.[10,11]

MAS is a rare and potentially fatal complication of childhood rheumatic disorders. It is even rarer for MAS to be an initial presentation of SLE. Only four cases have been reported to date.[11–14] Our patient is the fifth case to be published in the literature. Most physicians rely on diagnostic criteria for lupus that were developed by the American Rheumatism Association (ARA, now the American College of Rheumatology or ACR) (Table 2).[15,16] The proposed classification is based on 11 criteria, including malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder and antinuclear antibody. The diagnosis of SLE is made if four or more of the manifestations are present, either serially or simultaneously, during any interval of observation. However, delayed diagnosis or misdiagnosis may occur due to the absence of the typical findings of SLE at disease onset. Our patient only presented with leukopenia and positive antinuclear antibody initially, until complicated with MAS, SLE being diagnosed based upon four of the 11 criteria (seizure, proteinuria, cytopenia, positive antinuclear

Table 1 Revised diagnostic guidelines for hemophagocytic lymphohistiocytosis (HLH)

Diagnosis of HLH is established if either one or both of the criteria below are fulfilled.

(1) A molecular diagnosis consistent with HLH

(2) Diagnostic criteria for HLH fulfilled (≥5 of the 8 criteria below)

Fever

Splenomegaly

Cytopenias affecting ≥2 of 3 lineages in peripheral blood:
- hemoglobin <90 g/L (in infants <4 wk: hemoglobin <100 g/L)
- platelets $<100\times10^9$/L
- neutrophils $<1.0\times10^9$/L

Hypertriglyceridemia and/or hypofibrinogenemia:
- fasting triglycerides ≥3.0 mmol/L (≥265 mg/dL)
- fibrinogen ≤1.5 g/L

Hemophagocytosis in bone marrow, spleen, lymph nodes or cerebrospinal fluid:
- no evidence of malignancy

Low or absent natural killer cell activity (according to local laboratory reference)

Elevated ferritin (≥500 μg/L)

Soluble CD25 (i.e., soluble interleukin-2 receptor) ≥2400 U/mL

Table 2 American Rheumatism Association criteria for the diagnosis of systemic lupus erythematosus (SLE)

Diagnosis of SLE is made if four or more of the manifestations below are present, either serially or simultaneously during any interval of observation.

Malar rash	Fixed erythema, flat or raised, over the malar eminence, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
Arthritis	Nonerosive arthritis involving ≥2 peripheral joints, characterized by tenderness, swelling or effusion
Serositis	Pleuritis convincing history of pleuritic pain or rub heard by physician or evidence of pleural effusion OR pericarditis documented by electrocardiography, rub or evidence of pericardial effusion
Renal disorder	Persistent proteinuria >0.5 g/day or >3+ if quantitation not performed OR cellular casts may be red cell, hemoglobin, granular, tubular or mixed
Neurologic disorder	Seizure OR psychosis in the absence of offending drugs or known metabolic derangements (uremia, ketoacidosis or electrolyte imbalance)
Hematologic disorder	Hemolytic anemia with reticulocytosis OR Leukopenia <4000/mm^3 total on ≥2 occasions Lymphopenia <1500/mm^3 on ≥2 occasions Thrombocytopenia <100,000/mm^3 in the absence of offending drugs
Immunologic disorder	Positive antiphospholipid antibody OR Anti-DNA antibody to native DNA in abnormal titer OR Anti-Sm presence of antibody to Sm nuclear antigen OR False-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum*
Antinuclear antibody	Abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

antibody). We suggest that in the presence of a significant titer of antinuclear antibodies, children who present acutely with only fever should be considered to have an autoimmune disorder. Since the differentiation of an autoimmune disease flare from sepsis may be difficult, simultaneous treatment for both conditions is required.

Moderate to high titers of anti-dsDNA antibodies are very specific for SLE.[17] Serial measurement of anti-dsDNA is also used as an aid to monitor the activity of lupus nephritis. It has been reported that 85% of the patients who do not have SLE at the time high avidity anti-DNA is detected in their serum will develop the disease within the next few years. Patients with only low avidity anti-DNA in their circulation develop a milder form of SLE; the low avidity of their anti-DNA seldom increases during the course of their disease.[17] It is interesting that our case presented with negative anti-dsDNA initially and had progressed to 321.46 IU/mL about 8 months later.

The primary aim of MAS therapy is to suppress the hyperinflammatory state. The initial management of patients with MAS is usually with administration of high doses of corticosteroids.[18] Cyclosporine A has also been proven to be effective in treating severe or corticosteroid-resistant cases.[3] It has been reported that intravenous cyclosporine A therapy (3–7 mg/kg/day and trough levels between 200 and 400 ng/mL) during the early stage of the disease course will yield a better outcome.[14,19] If there is no response to this treatment, use of the HLH-2004 protocol is recommended.[8] In a retrospective survey, we found that all patients with MAS survived with early cyclosporine A treatment.[18]

In conclusion, although rare, MAS could be an initial presentation of SLE. A better prognosis can be obtained with early diagnosis and prompt administration of cyclosporine A.

References

1. Kogawa K, Lee SM, Villanueva J, Marmer D, Sumegi J, Filipovich AH. Perforin expression in cytotoxic lymphocytes from patients with hemophagocytic lymphohistiocytosis and their family members. *Blood* 2002;99:61–6.
2. Janka G. Familial and acquired hemophagocytic lymphohistiocytosis. *Eur J Pediatr* 2007;166:95–109.
3. Ravelli A. Macrophage activation syndrome. *Curr Opin Rheumatol* 2002;14:548–52.
4. Henter J-I, Elinder G, Ost A. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL Study Group of the Histiocyte Society. *Semin Oncol* 1991;18:29–33.
5. Janka GE, Schenider EM. Modern management of children with haemophagocytic lymphohistiocytosis. *Br J Haematol* 2004;124:4–14.
6. Henter J-I, Tondini C, Pritchard J. Histiocytic syndromes. *Crit Rev Oncol Hematol* 2004;50:157–74.
7. Kelly A, Ramanan AV. Recognition and management of macrophage activation syndrome in juvenile arthritis. *Curr Opin Rheumotol* 2007;19:477–81.
8. Henter JI, Horne A, Arico M, et al. HLH–2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007;48:124–31.
9. Hadchouel M, Prieur AM, Griscelli C. Acute hemorrhagic, hepatic, and neurologic manifestations in juvenile rheumatoid arthritis: possible relationship to drugs or infection. *J Pediatr* 1985;106:561–6.
10. Grom AA. Macrophage activation syndrome and reactive hemophagocytic lymphohistiocytosis: the same entities? *Curr Opin Rheumatol* 2003;15:587–90.
11. Avcin T, Tse SM, Schneider R, Ngan B, Silverman ED. Macrophage activation syndrome as the presenting manifestation of rheumatic diseases in childhood. *J Pediatr* 2006;148:683–6.
12. McCann LJ, Hasson N, Pilkington CA. Macrophage activation syndrome as an early presentation of lupus. *J Rheumatol* 2006;33:438–40.
13. Benarroch LMK, Sterba G, Bosque M. Macrophage activation syndrome as a debut of systemic lupus erythematosus. *J Allergy Clin Immunol* 2006;117:S210.
14. Stephan JL, Kone-Paut I, Galambrun C, Mouy R, Bader-Meunier B, Prieur AM. Reactive haemophagocytic syndrome in children with inflammatory disorders: a retrospective study of 24 patients. *Rheumatology* 2001;40:1285–92.
15. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
16. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271.
17. Smeenk R, Brinkman K, Van den Brink H, et al. Antibodies to DNA in patients with systemic lupus erythematosus: their role in the diagnosis, the follow-up and the pathogenesis of the disease. *Clin Rheumatol* 1990;9(1 Suppl 1): 100–10.
18. Chen HH, Kuo HC, Wang L, et al. Childhood macrophage activation syndrome differs from infection-associated hemophagocytosis syndrome in etiology and outcome in Taiwan. *J Microbiol Immunol Infect* 2007;40:265–71.
19. Mouy R, Stephan JL, Pillet P, Haddad E, Hubert P, Prieur AM. Efficacy of cyclosporine A in the treatment of macrophage activation syndrome in juvenile arthritis: report of five cases. *J Pediatr* 1996;129:750–4.