

헤르페스 바이러스 감염으로 발생한 대식 세포 활성화 증후군을 첫 증상으로 한 소아 전신 홍반 루푸스

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Macrophage Activation Syndrome Triggered by Herpes Viral Infection as the Presenting Manifestation of Juvenile Systemic Lupus Erythematosus

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Macrophage activation syndrome (MAS) is a rare complication in systemic lupus erythematosus (SLE) that can be triggered by infections. Due to the fact that MAS may mimic clinical features of underlying rheumatic disease, or be confused with an infectious complication, its detection can prove challenging. This is particularly true when there is an unknown/undiagnosed disease; and could turn into an even greater challenge if MAS and SLE are combined with a viral infection. A 14-year-old female came to the hospital with an ongoing fever for 2 weeks and a painful facial skin rash. Hepatomegaly, pancytopenia, increased aspartate aminotransferase, elevated serum ferritin and lactate dehydrogenase were reported. No hemophagocytic infiltration of bone marrow was reported. The patient was suspected for hemophagocytic lymphohistiocytosis. Her skin rashes were eczema herpeticum, which is usually associated with immune compromised conditions. With the history of oral ulcers and malar rash, positive ANA and low C3, C4 and the evidence of hemolytic anemia, she was diagnosed as SLE. According to the diagnostic guideline for MAS in SLE, she was diagnosed MAS as well, activated by acute HSV infection. After administering steroids and antiviral agent, the fever and skin rash disappeared, and the abnormal laboratory findings normalized. Therefore, we are reporting a rare case of MAS triggered by acute HSV infection as the first manifestation of SLE.

Key Words: Macrophage activation syndrome, Herpes viral infection, Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is uncommon in children, presenting varied clinical features and is often severe more than in adults¹⁾.

One of the fatal and perplexing complications of the SLE is macrophage activation syndrome (MAS)^{2,3)}. Its clinical characteristics include fever, pancytopenia, hepatosplenomegaly, deranged liver function, central nervous system dysfunction, coagulation abnormalities and distinctly increased serum ferritin. Deposition of

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hemophagocytic macrophage can be found in bone marrow, liver, spleen and lymph nodes. Due to the importance of the clinical features, MAS in SLE can be diagnosed without pathologic confirmation⁴⁾.

Known etiologies of MAS are changing medication, disease flaring and infections. Among infections, viral infection has been reported more frequently than other pathogens. Recognizing MAS in patients with SLE can be difficult, because it can mimic clinical presentations of the original disease or easily be confused with an infection³⁾. Furthermore, clinical features of viral infections in SLE are not typical due to their alterations of immune reactions to the virus in SLE^{2,4,5)}. So, when viral infections, MAS and SLE occur concurrently, diagnosis of the disease becomes difficult.

We report a case of SLE presented with eczema herpeticum and macrophage activation syndrome which is triggered by an acute herpes simplex virus (HSV) infection.

Case Report

A 14-year-old female visited the hospital with a fever and painful skin rash spreading from scalp to face which had been ongoing for 2 weeks.

No specific medical record was known, except suspicious mild atopic dermatitis during infancy and varicella zoster infection recovered without complication a year previously. In her familial history, her maternal uncle was treated for his Behcet's disease.

Her fever of over 38 degrees centigrade was ongoing for 2 weeks. Multiple diffuse erythematous papules, pustules, and patches were found on her face and scalp and tendered (Fig. 1). She had oral ulcers and complained of general easy fatigue and weakness for several weeks. On her abdomen examination, mild hepatosplenomegaly was observed at 3 cm. There were no palpable lymph nodes in her neck, both axillas and both inguinal areas.

Blood cell count showed a white blood cell count of $560/\text{mm}^3$, a hemoglobin concentration of 8.5 mg/dL, a platelet count of $51,000/\text{mm}^3$, which was pancytopenia.

Aspartate aminotransferase (AST) elevated to 451 U/L (normal range <40 U/L). Triglyceride 281 mg/dL (normal range <200 mg/dL), LDH 794 U/L (normal range <200 U/L), and ferritin $>1,650$ ng/mL (normal range 10-291 ng/mL) were noted. Coagulation profiles were reported within normal limits with prothrombin time of 10.8 sec (normal range 9.5-14 sec), partial thromboplastin time of 34.8 sec (normal range 2.79-37.8 sec), and INR of 0.97 (normal range 0.85-1.25).

Since hemophagocytic lymphohistiocytosis (HLH) was suspected with given evidence of the laboratory findings above, bone marrow aspiration was done. Bone marrow biopsy reported that marrow was normocellular and there was no evidence of hemophagocytosis in the marrow.

HSV Ig M of serum was positive, while HSV Ig G of serum and HSV PCR of the skin biopsy were negative.



Fig. 1. Multiple diffuse erythematous papules, pustules, and patches with edema were on the face and scalp.

On the histologic findings of skin lesions, there were perivenular and perifollicular lymphocytic infiltration with hydrophilic changes in the basal layer, which explains the inflammatory changes in the skin lesion but not enough for lupus skin lesions (Fig. 2). The multiple erythematous papules and umbilicated vesicles and serological evidence implied eczema herpeticum.

While testing for autoimmunity done on 1st and 3rd day of hospitalization, ANA positive (speckled, 1:160), direct Coomb's test positive (anti-IgG 2+), indirect Coomb's test negative and low C3 of 17.1 mg/dL (normal range 88-201 mg/dL), low C4 of 3.1 mg/dL (normal range 16-47 mg/dL) were reported. Over the course of treatment, the crust covering the face vanished, revealing 'malar rash' which was previously obscured by the crust. The oral ulcers were observed. With the laboratory findings above, the patient was diagnosed as the SLE⁶⁾.

When hemophagocytosis develops in autoimmune diseases, such as SLE, it is referred as secondary HLH or macrophage activation syndrome⁷⁾.

For eczema herpeticum, oral acyclovir was administered from the day of admission.

Following the oral administration of prednisolone from the 5th day, fever subsided and abnormal laboratory findings normalized. Her medication was changed

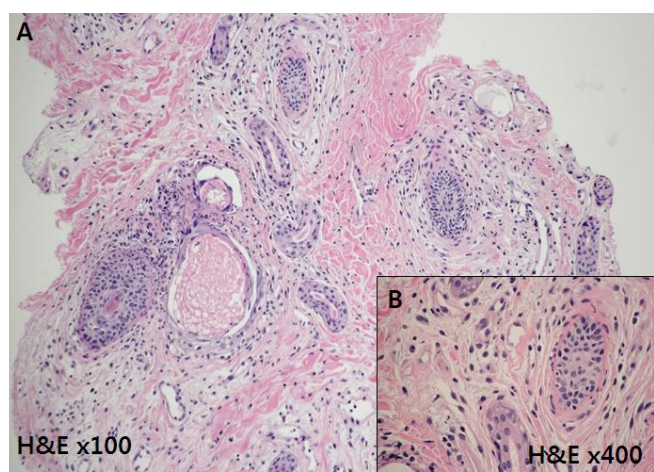


Fig. 2. Skin biopsy of erythematous macule on her face. In the microscopic view, mild spongiosis, focal basal vacuolar degeneration, dermal edema and minimal perivenular and perifollicular lymphocytic infiltration were observed, as signs of inflammatory changes in the skin lesions.

to deflazacort on the 10th day of hospitalization and she was discharged without any complications after 2 weeks of admission (Fig. 3). She has remained stable without relapse of MAS during the follow-up period of 2 years.

Discussion

MAS is a potentially fatal complication of autoimmune disease caused by uncontrolled activation and proliferation of T cell lymphocytes and macrophages¹⁻³⁾.

Incidence of MAS associated with juvenile SLE is about 0.9-4.6%⁸⁾. However, it has been reported more frequently during the last few years, probably because it was underdiagnosed in the past. MAS is found more commonly in pediatric age patients rather than in adults with autoimmune diseases^{4,8,9)}.

Its clinical manifestations include fever, pancytopenia, abnormal liver function, lymphadenopathy, skin rash and CNS involvement. Serum ferritin level is not only a distinctive biomarker of MAS but also an indicator of the disease's activity⁴⁾.

According to the preliminary diagnostic guidelines for MAS as a complication of juvenile SLE proposed by Parodi et al.⁴⁾, we diagnosed the presented case as MAS with SLE without pathologic confirmation. Parodi et al.⁴⁾ suggested that MAS in juvenile SLE can be diagnosed in the absence of hemophagocytosis in bone marrow, because in MAS bone marrow aspiration does not always demonstrate hemophagocytosis and hemophagocytosis is not always notable in the initial phase of the disease.

Known etiology of MAS includes changes in medication, disease flaring and acute infections. 76.5% of the patients developed MAS due to disease flaring and 27% due to infectious disease⁴⁾.

Among the infections associated MAS, viral infections were the most common. In a study which reviewed SLE with acute viral infections, 8% (7/88) were retrospectively confirmed as MAS⁵⁾. Among 12 pediatric patients with macrophage activation syndrome as the first manifestation of SLE, 5/12 (41%) cases were as-

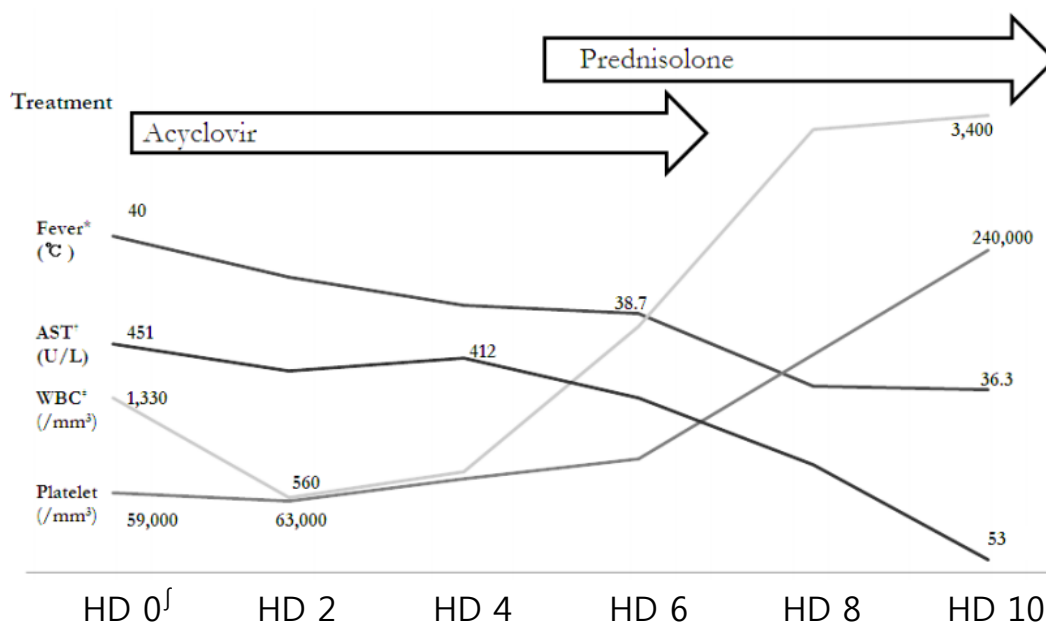


Fig. 3. Clinical course of the patient which shows the fever and laboratory changes as patient undergoes treatment. *Fever refers peak body temperature of the day. †aspartate aminotransferase, ‡white blood cell, ^jhospital day.

sociated with viral infections^{2,3,5,9-14}.

A dozen cases of MAS and SLE presenting concurrently in pediatric age have been reported to date.

Standard treatment of MAS has not been established yet. The most common treatment is high dose and/or pulsed corticosteroid administration, combined with immunosuppressive agents such as IV cyclophosphamide, cyclosporine A and IV globulin¹⁸. MAS in SLE is usually fatal and MAS develops in severe SLE^{10,11}. A review of cases with pediatric MAS in lupus revealed that it was often refractory or recurrent^{5,12,14,18}. In a study reviewing the long term outcomes of MAS with SLE, it was pointed out that this condition would be recurrent and necessitate prolonged immunosuppression¹⁴.

In Korea, several cases of MAS in pediatric age have been reported¹⁹⁻²³. In most of the cases, MAS was refractory and treated with immune suppressive agents, such as cyclosporine A, TNF-alpha inhibitor and etoposide¹⁹⁻²¹.

However in few cases, the patients recovered from MAS only by treating the underlying disease, SLE^{22,23}. In the case of this patient, MAS developed in mild SLE and was treated without any complications. This out-

come was possible because we managed to treat the underlying diseases, HSV infection and SLE immediately, which triggered MAS. Antiviral agent was administered from the day of hospitalization and systemic steroid was administered even though the bone marrow biopsy finding was negative, because clinical manifestations were compatible for SLE and MAS^{4,5}. Since MAS has been underdiagnosed, its spectrum of disease is still unknown.

Due to the fact that viral infections in SLE can be confused with flaring of SLE, and the fact that MAS in SLE can be confused with an infection, recognizing these three conditions can be very difficult when they present concurrently^{3,4,8,9}. We hereby report a case where viral infection was the main factor in developing SLE and MAS in SLE was triggered by a viral infection.

In conclusion, viral infections in patients with SLE have roles in exacerbating and masking the original disease simultaneously. For both acute viral infections and MAS in SLE, if recognized early and treated soon, detrimental outcomes can be avoided.

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요약

대식세포 활성화 증후군(MAS, Macrophage activation syndrome)은 전신 홍반성 루푸스(SLE, systemic lupus erythematosus) 환자에서 감염에 의해 나타날 수 있는 드문 합병증이다. MAS는 기저의 자가면역질환의 임상양상과 유사하게 나타나거나 혹은 감염성 합병증과 혼동될 수 있어 감별에 주의하여야 한다. 14세 여환이 2주간 지속되는 발열과 통증을 동반하는 얼굴의 피부 발진을 주소로 내원하였다. 피부 발진과 간비대, 범혈구 감소증, aspartate aminotransferase, lactate dehydrogenase, 혈청 ferritin이 상승하여, MAS를 의심하였다. 피부 병변과 항핵체 양성, C3와 C4의 감소, 간접 콕스 검사 양성으로 SLE를 진단하였다. 따라서 본 증례는 MAS가 HSV에 의하여 촉발된 것을, SLE의 첫 증상으로서 나타낸 증례로서, 촉발 요인 및 기저질환을 치료함으로써 중증의 합병증 없이 호전되었다.