Concurrent Occurrence of Hemophagocytic Syndrome and Myelofibrosis in a Case of SLE

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Abstract
We experienced a case of Systemic Lupus Erythematosus (SLE) with myelofibrosis and hemophagocytosis. Recently, it has become clear that hemophagocytosis can occur with autoimmune diseases, including SLE. By contrast, myelofibrosis is a rare complication of SLE, and only ten cases have been reported. The mechanism by which myelofibrosis complicates SLE remains unknown. There are several theories: myelofibrosis may result from microvasculitis in the marrow or the unusual release of cytokines. Myelofibrosis accompanying SLE appears to be reversible with immunosuppressive therapy, although primary myelofibrosis is not. The pathogenesis of myelofibrosis with SLE is quite different from that of primary myelofibrosis. This is the first report of SLE accompanied by myelofibrosis and hemophagocytosis. In our cases, serum TGF-β was elevated remarkably. Our case indicated that in the process of hemophagocytosis, activated macrophages produce monokines, such as TGF-β, which sequentially induce myelofibrosis. Hemophagocytosis may predispose SLE patients to myelofibrosis.

Keywords: SLE; Hemophagocytosis; Myelofibrosis

Introduction
Hematological abnormalities such as anemia, thrombocytopenia, and leukopenia are observed in Systemic Lupus Erythematosus (SLE). These abnormalities result from one or a combination of factors, including an autoimmune mechanism, chronic inflammation, the effect of therapy, and complicating infections. Patients with SLE sometimes develop Hemophagocytic Syndrome (HPS), which is characterized by pancytopenia or bcytopenia in the peripheral blood and histiocytotic hemophagocytosis in the bone marrow and remainder of the reticuloendothelial system. Conditions including virus infection and lymphoma can cause HPS, and SLE is reported to be one of the causative conditions [1]. Several cases of secondary myelofibrosis occurring in the setting of SLE have been described [2]. The pathogenesis of myelofibrosis remains incompletely understood, but the elevation of circulating immune complex, apoptotic body and cytokines are supposed to involve in it [3]. The myelofibrosis in SLE patients has been reported to respond well to immunosuppressive therapy, compared with the response of idiopathic myelofibrosis, suggesting that myelofibrosis in SLE is associated with an immunological mechanism. Here, we report a case of SLE with concurrent hemophagocytosis and myelofibrosis. To our knowledge, no cases of SLE accompanied by both hemophagocytosis and myelofibrosis have been reported. Our case is important for considering a cascade that can cause myelofibrosis in SLE.

Case Report
A 48-year-old woman suffered from polyarthralgia and low-grade fever. She was medicated with non-steroidal anti-inflammatory drugs at an open clinic. Her Anti-Nuclear Antibody (ANA) was elevated as much as 1280 fold (diffuse type) in January the following year. Beginning that June, urinary protein, anti-double strand (ds) DNA antibody, and myelofibrosis (Figure 1c). Her blood cell counts recovered to the normal range since.

Coagulation studies did not show any signs of disseminated intravascular coagulation (DIC). Serum IgG and IgA were increased (1982 mg/dl and 635 mg/dl, respectively). Direct and indirect Coombs' tests were negative. Hypercomplementemia was found (C4: 55 mg/dl, C2: <5.7 mg/dl, CH50: <5.0 U/ml); however, circulating immune complex was negative. ANA was as high as 1280 fold (diffuse type) and 2580 fold (speckle type). Anti-ds DNA antibody was elevated to 36.9 IU/ml compared with the level six months earlier. As compared with the patient's previous data, no other auto-antibodies were detected, except for anti-SS-A antibody (x 64). Urinalysis revealed telecospediments containing casts of granulocytes, epithelial cells, and red blood cells. Renal biopsy revealed mesangial lupus nephritis. She met five of the American College of Rheumatology (ACR) criteria. Bone marrow aspiration was almost a dry tap, and only a tiny sample was aspirated. The smear revealed hemophagocytosis (Figure 1a). Her bone marrow biopsy specimen revealed myelofibrosis (Figure 1b). Although the serum IL-1β was not elevated (<10 pg/ml), the TGF-β (31.2 ng/ml; normally undetected), TNF-α (40 pg/ml; normally undetected), and IL-6 (58.5 pg/ml; normally <40 pg/ml) levels were elevated remarkably. She was diagnosed with SLE complicated with hemophagocytosis and myelofibrosis. There were no clinical or laboratory findings that suggested active infection or malignant disorders. Consequently, she was treated with prednisolone (initially 60 mg/day) beginning July 31. After the therapy started, her symptoms and laboratory data improved gradually. After the prednisolone was tapered to 20 mg/day, she was discharged. Bone marrow aspiration and biopsy before discharge revealed a dramatic improvement in the hemophagocytosis and myelofibrosis (Figure 1c). Her blood cell counts recovered to the normal range (WBC: 8700/µl, Hb: 13.0 g/dl, platelets: 26.6 x 10^11/µl) and have remained in the normal range since.

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Discussion

HPS is a clinicopathologic entity characterized by a high-grade fever, hepatosplenomegaly, cytopenias, a high ferritin level, and increased macrophage proliferation and activation with hemophagocytosis throughout the reticuloendothelial system. It is classified into familial hemophagocytic lymphohistiocytosis and reactive hemophagocytosis. Reactive hemophagocytosis is associated with several underlying conditions, including infection, malignancy, and autoimmune disease. Wong et al. [1] reported HPS associated with SLE [1]. Recently, HPS associated with other autoimmune diseases has also been reported and is called Autoimmune-Associated Hemophagocytic Syndrome (AAHS) [4,5]. Our cases did not show any clinical or laboratory findings of active infection or malignant disorders and were therefore diagnosed as AAHS.

Secondary myelofibrosis can be observed in association with a variety of neoplasms, infections, and other diseases. The mechanism of secondary myelofibrosis is as poorly understood as is the cause of idiopathic myelofibrosis. In myelofibrosis, the marrow reticulin increases as the result of fibroblast proliferation and increased collagen synthesis or altered collagen turnover owing to decreased collagenase release from macrophages and neutrophils. It has also been reported that, in chronic myelofibrosis with myeloid metaplasia, the marrow megakaryocyte mass is increased, and it has been postulated that growth factors released by platelets or megakaryocytes stimulate fibroblast proliferation and collagen synthesis. Fibroblast proliferating factors such as TGF-β, PDGF, TNF-α, IL-1α, and IL-1β may play a part in inducing myelofibrosis [6-8]. In our case, the serum levels of TGF-β, TNF-α, and IL-6 were elevated, and IL-1β was also elevated. This suggests that these monokines were involved in the pathogenesis of myelofibrosis in our case.

Other mechanisms causing myelofibrosis in autoimmune diseases have been suggested. The excess release of PDGF from platelets, which is caused by the binding of immune complexes to platelet Fc receptors, may stimulate fibroblasts [9-11]. Alternatively, fibroblasts may be stimulated and may proliferate in response to bone marrow injury caused by vasculitis [12].

Myelofibrosis is a rare complication of SLE, and only small number of cases have been reported. High doses of corticosteroid were used as therapy in most of these cases, and the peripheral blood cytopenia improved in eight of the nine cases described. Surprisingly, although myelofibrosis is irreversible, six of the nine cases, including our case, showed a remarkable improvement in myelofibrosis with the high-dose prednisolone treatment. This suggests that the pathogenesis of myelofibrosis accompanying SLE differs from that of ordinary myelofibrosis.

In our cases, there was concomitant myelofibrosis and hemophagocytosis. To our knowledge, no other cases of SLE with both myelofibrosis and hemophagocytosis have been described. Although the mechanism inducing both myelofibrosis and hemophagocytosis in our cases remains unclear, the successful improvement of the myelofibrosis and hemophagocytosis with immunosuppressive therapy suggests that both conditions involve a dysregulated immune system in the underlying pathogenesis. In our case, TGF-β, TNF-α, IL-6 and IL-1β were elevated in the serum at the onset of the myelofibrosis and hemophagocytosis. As described above, TGF-β is involved in the pathogenesis of myelofibrosis, and TNF-α plays an important role in causing hemophagocytosis. Therefore, these cytokines may trigger myelofibrosis and hemophagocytosis, and successful immunosuppressive treatment may involve a reduction in the intense cytokine response. By contrast, an autoantibody-mediated mechanism has been proposed in AAHS. In this condition, specific auto-antibodies bind hematopoietic cells, and histiocytes phagocytize their Fc receptors (antibody-dependent cellular cytotoxicity; ADCC). Moreover, Wong et al. have proposed an immune-complex-mediated mechanism, in which the deposition of circulating immune-complex on marrow hematopoietic cells results in histiocytic hemophagocytosis via the antibody or activated complement in the complex binding to receptors on histiocytes [13]. The possible involvement of these mechanisms in our case cannot be ruled out; because our case shows hypocomplementemia and Case 2 had auto-antibodies against blood elements, as proven by the positive direct Coombs’ test.

In this report, we presented the first case of SLE complicated with both hemophagocytosis and myelofibrosis. Although the mechanisms inducing myelofibrosis and hemophagocytosis in SLE may be heterogeneous, our case suggests a common pathogenesis underlying both. Elevated serum levels of cytokines such as TGF-β may be involved in the pathogenesis of both myelofibrosis and hemophagocytosis. Our case also indicated another possible mechanism in which hemophagocytosis predisposes to myelofibrosis. Histiocytes stimulated by several mechanisms described above become hemophagocytes and are further activated in the process of eating bone marrow cells. These activated hemophagocytes may produce huge amounts of cytokines, including TGF-β, which are sufficient to stimulate fibroblasts. Therefore, our case suggests that hemophagocytes may predispose to myelofibrosis in SLE. Further studies are needed to understand the mechanisms triggering myelofibrosis and hemophagocytosis in SLE.

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