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Case Report

Treatment with Erythromycin and Tacrolimus for Primary Sjogren's Syndrome-Related Immune Thrombocytopenia: A Case Report

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Introduction

Sjogren's syndrome (SjS) is a systemic autoimmune disease characterized by a wide spectrum of clinical manifestations. Immune thrombocytopenia (ITP) is a common clinical manifestation of SjS and causes hemorrhagic events. The mechanism of ITP in SjS is due to anti-platelet (PLT) autoantibody-induced peripheral PLT destruction and splenic sequestration, as well as reduced PLT production by impaired megakaryocytes caused by anti-PLT autoantibodies.¹ Corticosteroids supplemented with immunoglobulin (Ig) are the first-line treatments for SjS-related ITP, while second-line treatments including danazol, cyclosporin A, azathioprine, eltrombopag (ELT), and rituximab have been proposed. However, clinical trials evaluating their efficacy and safety specifically in patients with SjS-related ITP are not documented.¹ Erythromycin (EM), a macrolide (MAC), provides not only anti-bacterial activities but also immunomodulatory effects. Similarly, tacrolimus (TAC), a calcineurin inhibitor and MAC, also provides immunomodulatory effects. Recently, successful cases of ITP using these two drugs have been reported. Herein, we report a case of refractory primary SjS-related ITP treated using EM and TAC.

Case

A 64-year-old woman with primary SjS which was not treated, was admitted to our hospital for nasal bleeding, oral bleeding, and purpura on her entire body. When she visited our hospital for a routine consultation 3 months ago, her PLT count was $20.7 \times 10^4/\mu\text{L}$. This time, laboratory findings were as follows: WBC counts, $8,910/\mu\text{L}$ (basophils, 0.1%; eosinophils, 0.3%; neutrophils, 74.3%; lymphocytes, 22.6%; and monocytes, 2.7%); hemoglobin, 9.9 g/dL; PLT counts, $0.1 \times 10^4/\mu\text{L}$; CRP, 0.32 mg/dL; IgG, 3,721 mg/dL; IgM, 244 mg/dL; and IgA, 408 mg/dL. Although the anti-PLT antibody was positive, other autoimmune antibodies such as anti-DNA and anti-cardiolipin IgG antibodies were negative. Moreover, cytomegalovirus IgM, Parbovirus B19 IgM, and *Helicobacter pylori* IgG antibodies were not detected. PT, APTT, fibrinogen, and FDP were all within normal levels. A bone marrow aspiration smear revealed normal bone marrow with a nucleated cell count of $15.1 \times 10^4/\mu\text{L}$ and a megakaryocyte count of $53/\mu\text{L}$ without dysplasia or hemophagocytosis. No abnormal findings suggestive of infection were identified in the systemic examination, including the chest X-ray film and urinalysis. Based on these findings, the patient was diagnosed with primary SjS-related ITP. The clinical course is shown in Figure 1.

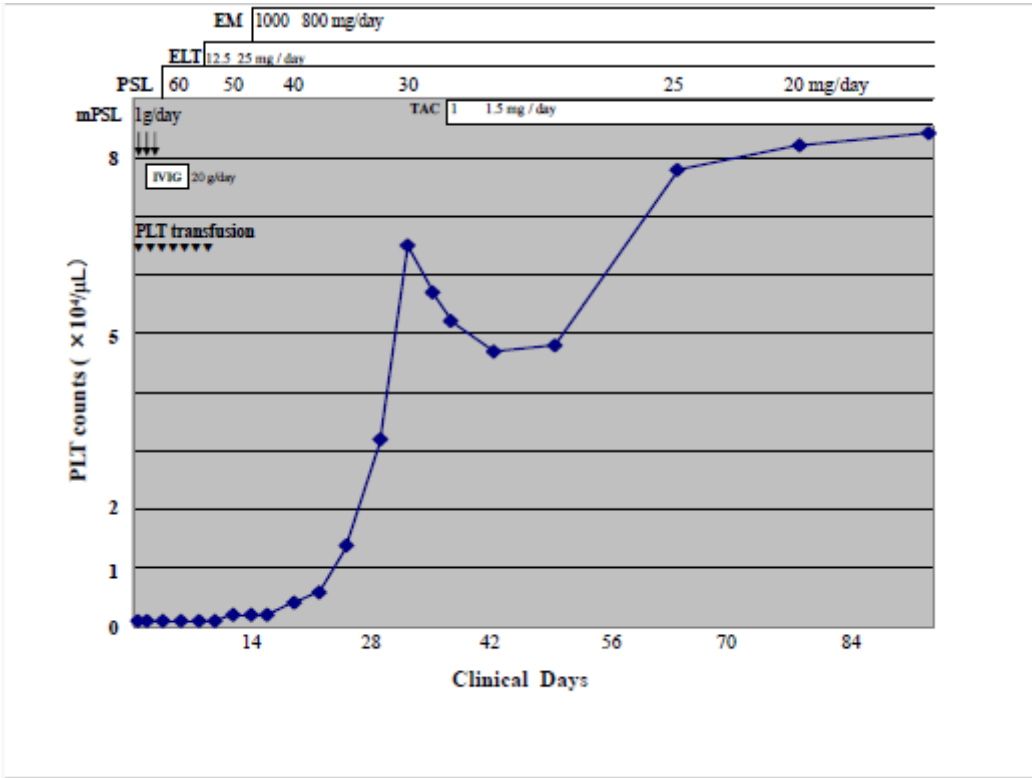


Figure 1. Laboratory data and prescribed agents on clinical days. **PLT:** platelet, **mPSL:** methyl prednisolone, **PSL:** prednisolone, **IVIG:** intravenous immunoglobulin, **ELT:** eltrombopag, **EM:** erythromycin, **TAC:** tacrolimus.

On the first day of admission, she received platelet transfusion and intravenous methyl prednisolone (PSL) (1,000 mg/day) for 3 days, followed by PSL (60 mg/day) for 7 days, and then PSL (50 mg/day) for 7 days. On the second day, she was treated with intravenous immunoglobulin (IVIG) (20 g/day) for 5 days. During this clinical course, she received PLT transfusions several times. However, the PLT counts did not increase and remained at 0.1–0.2 ×10⁴/μL. Seven days after initiating the IVIG treatment, eltrombopag (ELT) (12.5 mg/day), a thrombopoietin-receptor agonist, was added. However, the PLT counts did not increase; therefore, after 7 days of ELT treatment, the dosage was doubled. Considering the immunomodulatory effects of MACs,² intravenous EM (0.5 g, twice daily) for 7 days and subsequently oral EM (200 mg, four times daily) for the long-term were added after obtaining informed consent. Five days after initiating the EM treatment, the PLT counts increased to 0.4×10⁴/μL. Concurrently, the dosage of PSL was reduced to 40 mg/day. Subsequently, the PLT counts gradually increased. By 18 days after initiating the EM treatment, the PLT counts had increased to 6.5×10⁴/μL. Therefore, the PSL dosage was reduced to 30 mg/day. However, after 6 days of treatment with PSL (30 mg/day), the PLT counts decreased to 5.2 ×10⁴/μL. Instead of increasing the PSL dosage again, TAC (1 mg/day) was added. However, after 6 days of TAC (1 mg/day) treatment, the PLT counts decreased to 4.7×10⁴/μL. Subsequently, the TAC dosage was increased to 1.5 mg/day. Three weeks after initiating TAC (1.5 mg/day) treatment, the PLT counts increased to 7.8 ×10⁴/μL. Therefore, the PSL dosage was reduced to 25 mg/day. Two weeks after starting PSL (25 mg/day) treatment, the PLT counts increased 8.2 ×10⁴/μL. Therefore, the PSL dosage was further reduced to 20 mg/day. The trough levels of TAC (1.5 mg/day) measured 6.5 ng/mL.

Discussion

In this current case with hemorrhagic events, the patient initially received IVIG, methyl PSL pulse therapy, and subsequent high dose PSL without significant improvement. Due to the insufficient effectiveness of these combined treatments, ELT was added. Subsequently EM was also added, considering its immunomodulatory effects. The addition of EM treatment was considered

effective; however, it takes two weeks to confirm the effectiveness of ELT treatment. Therefore, the improvement in PLT counts observed with PSL (40 mg/day) may be attributed to the effects of EM and/or ELT.

Regarding the immunomodulatory and anti-inflammatory effects of MACs, they involve in augmenting the apoptosis of activated lymphocytes, thereby reducing inflammation. MACs, such as clarithromycin and azithromycin have been reported to modulate the function of dendritic cells, which are crucial antigen-presenting cells playing a central role in initiating and regulating immune responses. Additionally, MACs seem to suppress the production of proinflammatory cytokines by T cells.² In our previous reports, we have reported several cases of primary ITP showing increased PLT counts following MACs treatment.³⁻⁵ The improvement of ITP in these cases might be attributed to the immunomodulatory effects of MACs. Based on these findings, the immunomodulatory effects of EM may have contributed to the improvement in PLT counts in this case.

During the clinical course, the PLT counts gradually decreased while the patient was on PSL (30 mg/day) in combination with ELT and EM treatment. Instead of increasing the PSL dosage again, TAC was successfully added in this case. As mentioned earlier, TAC is a calcineurin inhibitor and also belongs to the class of MAC. Because calcineurin is a critical phosphatase in TCR signaling, TAC can restrain the activation and differentiation of helper T-cells. Additionally, TAC has been proven to inhibit the differentiation of T follicular helper cells and suppress B-cell function.⁶ TAC also inhibits the production and release of TNF- α , IFN- γ , and IL-2.⁷ In a study of TAC treatment for primary SjS-related ITP, Xu et al. recruited 23 patients with refractory primary SjS-related ITP and administered 2 or 3 mg/day of TAC in addition to conventional treatments such as glucocorticoids, IVIG, hydroxychloroquine, and others. Four weeks after initiating TAC treatment, 2 patients (8.7%) achieved a complete response (CR) showing PLT counts of over $10 \times 10^4/\mu\text{L}$ without bleeding, 15 patients (65.2%) achieved a partial response (PR) with PLT counts of over $3 \times 10^4/\mu\text{L}$ but under $10 \times 10^4/\mu\text{L}$ without bleeding or PLT counts at least doubled compared to before treatment, and the remaining 6 patients (26.1%) did not respond to TAC treatment. Additionally, they measured several cytokines, including IL-2, IL-4, and IFN- γ . Consequently, they found that the effect of TAC may be related to reduced expression of Th1 cytokine.⁶

In this case, TAC at 1.5 mg/day was sufficiently effective. MACs are known to suppress TAC metabolism by inhibiting cytochrome P450 3A4, thereby increasing TAC blood concentrations.⁸ Suzuki et al.⁹ measured TAC blood concentrations in patients with rheumatoid arthritis and observed that the trough levels of TAC in the 1, 2, and 3 mg/day groups were 2.96, 4.29, and 8.32 ng/mL, respectively, although these levels varied widely among individuals within the groups. In this case, the trough levels of TAC (1.5 mg/day) were 6.5 ng/mL, indicating that EM may have increased TAC blood concentrations, resulting in the reduction of expensive TAC dosages. However, repeated monitoring of TAC levels is necessary to prevent adverse reactions.

In conclusion, physicians should consider treatment with EM and TAC when conventional immunomodulatory treatments show limited effectiveness in primary SjS-related ITP.

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