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Severe Bone Marrow Aplasia Following Macrophage Activation Syndrome in Systemic Lupus Erythematosus

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Macrophage activation syndrome (MAS) is a potentially fatal complication of rheumatic diseases, characterized by activated macrophages with hemophagocytosis and multiple organ damage. We report a case of MAS associated with systemic lupus erythematosus that initially presented with severe liver dysfunction. Although it was improved with steroids and plasmapheresis, severe pancytopenia was subsequently experienced, and the bone marrow showed severe aplasia similar to aplastic anemia. Nevertheless, the administration of immunosuppressants resulted in the recovery of blood counts within two weeks. When severe MAS results in cytokine overproduction, bone marrow aplasia may occur, for which immunosuppressive therapy may be highly effective.

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Introduction

Macrophage activation syndrome (MAS) is a potentially fatal condition known as secondary hemophagocytic lymphohistiocytosis (HLH) that develops in patients with rheumatic diseases (Carter et al. 2019; Nam et al. 2022). It is characterized by excessive activation and expansion of cytotoxic T cells (CTLs) and macrophages, leading to a hyperinflammatory response, hemophagocytosis, and multiple organ damage (Ramos-Casals et al. 2014). MAS usually presents with fever, hepatosplenomegaly, and lymphadenopathy, accompanied by various laboratory abnormalities such as hyperferritinemia, liver dysfunction, cytopenia, and coagulopathy (Henter et al. 2007), which could overlap with the features of other systemic illnesses such as sepsis, malignancy, and autoimmune disease (Carter et al. 2019). MAS is therefore considered a heterogeneous clinical syndrome, and there are no validated strategies for its diagnosis and treatment.

Here, we report a case of severe MAS that developed in a patient with systemic lupus erythematosus (SLE). Although it progressed to severe pancytopenia and bone marrow aplasia, mimicking very severe aplastic anemia (AA), treatment with immunosuppressive agents resulted in a rapid and favorable recovery. Although cytopenia is a common symptom of MAS, its progression to bone marrow aplasia is rarely reported.

Case Presentation

A 53-year-old woman experienced abdominal pain, diarrhea, and fever for one week, which did not improve with levofloxacin (LVFX) administration. She was hospitalized because of general illness and the development of polyarthralgia. She had been diagnosed with SLE 30 years prior and experienced repeated remission and relapse of the disease. Her main symptoms of SLE in recent years were inflammatory arthritis and protein-losing gastroenteropathy, for which prednisolone (PSL, 17.5 mg/day) and hydroxychloroquine (300 mg/day) had been administered. At the time of hospitalization, her performance status was poor, with difficulty in moving due to arthralgia. Physical examination revealed tenderness in the epigastric area and lower

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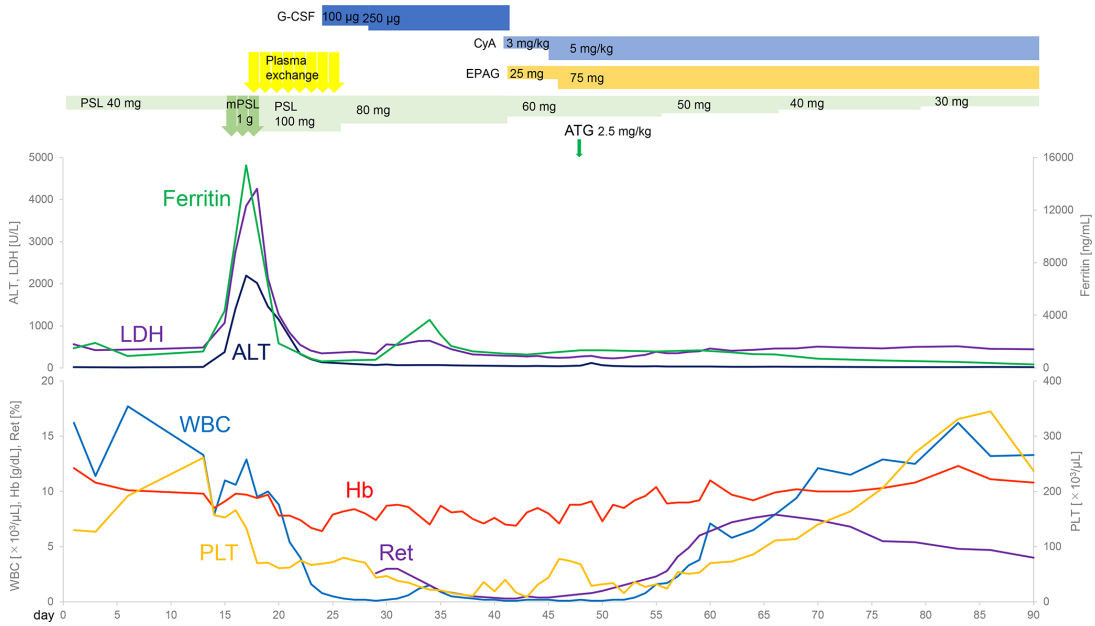

Fig. 1. Clinical course.
ALT, alanine aminotransferase; ATG, anti-thymocyte globulin; EPAG, eltrombopag; G-CSF, granulocyte-colony stimulating factor; Hb, hemoglobin; LDH, lactate dehydrogenase; mPSL, methylprednisolone; PLT, platelet count; PSL, prednisolone; Ret, reticulocyte count; WBC, white blood cell count.

abdomen. Swelling of the knee joints was also observed, which was considered SLE-associated arthritis. Complete blood count (CBC) showed increased white blood cell count (16,200/μL) with neutrophilia (94%) without detection of abnormal cells, anemia, or thrombocytopenia. Serum biochemistry revealed elevated levels of C-reactive protein (CRP, 10.78 mg/dL) and ferritin (1504.2 ng/mL). Mild renal dysfunction was also observed without abnormal urinalysis findings, whereas liver function was normal. Computed tomography (CT) revealed intestinal edema only. Based on the above findings, she was initially considered to have nonspecific enterocolitis with reactive arthritis due to aggravation of SLE, which was treated with the continuation of LVFX and a raised dose of PSL (from 17.5 to 40 mg/day).

The clinical course of the patient is shown in Fig. 1. After admission, her symptoms exacerbated with the re-emergence of fever. Polymerase chain reaction for SARS-CoV-2 nasopharyngeal swab and cytomegalovirus antigenemia were negative. Although blood, urine, and joint fluid cultures revealed no growth of organisms, the possibilities of some infectious diseases could not be ruled out. On the 15th day of admission, laboratory test results showed markedly elevated levels of aspartate aminotransferase (AST, 461 U/L), alanine aminotransferase (ALT, 379 U/L), lactate dehydrogenase (LDH, 1,073 U/L), and ferritin (4,338.9 ng/mL). CBC results showed the progression of anemia (Hb 9.1 g/dL) without neutropenia and thrombocytopenia. Coagulation test results showed an elevated fibrin degradation product (FDP, 86.4 μg/mL) without hypofibrinogenemia or abnormal values of activated partial thromboplastin time (APTT) and prothrombin time (PT). Bone marrow examination revealed mildly hypercellular marrow [nucleated cell count (NCC) 2.6 × 10^4/μL, megakaryocytes 16/μL] and significantly increased macrophages with phagocytosis (Fig. 2a). Infiltration of abnormal cells was not observed. Serological tests for the hepatitis virus were negative. CT revealed mild splenomegaly. Based on the above findings, we concluded that she had developed MAS, the background of which could be assumed to be aggravation of SLE and/or unidentified infectious diseases. Steroid pulse therapy (methylprednisolone 1 g/day for three days) and plasmapheresis were performed, which resulted in rapid improvement in laboratory findings, a decline in fever, and remission of polyarthralgia. However, pancytopenia with severe neutropenia developed, which did not respond to lenograstim administration and lasted for more than two weeks. Complete blood count on the 45th day of admission showed agranulocytosis (WBC 200/μL with no neutrophils), anemia (Hb 8.0 g/dL), and thrombocytopenia (44 × 10^3/μL). Bone marrow examination was performed again at this time, which showed extremely hypoplastic marrow (NCC 1,000/μL, megakaryocytes < 16/μL) without activated macrophages (Fig. 2b). No abnormal or dysplastic cells were detected using microscopic inspection or flow cytometry. Bone marrow biopsy revealed severely hypocellular marrow without evidence of abnormal cells. We judged the above findings as severe bone marrow aplasia in homology with severe AA. We immediately started the administration of cyclosporine (CyA, 3 mg/kg/day) and eltrombopag (EPAG, 25 mg/day). Thereafter, the CyA and EPAG doses were increased to 5 mg/kg/day and 75 mg/day, respectively.

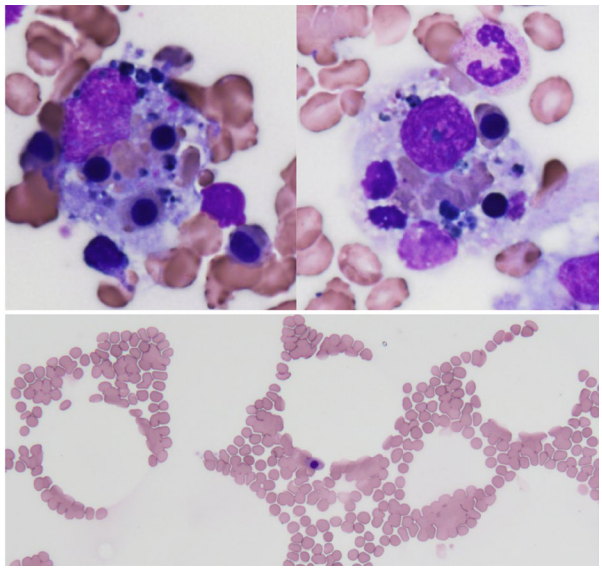

Fig. 2. Findings of bone marrow smear (May-Giemsa staining) on day 21 (a) and on day 45 (b).

We also started anti-thymocyte globulin (ATG, 2.5 mg/kg/day) therapy after a week. However, temporal abdominal pain of unknown etiology led us to stop the treatment after one dose. CyA and EPAG were administered uninterruptedly, and her blood cell count gradually increased ten days after initiation. Thereafter, cytopenia completely improved, and she became independent of blood transfusions on the 57th day of admission. After 15 weeks, CyA and EPAG levels tapered without recurrence of cytopenia.

This case report was approved by the Ethics Committee of Tohoku University Hospital (No. 31831).

Discussion

MAS is a potentially life-threatening complication of rheumatic diseases (Sawhney et al. 2001). This disease is a form of secondary HLH in the presence of autoimmune/autoinflammatory stimuli; malignancy and infection can also trigger secondary HLH (Ramos-Casals et al. 2014; Griffin et al. 2020). The main pathophysiological features of HLH are excessive activation and expansion of cytotoxic T cells (CTLs) and macrophages, leading to hemophagocytosis, inappropriate immune stimulation, and a self-perpetuating hyperinflammatory state known as cytokine storm (Schulert and Grom 2015; Carter et al. 2019). Under such conditions, remarkably elevated levels of circulating cytokines are observed, including interferon (IFN)-γ, interleukin (IL)-2, macrophage colony-stimulating factor, IL-1, IL-6, IL-18, and tumor necrosis factor (TNF), as well as cytokine inhibitors such as soluble TNF receptors and IL-1R antagonists (Schulert and Grom 2015), leading to typical findings of HLH such as fever, hepatosplenomegaly, cytopenia, coagulopathy, and liver dysfunction. The prevalence of MAS in SLE has been reported as 0.9-9% (Carter et al. 2019). The diagnosis of MAS in SLE can be challenging because the clinical features of SLE-associated MAS and active SLE are very similar (Granata et al. 2015). However, most studies have identified infections as the most common cause of HLH (Aziz et al. 2021). In this case, based on the findings of fever, acute liver dysfunction, and elevated ferritin levels, MAS could develop in association with some kind of infection in the background of SLE because there were no apparent signs of SLE flares.

There are no validated treatment protocols for secondary HLH in adults because of a lack of agreement in nomenclature and classification, the rarity of the condition, and the heterogeneity of triggering factors and underlying conditions (Carter et al. 2019). The treatment of secondary HLH in adults was based on the HLH-94 study (Henter et al. 1997) with an eight-week induction with etoposide (150 mg/m^2) (Schram and Berliner 2015). However, there is no consensus on MAS treatment, and personalized and graded treatment approaches are recommended for patients with MAS (La Rosee et al. 2019). Conventionally, steroid treatment such as high-dose pulse methylprednisolone (1 g/day for three-five consecutive days) appears to be a frequent initial approach (La Rosee et al. 2019). Intravenous immunoglobulin (IVIG), CyA, and IL-1-blocking therapy with anakinra or etoposide can be administered depending on the condition (Carter et al. 2019; La Rosee et al. 2019). It has also been reported that plasma exchange, in addition to glucocorticoids and immunosuppressive agents, rapidly improves organ function and reduces the mortality rate of MAS (Chen et al. 2022). In the present case, pulsed steroid administration and plasmapheresis resulted in rapid and marked improvement of clinical symptoms of MAS, which could support the appropriateness of the diagnosis and treatment.

Although the cellularity of bone marrow aspirates in HLH varies from hypocellular to hypercellular (Jordan et al. 2011), progression to bone marrow aplasia mimicking severe aplastic anemia has rarely been reported. Kumakura et al. (2003) investigated the bone marrow findings of 15 patients with HLH and described one case in which normocellular marrow with pancytopenia at the onset of HLH progressed into severe bone marrow aplasia despite intensive therapies for curbing HLH progression. They mentioned that HLH could be a causative agent of AA because the two diseases have similar cytokine profiles (Kumakura et al. 2003). Another report described a case of severe bone marrow hypoplasia after methylprednisolone pulse therapy for HLH, which was successfully treated with ATG and CyA (Kaito et al. 2003). The authors suggest the possibility that immunosuppressive therapy with ATG and CyA might be a useful strategy for this condition because activation of T lymphocytes could underlie both HLH and AA. In the present case, the patient developed severe bone marrow aplasia after treatment with MAS with steroid pulse therapy and plasmapheresis. It is possible that the progression from MAS to severe bone marrow aplasia, in this case, was a sequential condition caused by activated T cells, for which

immunosuppressive treatment with CyA could be specifically effective.

In summary, we report a case of MAS progressing into bone marrow aplasia similar to very severe AA that was successfully treated with immunosuppressive therapy. This case suggests reversible bone marrow aplasia could occur in association with MAS, for which immunosuppressive agents such as CyA might be highly effective. Further investigation is urgently required to elucidate the pathophysiology of these clinical conditions.

Conflict of Interest

The authors declare no conflict of interest.

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