A Case of Intractable Hemophagocytic Syndrome Associated with Systemic Lupus Erythematosus Resistant to Corticosteroids and Intravenous Cyclophosphamide that Was Successfully Treated with Cyclosporine A

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Abstract:
Hemophagocytic syndrome (HPS) associated with systemic lupus erythematosus (SLE), dubbed acute lupus hemophagocytic syndrome (ALHS), is an intractable complication of SLE. A 24-year-old man who had been diagnosed with SLE three months previously, presented with fever, rash, hallucination, and pancytopenia accompanied with hyperferritinemia and bone marrow hemophagocytosis. He was diagnosed with ALHS and neuropsychiatric (NP)-SLE. Although 4 courses of methylprednisolone pulse therapy and 1 course of intravenous cyclophosphamide (IVCY) improved his NP-SLE, his ALHS did not respond. However, the addition of cyclosporine A (CsA) led to a rapid remission from ALHS. This suggests the usefulness of CsA in the treatment of intractable, corticosteroid- and IVCY-resistant ALHS.

Key words: hemophagocytic syndrome, systemic lupus erythematosus, acute lupus hemophagocytic syndrome, cyclosporine A, cyclophosphamide

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by widespread inflammatory organ involvement and the production of autoantibodies such as antinuclear antibodies, anti-DNA, anti-Sm, and antiphospholipid antibodies. Patients with SLE present various manifestations including fever, rash, oral ulcers, arthritis, serositis, nephritis, and neurologic and hematologic disorders (1).

Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis (HLH) (2), one of the most serious and life-threatening complications of SLE (3), is characterized by macrophage or histiocytic activation followed by widespread hemophagocytosis in the reticuloendothelial network, especially the bone marrow (4). HPS manifests as fever, pancytopenia, and increased liver enzyme and ferritin levels, and may be divided into primary and secondary (or reactive) forms. Reactive HPS is associated with various conditions, including infections, malignancies, and autoimmune diseases, such as SLE and adult onset Still’s disease (AOSD) (5). The HPS associated with SLE is often called acute lupus hemophagocytic syndrome (ALHS) (6) and represents a severe, intractable complication of SLE, for which there is no established therapeutic strategy (7).

We herein present a case of intractable, methylprednisolone (mPSL) pulse- and intravenous cyclophosphamide (IVCY)-resistant ALHS accompanied by neuropsychiatric...
Case Report

A 24-year-old Japanese man presented to a general hospital with a gradually deteriorating malar rash, discoid rash, and oral ulcers. The patient’s laboratory data revealed leukopenia and tests for anti-nuclear, anti-DNA, anti-Sm, and antiphospholipid antibodies were positive. He was diagnosed with SLE based on the 1997 American College of Rheumatology (ACR) classification criteria (1). Prednisolone (PSL; 30 mg/day [0.5 mg/kg/day]) improved his malar rash, discoid rash, and oral ulcers within a few weeks.

Three months later, he developed a spiking fever of 39°C, and his malar rash, discoid rash, and oral ulcers deteriorated again. He was admitted to a general hospital, and his PSL dose was increased from 17.5 mg/day to 60 mg/day because of an SLE flare-up; however, his fever and rash did not improve. Moreover, laboratory data showed a decreased white blood cell (WBC) count (3,000/μL), a hemoglobin (Hb) level of 11.6 g/dL, a platelet count of 105,000/μL, and elevated levels of C-reactive protein (CRP) (1.38 mg/dL), lactate dehydrogenase (LDH) (716 IU/L), and ferritin (829 ng/mL). Computed tomography (CT) of the whole body showed no evidence of infection or malignancy. He was diagnosed with HPS according to Imashuku’s criteria (5) based on fever persisting for more than seven days, pancytopenia, hyperferritinemia, and an increased LDH level without any evidence of infection or malignancy. His was considered to have ALHS and underwent two courses of mPSL pulse therapy (1,000 mg/day for 3 days), followed by oral PSL (40 mg/day), and concomitant tacrolimus (TAC; 2 mg/day) as induction therapy. Nevertheless, his fever, pancytopenia, and hyperferritinemia persisted. Furthermore, he developed hallucinations and was referred to our hospital for further treatment in the face of intractable ALHS and suspected NP-SLE.

Upon referral to our hospital, his fever, malar rash, facial discoid lesions (Fig. 1A), palm erythema, and chilblain-like rash of the hands and feet persisted. The laboratory data on admission showed decreased WBC (2,100/μL) and platelet (105,000/μL) counts, and elevated levels of aspartate aminotransferase (AST) (63 IU/L), alanine aminotransferase (ALT) (85 IU/L), LDH (583 IU/L), CRP (2.9 mg/dL), and ferritin (5,955 ng/mL). His anti-nuclear antibody titer was increased 320-fold (homogeneous and speckled pattern) and his anti-DNA antibody (9.0 U/mL), immune complex (measured by C1q method [C1q; 6.1 μg/mL]), and lupus anticoagulant (LAC; 1.4 ratio) levels were slightly elevated, while other immunological findings, such as C3, C4, CH50, anti-Sm antibody, and anti-RNP antibody were all negative. A disintegrin-like and metalloproteinase with thrombospondin type 1 motifs-13 (ADAMTS13) activity (89.0%) was also normal. Importantly, the patient’s serum levels of interleukin-6 (IL-6) (26.1 pg/mL), interleukin-18 (IL-18) (7,870 pg/mL), and interleukin-18 (IL-18) (7,870 pg/mL) had both deviated greatly from the normal range of <2.41 pg/mL and <211 pg/mL, respectively. An examination of the patient’s cerebrospinal fluid revealed an elevated level of IL-6 (27.8 pg/mL) while the cell counts, and glucose, protein, anti-DNA antibody and C1q levels, and the immunoglobulin G index were within normal ranges. Panels for ß-D glucan, the tuberculosis-specific interferon gamma release assay, two sets of blood cultures for bacteria were negative and tests of the serum for antiviral antibodies against hepatitis B surface, hepatitis B core, hepatitis C virus, Epstein-Barr virus, herpes simplex virus, human parvovirus B19, and cytomegalovirus antigenemia were all negative. Magnetic resonance imaging (MRI) of the brain using T2-weighted, fluid-attenuated inversion recovery (NP)-SLE that was successfully treated with the addition of cyclosporine A (CsA).

Figure 1. Skin lesions of the face on admission to our hospital and 3 weeks later. (A) Malar rash and discoid lesions of the face on admission to our hospital. (B) The malar rash and discoid lesions on the patient’s face disappeared at 3 weeks after therapy, leaving pigmented areas.
Figure 2. Brain magnetic resonance imaging on admission to our hospital and after treatment with intravenous cyclophosphamide. (A and B) Magnetic resonance imaging (MRI) of the brain using T2-weighted fluid attenuated inversion recovery (FLAIR) imaging on admission to our hospital. High intensity areas were detected in the cerebral peduncle (coronal image) (A) and putamen (axial image) (B). (C and D) FLAIR MRI of the brain after treatment with one course of intravenous cyclophosphamide (IVCY). The high intensity areas in the cerebral peduncle were decreased (coronal image) (C), and the areas in the putamen disappeared (axial image) (D) in comparison to the images obtained on admission.

Figure 3. Bone marrow smears and the pathological findings. (A) A bone marrow smear showing histiocytic phagocytosis of hematopoietic cells (May-Giemsa staining, ×100 magnification). (B) An enlarged image of the boxed area in panel A (May-Giemsa staining, ×400 magnification).

(FLAIR) revealed high intensity areas in the cerebral peduncle (Fig. 2A) and putamen (Fig. 2B). Bone marrow smears revealed that histiocytes were phagocytosing hematopoietic cells (Fig. 3). He did not have urinary abnormalities or sepsis. These findings led to a final diagnosis of intractable
ALHS complicated by NP-SLE without other organ involvement such as lupus nephritis or serositis. TAC was discontinued on admission and two courses of mPSL pulse therapy, followed by oral PSL (50 mg/day), and one course of intravenous cyclophosphamide (IVCY) were administered as re-induction therapy, resulting in the improvement of NP-SLE. The high intensity areas in the cerebral peduncle were decreased and putamen areas disappeared on FLAIR MRI (Fig. 2C and D). However, his fever and rash were not improved and pancytopenia and hyperferritinemia persisted. Because his ALHS seemed to be resistant to IVCY, 1 course of intravenous immunoglobulin (IVIg; 400 mg/kg×5 days) and intravenous cyclosporine A (CsA; 100 mg/day) were added to his treatment. Thereafter, his fever was dramatically alleviated (within three days), his ferritin level decreased from 13,070 ng/mL to 6,780 ng/mL, and his platelet count gradually increased from 33,000/μL to 58,000/μL. The malar rash and discoid lesions on his face disappeared, while the pigmentation remained (Fig. 1B). Intravenous CsA was switched to oral CsA and the dosage was increased to 170 mg/day (two 50 mg capsules, two 25 mg capsules, and two 10 mg capsules) under serum trough concentration monitoring. The target trough concentration of CsA was set to 150 ng/mL. The concomitant use of CsA led to a rapid remission from intractable ALHS. Interestingly, we found that both the serum IL-6 and IL-18 levels decreased sharply within 4 weeks to 2.6 pg/mL and 732 pg/mL, respectively. An additional two courses of IVCY were administered as consolidation therapy for his NP-SLE. Although the dosage of PSL given in combination with CsA was gradually tapered, he has not experienced any relapse of ALHS or NP-SLE, which is indicative of continuous remission (Fig. 4).

Discussion

We herein present a case of severe ALHS accompanied by NP-SLE. Although the patient’s NP-SLE was improved by mPSL pulse therapy and 1 course of IVCY, his ALHS was resistant to the treatment and the addition of CsA+IVIg led to a rapid remission from intractable ALHS. While dealing with this unique successfully-treated case, we found three clinically important observations.

First, IVCY was not effective for ALHS, even though it rapidly improved the patient’s NP-SLE, indicating differences in the pathogeneses of ALHS and NP-SLE. Reports have proposed several pathogenic mechanisms to explain autoimmune-associated hemophagocytic syndrome (AAHS). Kumakura et al. suggested that histiocytes are activated by cytokines and then hemophagocytose hematopoietic cells sensitized by autoantibodies or deposited immune complexes (8). On the other hand, the pathogenesis of NP-SLE includes inflammatory processes caused by numerous autoantibodies and cytokines (9, 10). Neuronal dysfunction induced directly by these inflammatory mediators or vascular injury could contribute to the pathogenesis of NP-SLE (11). In our case, although some pathogenic mediators
might be common between ALHS and NP-SLE, the clearly differential response to IVCY between ALHS and NP-SLE suggests that the pathogenic mechanisms might be different. We could therefore speculate that ALHS might be induced by a cytokine-mediated mechanism that includes the elevation of the serum levels of IL-6 and IL-18, while NP-SLE might be related to an autoantibody-mediated mechanism, which was indicated by our patient’s positivity for LAC.

Secondly, the addition of CsA to corticosteroids and IVCY dramatically suppressed the intractable ALHS of our case resulting in the alleviation of fever and the improvement of thrombocytopenia and hyperferritinemia. However, we could not deny the possibility that the response of ALHS to first IVCY was delayed, second and third IVCY might have contributed to maintaining control of the patient’s ALHS, while concomitant IVIG might have had synergistic effects on the activated macrophages. Indeed, our previous study revealed a significant and negative correlation between the serum ferritin and anti-dsDNA antibody levels among reviewed ALHS cases (12). Moreover, among 32 ALHS patients treated with CsA, the serum ferritin level was significantly higher and the leukocyte count was significantly lower in CsA responders than in non-responders (12). A receiver operating characteristic (ROC) analysis identified hyperferritinemia (>1,722 ng/mL) and leukopenia (<3,000/µL) as significant predictors of a positive response to CsA in ALHS cases (12). Thus, we proposed that ALHS could be divided into two types: the high-ferritin low-anti-DNA antibody type; and the low-ferritin high-anti-DNA antibody type (12). The former type is expected to be induced by excessive cytokine production, reflected by hyperferritinemia (13), while the latter type is expected to be induced by antibodies or immune complexes that bind to hematopoietic cells (8, 12). Excessive cytokine production from pathogenic T cells could be the underlying pathological process in the cytokine-mediated, high-ferritin low-anti-DNA antibody type of ALHS. The excessive production of cytokines by pathogenic T cells might play a crucial role in the pathogenesis of this condition. As we managed to confirm that precise predictive factors exist, CsA should be considered as a promising therapeutic option for patients with the high-ferritin low-anti-DNA antibody type of ALHS.

The authors state that they have no Conflict of Interest (COI).

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References

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