

# CASE REPORTS OF IDIOPATHIC THROMBOCYTOPENIA UNRESPONSIVE TO FIRST-LINE THERAPIES TREATED WITH TRADITIONAL HERBAL MEDICINES BASED ON SYNDROME DIFFERENTIATION

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The objective of our study is to present two cases showing the effects of traditional Korean herbal medicines based on traditional Korean medicine (TKM) for the treatment of immune thrombocytopenic purpura (ITP). One patient showed no response to treatment with steroids and an immunosuppressive agent. Moreover, liver toxicity and side effects of steroids were evident. However, after he ceased conventional treatment and started to take an herbal medicine, his liver function normalized and the steroid side effects resolved. Ultimately, he achieved complete remission. Another patient with ITP had sustained remission after steroid therapy in childhood, but extensive uterine bleeding and thrombocytopenia recurred when she was 16 years old. She was managed with steroids again for 2 years, but severe side effects occurred, and eventually she ceased taking steroids. She refused a

splenectomy, and was then treated with a herbal medicine for 7 months, ultimately leading to sustained remission again. Many patients with resistance to first-line treatments tend to be reluctant to undergo a splenectomy, considered a standard second-line treatment. In conclusion, herbal medicines, based on TKM, may offer alternative treatments for persistent or chronic ITP that is resistant to existing first-line treatments.

**Keywords:** idiopathic thrombocytopenic purpura, traditional Korean medicine, syndrome differentiation, herbal medicine

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## INTRODUCTION

Primary idiopathic thrombocytopenic purpura (ITP) or primary immune thrombocytopenia, is characterized by platelet destruction (to  $<100 \times 10^9/L$ ) in the absence of other causes or disorders that may be associated with thrombocytopenia. The main clinical challenge of primary ITP lies in the increased risk of bleeding, although bleeding symptoms, including epistaxis, petechiae, bruising, and purpura, are not always present.<sup>1</sup>

The primary first-line treatment of ITP is corticosteroids and intravenous immunoglobulin (IVIG) or anti-D globulin (anti-D). Corticosteroids are usually the first choice, and IVIG or anti-D is used as first-line treatment for patients for whom steroids are contraindicated. If first-line therapies fail, splenectomy, rituximab, immunosuppressive agents (e.g., cyclophosphamide and azathioprine), and thrombopoietin-receptor agonists (e.g., romiplostim and eltrombopag) may be considered as second-line treatments.<sup>2,3</sup>

Splenectomy has also been regarded as a standard second-line treatment in the management of patients who are refractory to first-line treatments. Other second-line therapies are considered after the failure of splenectomy, but they are expensive and have various side effects.<sup>3</sup> However, many patients are reluctant to undergo a splenectomy because of the unpredictability of the response,<sup>4</sup> its invasiveness,<sup>5</sup> and possible complications.<sup>6,7</sup> Thus, many patients tend to postpone or avoid a splenectomy when possible.<sup>8</sup>

Between adults and children with ITP, there are several clinical differences. In the case of adult ITP treatment, the spontaneous remission rate is lower, corticosteroids are used more frequently, and splenectomy is more often considered.<sup>9</sup>

Syndrome differentiation is not only a typical traditional Korean medical diagnostic system but also a key concept in the practice of traditional Korean medicine (TKM). According

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to the syndrome differentiation diagnostic system, a disease can be categorized into any of several different patterns based on the analysis of clinical information obtained from the following four major traditional diagnostic procedures: observation, listening, questioning, and pulse analyses. These patterns are also used in traditional medical treatments, including the prescription of herbal medicine and acupuncture.<sup>10–12</sup>

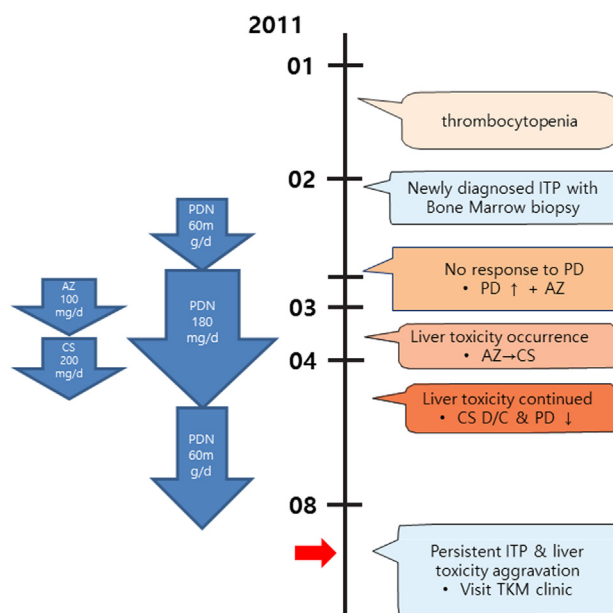
There have been some reports demonstrating the efficacy of herbal medicine instead of first-line treatments for ITP,<sup>13,14</sup> and there was one report of treatment of childhood persistent ITP with herbal medicine.<sup>15</sup> However, there has been no report demonstrating the effectiveness of herbal medicine in treating adult persistent or chronic ITP patients who were unresponsive to standard first-line therapies, based on the syndrome differentiation diagnostic system.

Thus, in this article, we present two ITP patients, both of whom were unresponsive to the first-line treatment or discontinued conventional treatment due to the side effects of steroids. Nonetheless, they achieved complete or partial remission by taking herbal medicines based on syndrome differentiation without requiring a splenectomy.

### CASE 1

A 25-year-old male patient, a Korean student who resided in the Philippines, visited a local hospital with high fever ( $>40^{\circ}\text{C}$ ) and a decreased platelet count ( $<100 \times 10^9/\text{L}$ ) in January 2011, and was treated for dengue fever. The fever became stable after 1 week, but the thrombocytopenia persisted. A bone marrow biopsy showed moderate megakaryocytic hyperplasia, and treatment with oral prednisone 60 mg/d was started for newly diagnosed ITP on February 4. However, the patient was unresponsive to the treatment, and azathioprine 100 mg/d and prednisone 180 mg/d were administered orally on February 18. Subsequently, the patient started to suffer from side effects of the steroid, including weight gain and swelling, and liver toxicity was detected in a biochemical analysis on March 22. The azathioprine was replaced by cyclosporine 200 mg/d due to the liver toxicity. On April 26, because of persistent liver toxicity, the immunosuppressive drug—cyclosporine was stopped, and prednisone was reduced to 60 mg/d. However, the platelet count still did not increase. Moreover, the patient could not walk properly due to vertebral pain, weight gain, and peripheral edema in both legs. The patient eventually came to Korea and visited our clinic in a wheelchair on August 5 (Fig. 1).

On physical examination, the patient was unable to walk due to severe back pain and peripheral edema and had a cutaneous wound on his ankle that was not healing well. He was suffering from side effects of the steroid: moon face, edema, weight gain, muscle weakness, and pain in the back and knees. An erythematous facial complexion and dark red-colored tiny petechiae were observed around his trunk and neck. The patient also reported fatigue, mild irritability, insomnia, thirst, and yellow urine. A taut, rapid, and weak pulse was found on pulse examination. A dark red and dry tongue was observed. However, he had no bleeding symptoms, and no splenomegaly. Laboratory analyses showed a



**Fig. 1.** Timeline of interventions and outcomes in case 1. PDN, prednisone; AZ, azathioprine; CS, cyclosporine; TKM, traditional Korean medicine, red arrow: TKM clinic visit day.

platelet count of  $49 \times 10^9/\text{L}$  and aspartate aminotransferase (AST)/alanine transaminase (ALT) of 211/230 UI/L. The patient was taking oral prednisone 60 mg/d, calcium carbonate 40 mg/d, furocemide 40 mg/d, and celecoxib 400 mg/d.

The patient was administered modified *jigolpium* water extract orally (Table 1) three times per day under a diagnosis of persistent ITP, and furocemide was stopped. After three weeks, his platelet count increased to  $126 \times 10^9/\text{L}$ , and the AST/ALT ratio decreased to 130/150 UI/L. The prednisone was tapered down to 30 mg/d. However, the platelet count then fell to  $49 \times 10^9/\text{L}$  because of the reduced steroid dose. Thus, the herbal medicine was changed to a modified *seongyutang* with *Salviae miltiorrhizae radix* and *Scutellariae radix* water extract (Table 2). Subsequently, the platelet count increased again, and the AST/ALT ratio decreased gradually. After three months, the steroid was discontinued. After four months, the platelet counts and AST/ALT ratio were  $232 \times 10^9/\text{L}$  and 54/62 IU/L, respectively, the cutaneous wound had healed, and the general condition of the patient had improved. Thus, the dose of the herbal medicine was tapered to two-thirds the previous dose. After five months, the platelet counts and AST/ALT ratio were  $184 \times 10^9/\text{L}$  and 41/47 IU/L, respectively, indicating a complete response; however, the platelet count was maintained at  $>100 \times 10^9/\text{L}$ .<sup>3</sup> Given the patient's recovery, the herbal medicine was discontinued on January 7, 2012. Even with no medication, there was no bleeding sign, and the platelet count was still  $>150 \times 10^9/\text{L}$  on May 15, 2014 (Fig. 2).

### CASE 2

This 20-year-old female patient suffered from a common cold when she was eight years old. A local pediatric doctor administered a cutaneous intermuscular injection of

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