

Successful Treatment of Refractory Thrombocytopenia with Mycophenolate Mofetil in a Patient with Systemic Lupus Erythematosus

While mild thrombocytopenia in systemic lupus erythematosus (SLE) is frequently seen in the context of active disease, severe thrombocytopenia causing significant bleeding is not that common. Corticosteroids are considered the first line therapy for severe thrombocytopenia in SLE. Second-line therapeutic agents or splenectomy have been reported to be effective for patients who fail to respond to steroids or those who require moderate doses of steroids to maintain the platelet counts. Recent randomized controlled studies have shown that mycophenolate mofetil (MMF) is an efficacious and safe therapeutic agent in patients with proliferative forms of lupus nephritis. However, little information has been available regarding the role of MMF in the treatment of immune thrombocytopenia complicated with SLE. Hereby I describe a patient with SLE in whom thrombocytopenia was refractory to corticosteroids, intermittent intravenous cyclophosphamide, azathioprine, cyclosporine, intravenous gamma globulin, danazol, and splenectomy, and whose platelet counts eventually normalized during therapy with MMF. In this patient, thrombocytopenia is initially thought to be associated with active SLE involving major organ. However, after immunosuppressive agents were given, the refractory nature of thrombocytopenia seems to be an isolated phenomenon, independently of SLE activity.

Key Words : *Lupus Erythematosus, Systemic; Thrombocytopenia; mycophenolate mofetil*

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INTRODUCTION

Whereas mild thrombocytopenia frequently occurs during an active stage of systemic lupus erythematosus (SLE) without causing bleeding tendency, severe immune thrombocytopenia, which can lead to a significant hematological problem, is relatively uncommon in SLE. In the latter condition, systemic corticosteroids are considered the first line treatment. When this therapeutic modality does not result in a sustained response, other therapeutic agents, including azathioprine, intermittent intravenous cyclophosphamide, cyclosporine, danazol, dapson, vincristine, and intravenous gamma globulin, have been reported to be efficacious in the treatment of thrombocytopenia in SLE. In addition, splenectomy may be indicated for SLE patients with severe thrombocytopenia who are refractory to corticosteroids and/or other agents described above. However, these conventional therapeutic modalities may cause significant side effects (1).

Mycophenolate mofetil (MMF), originally developed for organ transplantation, is a prodrug of mycophenolic acid, which blocks inosine monophosphate dehydrogenase, a crucial enzyme in purine synthesis. Consequently, mycophenolic acid inhibits lymphocyte proliferation and T-cell dependent antibody responses (2, 3). MMF has been reported to be effec-

tive in mouse models of lupus nephritis (4). Moreover, recent randomized controlled trials in humans have suggested that MMF could also be efficacious and safe in the management of proliferative lupus nephritis (5, 6). However, little information has been available regarding the role of MMF in the treatment of immune thrombocytopenia complicated in SLE. Hereby I describe a patient with SLE in whom thrombocytopenia was refractory to corticosteroids, intermittent intravenous cyclophosphamide, azathioprine, cyclosporine, intravenous gamma globulin, danazol, and splenectomy, and whose platelet counts eventually normalized during therapy with MMF.

CASE REPORT

In November 2001, a 26-yr-old female was admitted with a one-week history of pedal edema, nasal bleeding, and petechiae on the lower limbs. She did not take any medications for current illness. There was no medical history of photosensitivity, oral ulcer, and Raynaud's phenomenon. On physical examination, mildly anemic conjunctiva and petechiae and pitting edema on the lower extremities were noted. Laboratory studies at this time showed a hemoglobin level of 9.8

g/dL, a white blood cell count of 3,600/ μ L, and a platelet count of 11,000/ μ L. Urinalysis revealed over 30 red blood cells per high-power field and 3+ proteinuria. Creatinine clearance and urinary total protein were 59 mL/min and 2.6 g/day, respectively. The antinuclear antibody titer was 1:1,280 with a homogenous pattern, the level of anti-double stranded DNA was 420 IU/mL (normal, <5 IU/mL), and a profound hypocomplementemia was observed. IgM and IgG anticardiolipin antibodies and lupus anticoagulant were negative. Anti-platelet antibody was also negative. Renal biopsy showed a segmental endocapillary proliferation with active necrotizing lesions on some glomeruli, which was consistent with focal proliferative glomerulonephritis, class IIIb lupus nephritis.

In view of severe thrombocytopenia and the proliferative form of lupus nephritis, prednisolone (PD) 1 mg/kg, hydroxychloroquine 200 mg b.i.d., and monthly intravenous cyclophosphamide 500 mg/m² were prescribed. She was discharged, since the platelet counts rose to over 50,000/ μ L on these medications. During initial six months of the follow-up, despite 6 cycles of intravenous cyclophosphamide was monthly given, PD doses could not be tapered to below 20 mg/day to maintain the platelet counts of over 50,000/ μ L. However, the proteinuria level decreased, and SLEDAI scores and serologic markers for disease activity improved. During the next 18 months, several agents, including cyclosporine, azathioprine, intravenous gamma globulin and danazol were sequentially given to sustain the platelet counts, in combination with moderate doses of PD. However, she had to admit four times to the hospital because of severe thrombocytopenia with the platelet counts of below 10,000/ μ L and the development of spontaneous bleeding, such as epistaxis, petechiae, heavy menstrual blood flow, and gingival bleeding, whenever the PD doses decreased to less than 20 mg/day. However, there were no specific abnormal findings on the bone marrow biopsy. During this period, serologic markers for disease activity normalized and proteinuria also resolved, independently of the refractory nature of thrombocytopenia. She, therefore, underwent splenectomy in September 2003, but failed to contribute to increment of the platelet counts to the adequate level. Spleen scintigraphy did not detect any evidences for accessory spleen and Howell-Jolly bodies were not found on a peripheral blood smear, such that the possibility of the presence of accessory spleen was excluded.

In December 2003, MMF 500 mg b.i.d. and PD 40 mg/day were then commenced. Within 2 weeks, the platelet counts increased to over 100,000/ μ L. During the following three months, the platelet counts normalized and PD was successfully tapered to 10 mg/day. In addition, clinical and serologic markers for SLE activity also remained stable. In June 2004, she was very well on PD 5 mg/day and MMF 750 mg/day, with stable disease activity and normal level of the platelet counts.

DISCUSSION

In general, the clinical features of thrombocytopenia in SLE are similar to those seen in other causes of thrombocytopenia, such as immune thrombocytopenic purpura (ITP). When the platelet counts decreased to below 50,000/ μ L, spontaneous bleeding may occur. While mild thrombocytopenia in SLE is frequently seen in the context of active disease, severe thrombocytopenia causing significant bleeding is not that common (1). Two distinct subsets of SLE patients with thrombocytopenia have been identified; one is related to an active disease of SLE, and the other is that thrombocytopenia is an isolated finding, independently of SLE activity (7). In the present patient, thrombocytopenia is initially thought to be associated with active SLE involving major organ. However, after immunosuppressive agents were given, the refractory nature of thrombocytopenia seems to be an isolated phenomenon, since other clinical and serologic markers for disease activity became improved.

Corticosteroids are considered the first line therapy for severe thrombocytopenia in SLE. Although most patients with thrombocytopenia in SLE initially respond to this therapy, long-term response has been reported to be sustained in only 22% of patients (8). For patients who fail to respond to steroids or those who require moderate doses of steroids to maintain the platelet counts, second-line therapeutic agents, including azathioprine, intermittent intravenous cyclophosphamide, cyclosporine, danazol, dapsone, vincristine, and intravenous gamma globulin, have been described to be effective in the treatment of steroids-resistant thrombocytopenia in SLE (1). On the other hand, the efficacy of splenectomy in the treatment of steroids-resistant thrombocytopenia in SLE is controversial (1, 9). Several investigators have reported that splenectomized patients with SLE may have a significantly higher incidence of cutaneous vasculitis and serious infections without obvious benefits over those treated medically (10). In contrast, since long-term responses by splenectomy in SLE patients with steroids-resistant thrombocytopenia have also been reported, splenectomy may be indicated for some patients refractory to steroids or other second-line agents (1, 8, 11).

In the current patient, in spite of administrations of several immunosuppressive or immunomodulating agents, moderate doses of PD were required to maintain the platelet counts. Moreover, splenectomy failed to contribute to increment of the platelet counts to the adequate level. However, severe, refractory thrombocytopenia was successfully treated with MMF without any overt adverse effects.

MMF is a potent immunosuppressant with good safety profile, the commonest side effects being nausea, diarrhea, and dose-related leukopenia (2, 3). Recent randomized controlled studies have shown that MMF is an efficacious and safe therapeutic agent in patients with proliferative forms of lupus nephritis (5, 6). Moreover, there has been extensive use of MMF in several other autoimmune diseases, such as rheuma-

toid arthritis, psoriasis, and inflammatory eye disease (12). However, although little information has been available regarding the role of MMF in the treatment of immune thrombocytopenia complicated with SLE, its immunomodulating functions, including selective inhibition of T and B cells proliferation, and suppression of antibody production and adhesion molecule expression, are speculated to be an action of mechanism for immune thrombocytopenia (2, 13). To date, there has been only one formal report showing that steroids-refractory thrombocytopenia in SLE successfully responded to MMF (13). The present patient seems to take much more refractory course of thrombocytopenia when compared with that patient. In addition, in the case of ITP, there have been recent investigations indicating that MMF could be used as a second-line agent for the treatment of steroid-resistant ITP (14, 15). In these previously published reports, MMF doses have usually been used in 2 g/day, which is a usual maintenance dosage used in other conditions. However, the MMF dosage was not increased to 2 g/day, since the current patient responded well at lower dosage, 1 g/day. More studies are required which dosage of MMF is optimal for the management of thrombocytopenia in SLE.

In summary, I describe a patient with SLE in whom thrombocytopenia was refractory to corticosteroids, intermittent intravenous cyclophosphamide, azathioprine, cyclosporine, intravenous gamma globulin, danazol, and splenectomy, and whose platelet counts eventually normalized during therapy with MMF. Further studies are required to confirm this observation in a larger number of SLE patients with steroid-refractory thrombocytopenia.

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