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Treatment of Secondary Immune Thrombocytopenia with Tacrolimus

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Abstract

Immune thrombocytopenia is an acquired thrombocytopenia caused by antiplatelet autoantibodies. Corticosteroids is used as first-line therapy. In the cases of refractory with corticosteroids, splenectomy, rituximab and thrombopoietin receptor agonists are tried as second-line treatments. However, there are some concerns such as serious infections, thrombosis or bone marrow fibrosis although these treatments have high efficacy rate. We herein described three cases of secondary immune thrombocytopenia with treated with tacrolimus with a brief review of literature. Tacrolimus may have therapeutic potential for secondary immune thrombocytopenia, particularly in patients with low complement levels and/or non-responders to *H. pylori* eradication therapy.

Keywords: Immune thrombocytopenia; Tacrolimus; *Helicobacter pylori*; Sjogren's syndrome; Systemic lupus erythematosus

Introduction

Immune thrombocytopenia (ITP, also called idiopathic thrombocytopenic purpura, immune thrombocytopenic purpura) is an acquired thrombocytopenia caused by autoantibodies against platelet antigens [1-3]. The pathogenesis of ITP has not been completely elucidated. Reduced platelet lifespan due to antibodies and/or complement-mediated destruction, as well as impaired platelet production due to humoral and cellular autoimmunity directed at megakaryocytes, have been described [4-8]. Malignant neoplasms, infections, hematologic diseases, and autoimmune diseases may be major causative events. However, these factors alone may be insufficient to induce the onset of ITP and additional triggers such as immune tolerance failure may be required for antibody production. Infection of *Helicobacter pylori*, HIV, hepatitis C virus (HCV), cytomegalovirus (CMV), and varicella zoster virus (VZV) may cause secondary ITP [9-12].

In autoimmune diseases, systemic lupus erythematosus (SLE) and antiphospholipid syndrome account for a large proportion of secondary ITP cases [9]. Immune thrombocytopenia in Sjögren's syndrome (SS) is relatively rare [9] and thrombocytopenia and/or ITP is found in 3.7–12.0% of SS [13-15].

In regard to the treatment of ITP, corticosteroids is used as first-line therapy. In the cases of refractory with these drugs, splenectomy, rituximab and thrombopoietin receptor agonists are tried as second-line treatments [16]. However, there are some concerns although these treatments have high efficacy rate. Splenectomy may cause serious infections, especially such as Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae. Thrombopoietin receptor agonists need for long-term administration may cause thrombosis or bone marrow fibrosis. Rituximab may cause severe infusion reaction or reactivation of HBV or JC virus resulting in progressive multifocal leukoencephalopathy. In the cases of the patients who did not respond with second-line treatments or is contraindicated with second-line treatments, several agents such azathioprine, cyclosporine, cyclophosphamide, diaminodiphenyl sulfone and danazol are used as third-line treatments [16]. However, there are no large-scale studies or RCT and the efficacy of these agents have yet to be identified. Interestingly, tacrolimus is not involved in third-line treatments. We herein describe three cases of secondary immune thrombocytopenia with treated with tacrolimus with a brief review of literature.

Case Presentation

Case 1: A 62-year-old woman visited our hospital with a 1-week history of anorexia, discomfort in the epigastric region, and general fatigue. Severe thrombocytopenia (platelets: $1.8\times10^4/\mu L$) was observed. She showed cervical lymphadenopathy and purpura of the lower extremities. No oral ulcer, arthritis, muscle weakness, headache, digital ulcers, or Raynaud's phenomenon was present. She had no family history of thrombocytopenia or autoimmune diseases. She was diagnosed with cervical cancer and underwent a hysterectomy at 32 years. She had no comorbidity and was not taking any medication. Initial blood analysis showed thrombocytepenia (platelets, $1.8\times10^4/\mu L$). PA-IgG was 2290 ng/10^7 cells and *H. pylori* antibody was positive (65 IU/L). Blood test results were summarized in table 1. In bone marrow examination, numbers of megakaryocytes were increased. Abdominal computed tomography showed enlarged lymph nodes in the periportal and lesser curvature regions. Upper gastrointestinal fiberscopy revealed active gastritis and *H. pylori* was detected in the biopsy specimen. Therefore, antibiotic therapy (amoxicillin and clarithromycin) with a proton pump inhibitor was started. However, these therapies were ineffective, even after 4 weeks of treatment. Extensive screening for the underlying disease of thrombocytopenia was performed. Blood analysis showed positive anti-nuclear antibody and low complement. Anti-Sm antibody, anti-RNP antibody, anti-CLB2GP1 antibody, anti-cardiolipin IgG antibody, and anti-ds-DNA antibody were all negative (Table 1). Urinalysis showed no proteinuria and hematuria. Joint ultrasonography detected no synovitis findings. As she showed low complement and positive anti-ANA antibody levels, we considered the possibility of ITP with SLE. However, the patient did not fulfill any criteria for SLE [17-20]. IVIG therapy was performed with the expectation of a rapid response. However, platelet counts remained low. Thrombopoietin-receptor agonists were not administrated. Further blood analysis was performed. Laboratory testing showed positive anti-SS-A antibody. Anti-SS-B antibody was negative (Table 1). HLA analysis showed A*24:20, A*26:01, B*35:01(Homo), DRB1*15:01, and DRB1*11:01 alleles. Therefore, we considered the possibility of ITP with SS. During the in-depth medical interview, she complained of dry eye and dry mouth. She also showed positive results on Schirmer's test and fluorescein staining test. The patient fulfilled the 1999 revised criteria of the Japanese Ministry of Health, Labour, and Welfare for SS [21].

Taken together, the patient was diagnosed with *H. pylori*-associated immune thrombocytopenia in SS. The patient was treated with oral prednisolone [50 mg/day (1.0 mg/kg)]. Her general fatigue and cervical lymphadenopathy disappeared 1 week after the initiation of prednisolone therapy. Platelet counts gradually increased (day 7: 5.1×10^4/μL, day 14: 7.8×10^4/μL, and day 21: 9.6×10^4/μL). However, platelet count reached a plateau around 10×10^4/μL.

Therefore, the prednisolone was subsequently tapered and tacrolimus was added. Thereafter, platelet counts and C4 levels gradually increased. In regard to safety, the patient had no opportunistic infection, diabetes mellitus, increased serum creatinine, mental status changes during the observation period. Her clinical course is shown in Figure 1.

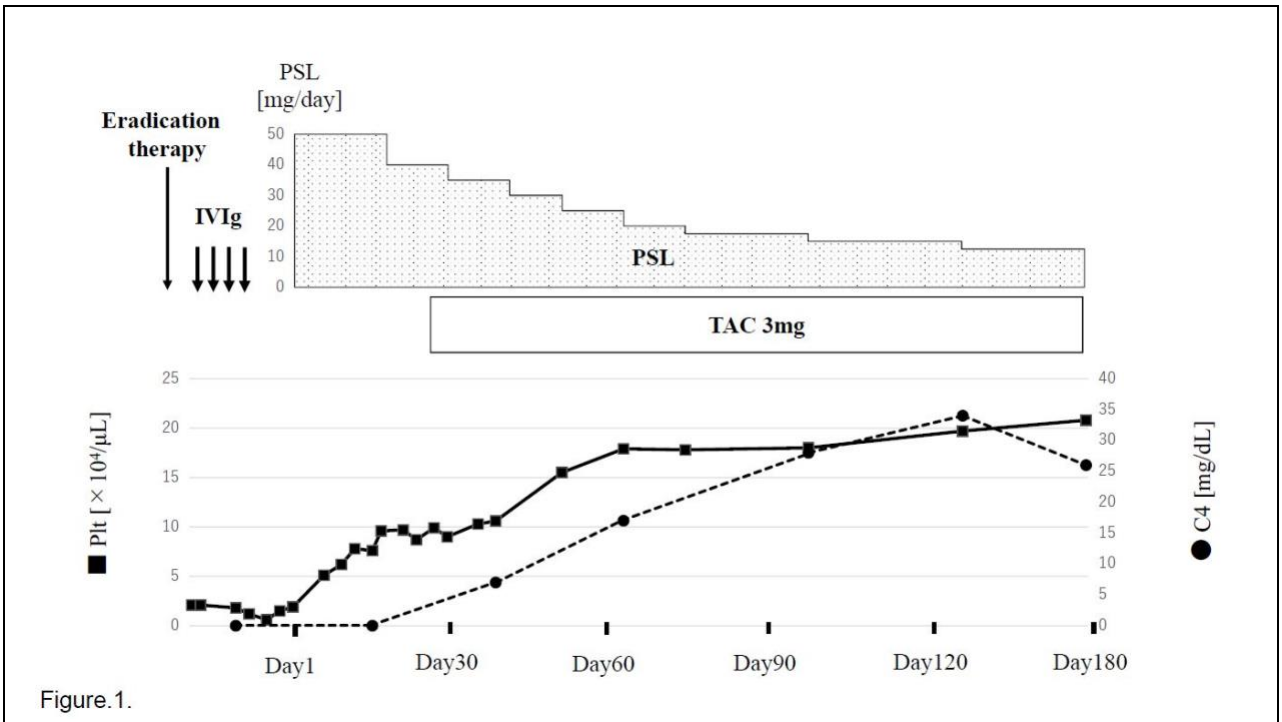

Figure 1: Clinical course of case 1.

Platelet counts reached a plateau around 10×10^4/μL even 1 month after the initiation of steroids. Platelet counts increased 2 weeks after the tacrolimus was added.

Case 2: A 33-year-old woman visited our hospital with a 1-week history of purpura of the lower extremities and oral bleeding. Severe thrombocytopenia (platelets, 0.4×10^4/μL) was observed. No oral ulcer, arthritis, muscle weakness, headache, digital ulcers, or Raynaud's phenomenon was present. She had no family history of thrombocytopenia or autoimmune diseases. She had no comorbidity and was not taking any medication. She was diagnosed with idiopathic ITP at 23 years. She was treated with IVIG and corticosteroids and achieved remission. However, during corticosteroid tapering, she had recurrence. Therefore, splenectomy was performed at 25 years. Platelet counts were finally within the normal range without treatment by 33 years. On this admission, PA-IgG was 1290 ng/10^7 cells and *H. pylori* antibody was positive (22 IU/L). Blood test results were summarized in Table 1. IVIG and eradication therapy for *H. pylori* were initiated with partial response. Thrombopoietin-receptor agonists were not administrated. As platelet recovery was not as prompt as observed for case 1, underlying disease screening was performed. Extensive blood analysis showed positve anti-SS-A antibody and low complement. Anti-Sm antibody, anti-RNP antibody, anti-CLB2GP1 antibody, and anti-ds-DNA antibody were all negative (Table 1).

Urinalysis showed no proteinuria and hematuria. As she did not complain of dry eye and dry mouth, the patient did not fulfill the 1999 revised criteria of the Japanese Ministry of Health, Labour, and Welfare for SS [21] at that time. Taken together, the patient was diagnosed with immune thrombocytopenia in *Helicobacter pylori* infection with positive SS-A antibody. The patient was subsequently treated with oral prednisolone [30 mg/day (0.6 mg/kg)]. Platelet counts gradually increased (day 7: 5.0×10^4/μL, day 45: 17.5×10^4/μL). However, when the prednisolone was tapered to 20 mg/day, platelet counts decreased to 2.0×10^4/μL. Therefore, the prednisolone was increased to 30 mg/day and tacrolimus was added. Thereafter, platelet counts and C4 levels gradually increased. Although the prednisolone was tapered to 15 mg/day, platelet counts maintained around 30×10^4/μl. In regard to safety, the patient had no opportunistic infection, diabetes mellitus, increased serum creatinine, mental status changes during the observation period. Her clinical course is shown in Figure 2.

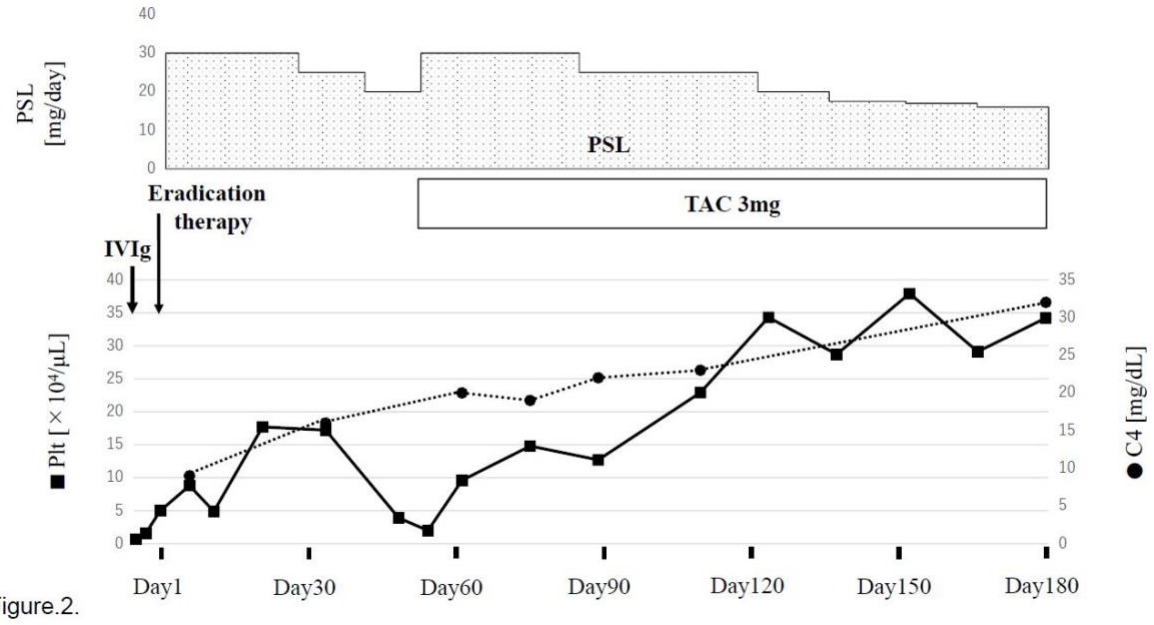

Figure 2: Clinical course of case 2.

Relapsed thrombocytopenia recovered 2 weeks after the tacrolimus was added. Note that platelet counts maintained around 30×10^4/μl although the prednisolone was tapered to 15 mg/day.

Case 3: A 61-year-old woman visited our hospital with a 1-week history of anorexia, fever, and general fatigue. Severe thrombocytopenia (platelets: 2.8×10^4/μL) was observed. She showed cervical lymphadenopathy, purpura of the lower extremities, and arthritis. No oral ulcer, muscle weakness, headache, digital ulcers, or Raynaud's phenomenon was present. She had no family history of thrombocytopenia or autoimmune diseases. She was diagnosed with rheumatoid arthritis at 49 years and she was taking bucillamine and loxoprofen. Initial blood analysis showed leukocytopenia (white blood cell counts, 1800/μL) and thrombocytopenia (platelets, 2.8×10^4/μL). PA-IgG was 222 ng/10^7 cells and *H. pylori* antibody was negative. Blood test results were summarized in Table 1. In bone marrow examination, numbers of megakaryocytes were increased. Abdominal computed tomography showed enlarged lymph nodes in cervical, mediastinum and abdominal para-aortic region. Extensive screening for the underlying disease of thrombocytopenia was performed.

Blood analysis showed positive anti-nuclear antibody and low complement. Anti-ds-DNA antibody was positive. Anti-Sm antibody, anti-RNP antibody, anti-CLB2GP1 antibody, anti-SS-A antibody and anti-cardiolipin IgG antibody were all negative (Table 1). Urinalysis showed no proteinuria and hematuria. Joint ultrasonography detected synovitis findings in wrist and finger joints. The patient fulfilled criteria for SLE [17-20]. Taken together, the patient was diagnosed with immune thrombocytopenia in SLE. Steroid pulse therapy was performed with the expectation of a rapid response. Her general fatigue and cervical lymphadenopathy disappeared 1 week after the initiation of steroid pulse therapy. However, platelet counts remained low. The effect of steroid was limited. Then, the patient was treated with oral prednisolone [45 mg/day (0.8 mg/kg)] and tacrolimus. Thrombopoietin-receptor agonists were not administrated. Platelet counts gradually increased (day 25: $6.9\times10^4/\mu L$, and day 45: $12.4\times10^4/\mu L$). In regard to safety, the patient had no opportunistic infection, diabetes mellitus, increased serum creatinine, mental status changes during the observation period. Her clinical course is shown in Figure 3.

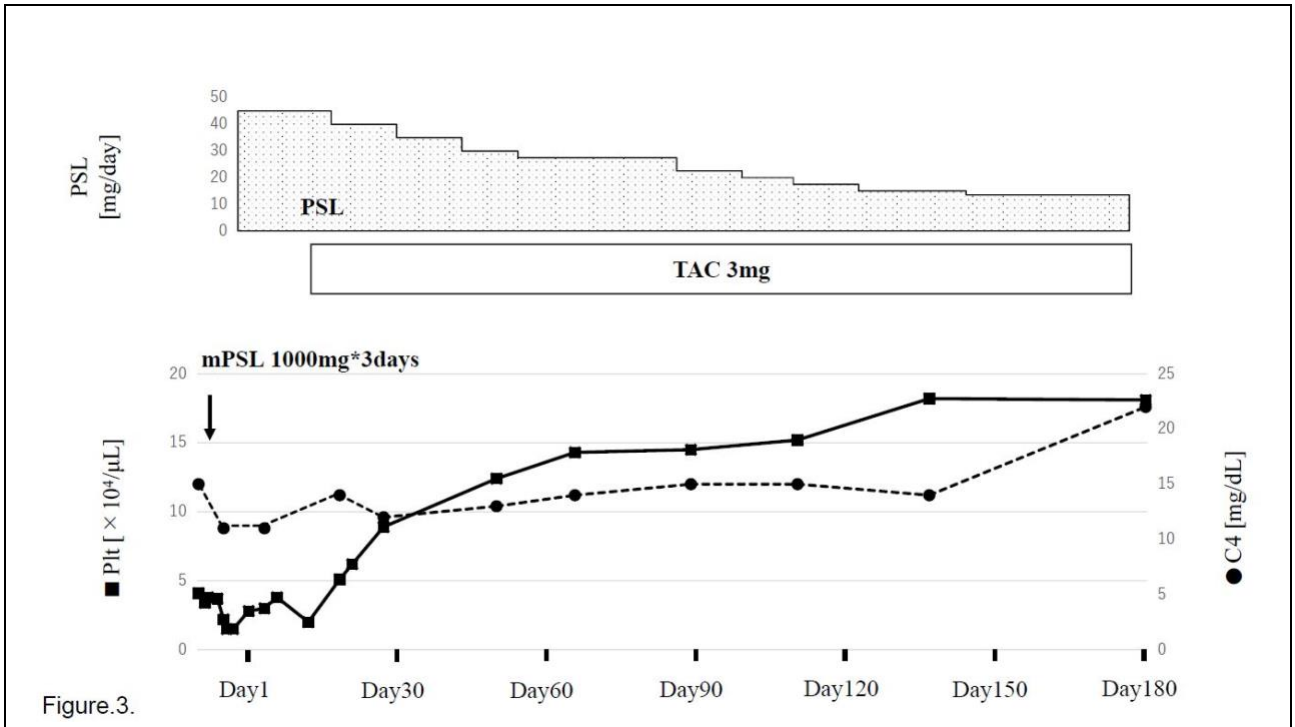

Figure 3: Clinical course of case 3.

Platelet counts remained low after the initiation of steroid pulse therapy. Platelet counts increased 2 weeks after the tacrolimus was added.

Table 1: Summary of blood test results.

	Case 1	**Case 2**	**Case 3**
Initial analysis			
White blood cell count, /μL	3700	5900	1800
Neutrophil, %	75.1	50.6	67.9
Neutrophil count, /μL	2790	3000	1230
Lymphocyte, %	16.9	37.4	29.8
Lymphocyte count, /μL	630	2220	540
Monocyte, %	3.2	8.8	1.7
Monocyte count, /μL	120	520	30
Eosinophil, %	4.3	2.2	0.0
Eosinophil count, /μL	160	130	0
Basophil, %	0.5	1.0	0.6
Basophil count, /μL	20	60	10
Hemoglobin, g/dL	11.3	13.7	11.8
Platelet count, $\times 10^4/\mu L$	1.8	0.4	2.8
AST, IU/L	147	16	57
ALT, IU/L	217	8	11
GTP, IU/L	149	14	22
LDH, IU/L	225	160	607
CRP, mg/dL	1.63	0.02	2.36
PA-IgG, cells (<46 ng/10^7 cells)	2290	1290	222
Anti-*H. pylori* antibody	positive	positive	negative
Extensive analysis			
Anti-nuclear antibody (<1:40)	1:640	<40	1:1280
RF, IU/mL (<5 IU/mL)	333	25	<10
CH50, U/mL (25-48 U/mL)	12	15	<21
C3, mg/dL (86–160 mg/dL)	41	89	41
C4, mg/dL (17–45 mg/dL)	<1	9	15
Anti-Sm antibody	negative	negative	negative
Anti-RNP antibody	negative	negative	negative
Anti-CLB2GP1 antibody	negative	negative	negative
Anti-ds-DNA antibody, IU/mL	<12	<12	334
Anti-SS-A antibody, U/mL	124	15.9	<7.0

Discussion

Is tacrolimus really effective?

We herein described three cases of immune thrombocytopenia with treated with tacrolimus in detail. However, our cases are only three. Is tacrolimus really effective? We searched PubMed and the Web of Science for articles describing the effect of tacrolimus on immune thrombocytopenia. The search terms of this search were “tacrolimus” and “thrombocytopeneia”, with no time limits. We reviewed the articles of the relevant studies and retrieved the appropriate articles. The search produced 273 hits, of which 5 were articles related to the effect of tacrolimus on immune thrombocytopenia. Two of 5 were retrospective studies [22,23]. Two of 5 were a single case report [24,25]. One was article in mouse model [26]. Most of articles were related to thrombotic thrombocytopenia and these were excluded.

Indeed, Du et al. reported 66 cases with relapsed/refractory autoimmune thrombocytopenia successfully treated with tacrolimus although underlying diseases were not described [22]. The complete response rate was 30.3%. The overall response rate was 63.6%. Li et al. reported 20 SLE cases with relapsed/refractory autoimmune thrombocytopenia successfully treated with tacrolimus [23]. Three patients (15%) did not respond, three patients (15%) achieved a complete response and the other 14 patients (75%) achieved a partial response. Thus, tacrolimus may have therapeutic potential for immune thrombocytopenia. However, these cases and our 3 cases have an enormously heterogeneous background and are difficult to be compared. Therefore, evaluating the efficacy of tacrolimus is limited, particularly with a retrospective design.

Thrombocytopeneia in autoimmune diseases

ITP is caused by increased platelet destruction and/or decreased platelet production. Some cases of ITP are associated with a preceding viral or bacterial infection. Antibodies against viral or bacterial antigens may cross-react with normal platelet antigens (molecular mimicry). In *H. pylori*-associated ITP, molecular mimicry between *H. pylori* CagA and platelet-surface antigens [27, 28] and inhibition of the immunosuppressive FcγRIIB signals [29-33] are thought to be key roles in initiating antiplatelet autoantibody production. However, *H. pylori* infection alone is insufficient to induce the onset of ITP. Additional factors such as immune tolerance failure are required for the antiplatelet autoimmune response [33]. In SS and SLE, autoreactive B cell stimulation and autoantibody production are increased [34,35]. In respect to genetics, DRB1*15:01 alleles are strongly associated with autoantibody production in SS [36-38]. Interestingly, HLA typing revealed that the first case has A*24:20, A*26:01, B*35:01(homozygous), DRB1*11:01, and DRB1*15:01 alleles. Therefore, the patient may have some underlying genetic factors. Additionally, the expression of immunosuppressive FcγIIB on B cells is significantly decreased in SS and SLE with thrombocytopenia [39, 40]. Thus, alterations in immune homeostasis in both SS/SLE and *H. pylori* infection may synergistically promote the development of self-reactive antibodies. Interestingly, Samuelsson et al. demonstrated that IVIG requires the presence of FcγRIIB to prevent antibody-induced thrombocytopenia in a murine model of ITP [32]. In our cases, IVIG as initial treatment was not effective for platelet recovery. Suppression of antibody production may have been inadequate due to low FcγRIIB on B cells.

As abovementioned, autoantibody production plays an important role in the pathogenesis of ITP. Platelet autoantibodies may contribute to peripheral platelet destruction by Fc-mediated platelet clearance by the reticuloendothelial system, primarily in the spleen but also in the liver and bone marrow. Moreover, autoantibodies may have direct effects on platelets through complement activation or apoptosis. One study showed that PA-IgG is 252.3 ± 79.1 ng/10^7 cells even in non-responding *H. pylori*-associated ITP and another study showed that acute ITP patients had PA-IgG levels ranging from 55.8 to 562 ng/10^7 cells [28, 41]. In our two cases, PA-IgG levels were extremely elevated (PA-IgG: 2260 ng/10^7 cells and 1260 ng/10^7 cells). Alterations in immune homeostasis in both autoimmune diseases and *H. pylori* infection may cooperatively promote PA-IgG production.

Although the role of complement and complement receptors in the pathogenesis of ITP has yet to be defined, some studies demonstrated that platelet associated complement is increased in ITP [42]. Additionally, enhanced complement activation capacity is found in the plasma with ITP, which is associated with thrombocytopenia [43]. Furthermore, Cheloff et al. demonstrated that complement levels are reduced in one-third of patients with ITP and are associated with more severe disease [44]. Serum C4 levels were initially undetected or low in our cases. Most C4 molecules may have been bound to platelets in these patients.

Conclusion

We described three cases of secondary immune thrombocytopenia with treated with tacrolimus. As there are no large-scale studies or RCT and the efficacy of tacrolimus have yet to be identified, our report would justify clinical investigations of this drug for secondary immune thrombocytopenia.

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