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# Intravenous Immune Globulin (IVIG) Therapy After Unsuccessful Treatment with Corticosteroid and Cyclosporine A in Pfeifer-Weber-Christian Disease: A Case Report

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
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**Conflict of interest:** None declared

**Patient:** Female, 35-year-old  
**Final Diagnosis:** Weber-Christian Disease  
**Symptoms:** Breast mass • fever • malaise • pain  
**Medication:** —  
**Clinical Procedure:** Biopsy • CT scan  
**Specialty:** Allergology • Rheumatology

**Objective:** Rare disease

**Background:** Pfeifer-Weber-Christian disease (PWCD), also referred to as idiopathic nodular panniculitis, is a rare idiopathic disease characterized by lobular panniculitis of adipose tissue with systemic symptoms and multiple organ involvement and is usually treated with corticosteroids and cyclosporine A. We report a case of PWCD that was unresponsive to standard treatment but responded to intravenous immune globulin (IVIG) therapy.

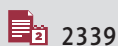
**Case Report:** A 35-year-old Korean woman presented with fever, malaise, myalgia, and painful nodules in the left breast. Histology of the breast nodules showed lobular panniculitis consistent with PWCD. She did not respond to corticosteroid and cyclosporine A. She was effectively treated with intravenous immune globulin (IVIG). IVIG therapy began with 60 g (1 g/kg) 4 times per week, 2 times every other week. Subsequently, the IVIG dose was reduced for maintenance therapy to 25 g (400 mg/kg) twice every other week and monthly. The patient showed immediate and dramatic improvement. General signs and symptoms, such as fever, malaise, and myalgia, were absent, and the masses had nearly subsided, with several very small hard nodules remaining for 3 months until the time of this report.

**Conclusions:** IVIG was an effective immunomodulatory therapeutic for PWCD in this case. This report shows that PWCD is a rare condition that is difficult to diagnose, but the histopathology of nodular panniculitis supports the diagnosis. In cases that do not respond to standard immunosuppressive therapy, including corticosteroids and cyclosporine A, IVIG therapy may lead to a favorable response with rapid symptomatic relief.

**MeSH Keywords:** Immunoglobulins, Intravenous • Immunotherapy • Lymphoma, Large B-Cell, Diffuse • Panniculitis, Nodular Nonsuppurative

**Abbreviations:** PWCD – Pfeifer-Weber-Christian disease; IVIG – intravenous immune globulin

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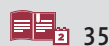
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## Background

Pfeifer-Weber-Christian disease (PWCD) was first described by Pfeifer in 1892 [1]. The syndrome became known as PWCD with a description of the disease entity further detailed as relapsing and nonsuppurative panniculitis by Weber in 1925 [2] and the addition of its febrile character by Christian in 1928 [3]. The symptom complex includes fever, systemic inflammation, and lobular panniculitis of relapsing character [4]. The characteristic presentation of PWCD is a recurrent fever associated with the appearance of nodule(s) and of further lesions and even visceral involvement [5]. Because its etiology is unknown, PWCD is described as idiopathic lobular panniculitis [6].

Although no uniformly effective therapy for PWCD is known, the standard treatment involves corticosteroids [7] and immunosuppressive agents, such as cyclosporin A [8] and corticosteroids, which have been reported to cause dramatic improvement [7]. Alternative therapeutics, including mycophenolate mofetil, were reported to be effective [9]. Recently, a combination therapy of corticosteroids with mofetil mycophenolate was reported to be effective in a PWCD case of visceral involvement. This report describes a case of PWCD in a 35-year-old Korean woman who was unresponsive to standard treatment but responded to intravenous immune globulin (IVIg) therapy.

## Case Report

A 35-year-old Korean woman presented with fever, malaise, myalgia, and painful nodules in the left breast in the Department of Allergy and Clinical Immunology at Cheju Halla General Hospital (Jeju, Jeju Special Self-Governing Province, Korea). She was transferred from another hospital due to allergic rhinitis and atopic dermatitis with high serum total IgE. She had a 20-year history of allergic rhinitis and atopic dermatitis. The patient had rhinorrhea, sneezing, tearing, and eczematous lesions on her whole body, and Histobulin™ therapy was initiated.

She was diagnosed with an abscess and treated with antibiotics without any improvement in her signs and symptoms. Excision and biopsy were performed on the lesions of the left breast and lymph nodes of the related left axilla. Despite intensive study and clinical study, a clear diagnosis had not been made despite the cyclic aggravation of severe pain and systemic symptoms with growth of the breast masses. With a suspected diagnosis of large diffuse B cell subcutaneous lymphoma, it was recommended that she undergo chemotherapy.

Systemic symptoms included fever, malaise, and myalgia. Several tender masses of variable sizes were palpated on and around the left breast. The masses had been growing and increasing in number with progression of the disease during the

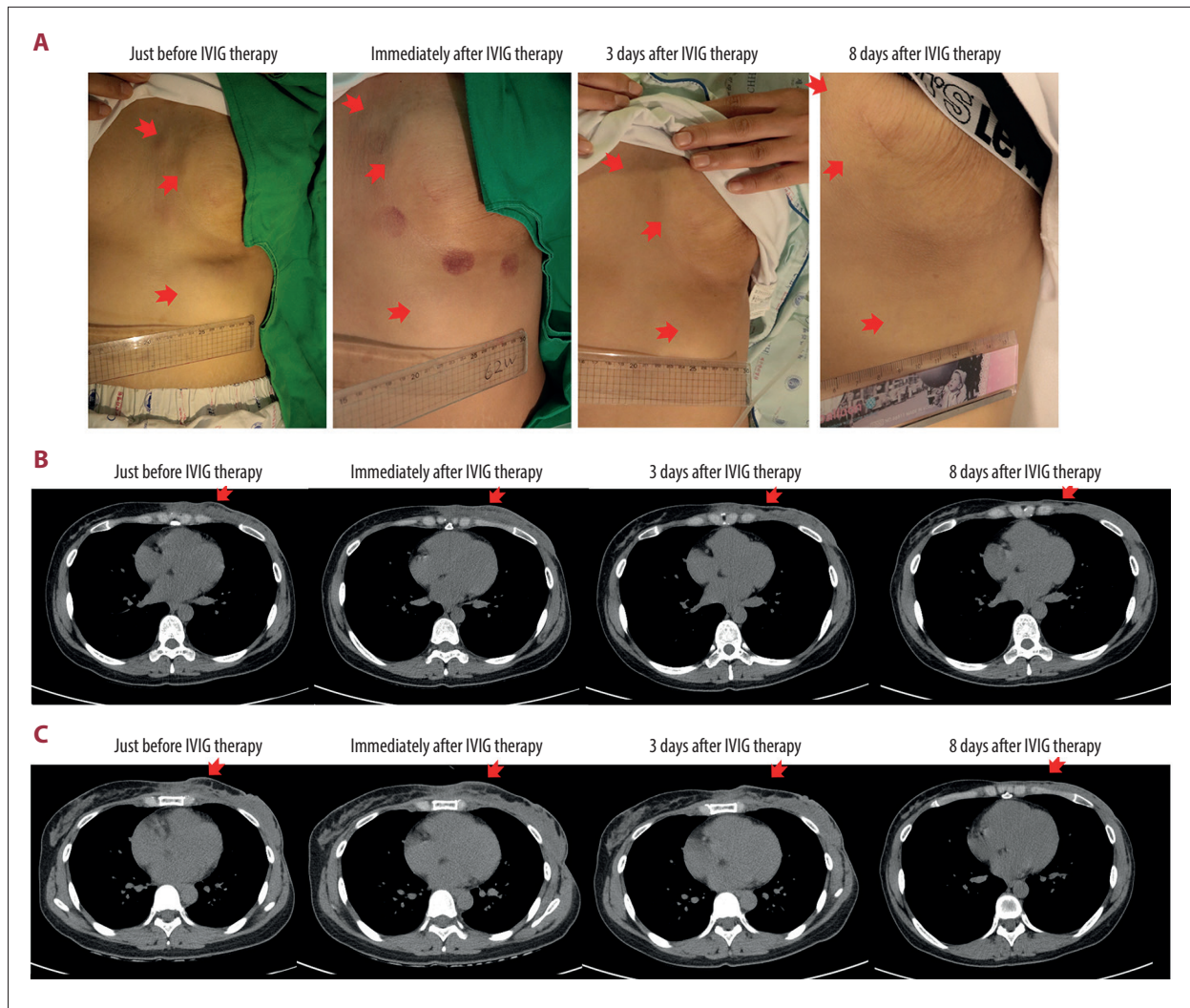
last 3 years. Characteristically, her signs and symptoms began to become aggravated during ovulation, and severe excruciating pain developed on the lesions during menstruation.

In the physical examination, she showed multiple crops of palpable masses on her left anterior chest (**Figure 1A**) without hepatomegaly or splenomegaly. A biopsy revealed angiocentric lymphoid infiltration with necrosis. An initial CT finding in our hospital was diffuse extensive infiltrative lesions involving the left anterior abdominal wall, mainly involving the subcutaneous layer with focal skin thickening, and probable lymphoma infiltrating subcutaneous fat was suggested with a probable diagnosis of cutaneous lymphoma (**Figure 1B, 1C**). In the laboratory findings, the complete blood count was normal. Alanine transaminase, aspartate aminotransferase, alkaline phosphatase, blood urea nitrogen, and creatinine were normal. Tuberculosis screening was negative. The antinuclear antibody was negative. However, rheumatoid factor was positive. There were no signs of other organ involvement in the clinical presentations, physical examination, radiologic findings, or laboratory findings.

Histobulin™ (Green Cross PD, Korea) therapy was started for allergy treatment. During allergic treatment with Histobulin™, the sizes of the masses fortunately began to decrease, and the signs and symptoms began to improve. The final pathologic finding considering the clinical history and presentation was diffuse necrotic panniculitis with multifocal reactive lymphoid hyperplasia (**Figure 2**). All data, including the clinical course, laboratory results and, especially, the pathologic examination, were revised, and the diagnosis was consistent with Pfeifer-Weber-Christian disease (PWCD). Due to the urgency of PWCD treatment, the treatment of allergic disease was stopped and she was referred to a rheumatology expert.

For the treatment of PWCD, colchicine was administered, without improvement. The patient received high-dose steroid therapy. However, she developed hypertension, severe weight gain, and generalized edema, without improvement. Subsequently, she underwent cyclosporine A treatment. However, the mass size increased, and her excruciating pain and general systemic symptoms persisted. She was transferred to the Department of Allergy and Clinical Immunology at Cheju Halla General Hospital for immunotherapy for PWCD. She had a history of brain surgery to investigate an arteriovenous malformation. Her mother had rheumatoid arthritis.

She showed a favorable response to previous Histobulin™ therapy, but new masses developed, and there was no way to control her disease. Considering the effects of Histobulin™, which is therapeutic containing a small amount of immunoglobulin, intravenous immune globulin (IVIg) was considered as a therapy for PWCD. The IVIg therapy was approved by the IRB of Cheju Halla General Hospital (IRB No. 2020-L05-01).

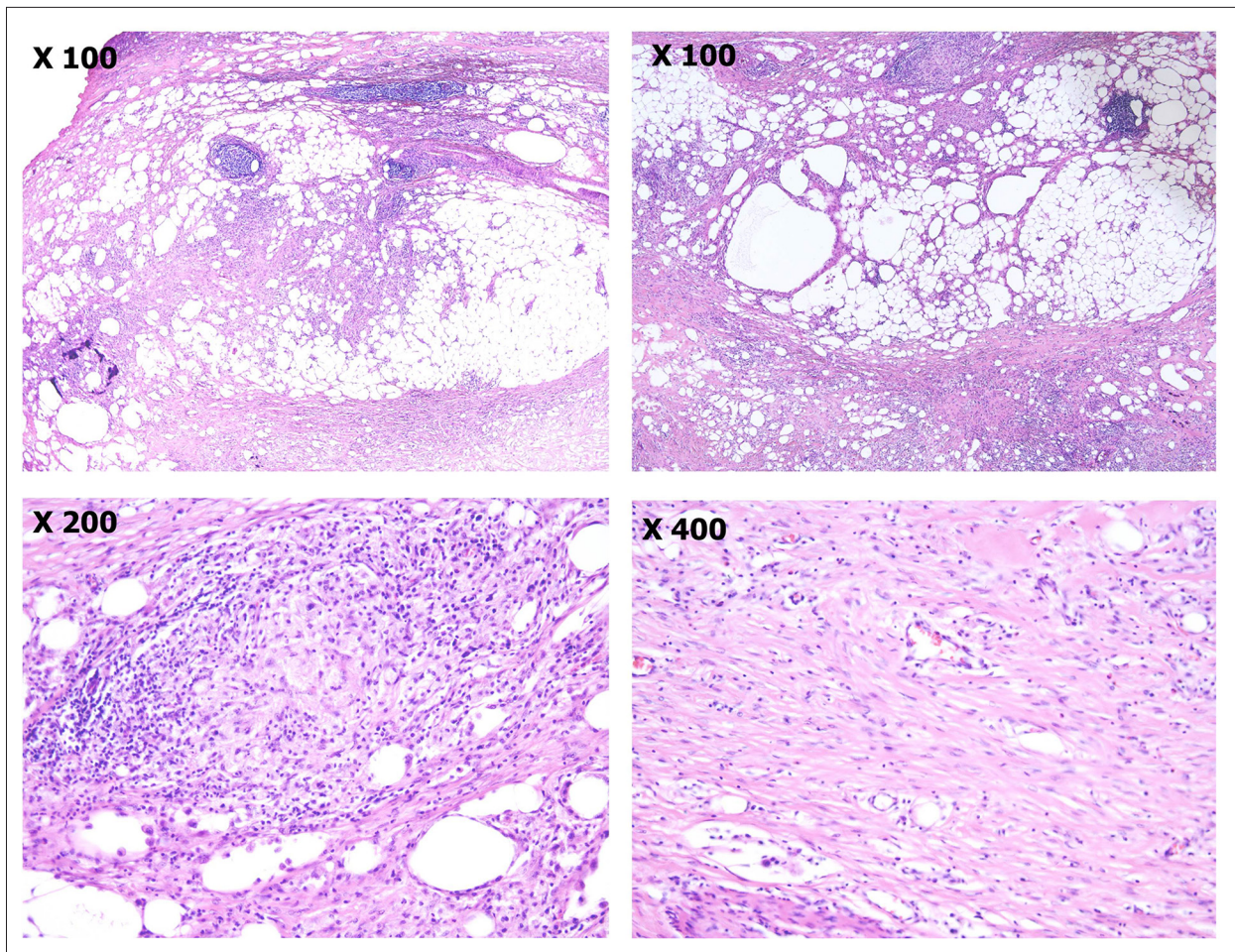


**Figure 1.** Effects of intravenous immunoglobulin (IVIg) therapy in Pfeifer-Weber-Christian disease (PWCD). (A) Change in skin nodules by IVIG therapy. Multiple crops of palpable masses on the left anterior chest decreased in size after IVIG therapy (before, immediately after, 3 days after, and 8 weeks after IVIG therapy). Chest deformities remained. The red arrows indicate masses. (B, C) Changes in computed tomography (CT) scan findings. The initial computed tomography (CT) scan findings were diffuse extensive infiltrative lesions involving the left anterior chest and abdominal wall, mainly involving the subcutaneous layer, with focal skin thickening, and probable lymphoma infiltrating subcutaneous fat was suggested with a probable diagnosis of cutaneous lymphoma as in the previous diagnoses in the other hospitals. On CT scan, the improvement in infiltrative multiple lesions on the left anterior chest began after 3 days. The lesions on the CT scan were much improved 8 weeks after IVIG therapy. Red arrows indicate masses. Figure B is the middle mass, and Figure C is the lower mass in Figure A.

LivGamma (SK plasma, Korea) therapy began with 60 g (1 g/kg) 4 times per week and 2 times every other week (Figure 3). Subsequently, the IVIG dose was reduced for maintenance therapy to 25 g (400 mg/kg) twice every other week and monthly. IVIG (50 mg/ml) was infused at a rate of 1.2 ml/min. She complained of headache twice in the early period of infusion and that was controlled by acetaminophen, and there were no other adverse effects. Before and after IVIG therapy, a chest CT was performed. The patient showed immediate and dramatic improvement in her systemic symptoms, as she felt improvement just 4 hours after the initiation of IVIG therapy,

and the mass size markedly decreased 10 hours after the initiation of IVIG therapy.

Her signs and symptoms recurred within 7 days during 1 month of IVIG therapy. However, after the fourth administration of IVIG, her signs and symptoms did not further develop, leaving a chest deformity at the lesion sites. On chest CT, inflammatory infiltration in the lesion areas began to improve 3 days after the first IVIG administration and markedly improved 12 weeks after the first IVIG administration. Despite the dramatic clinical improvement, there was no remarkable interval change in the



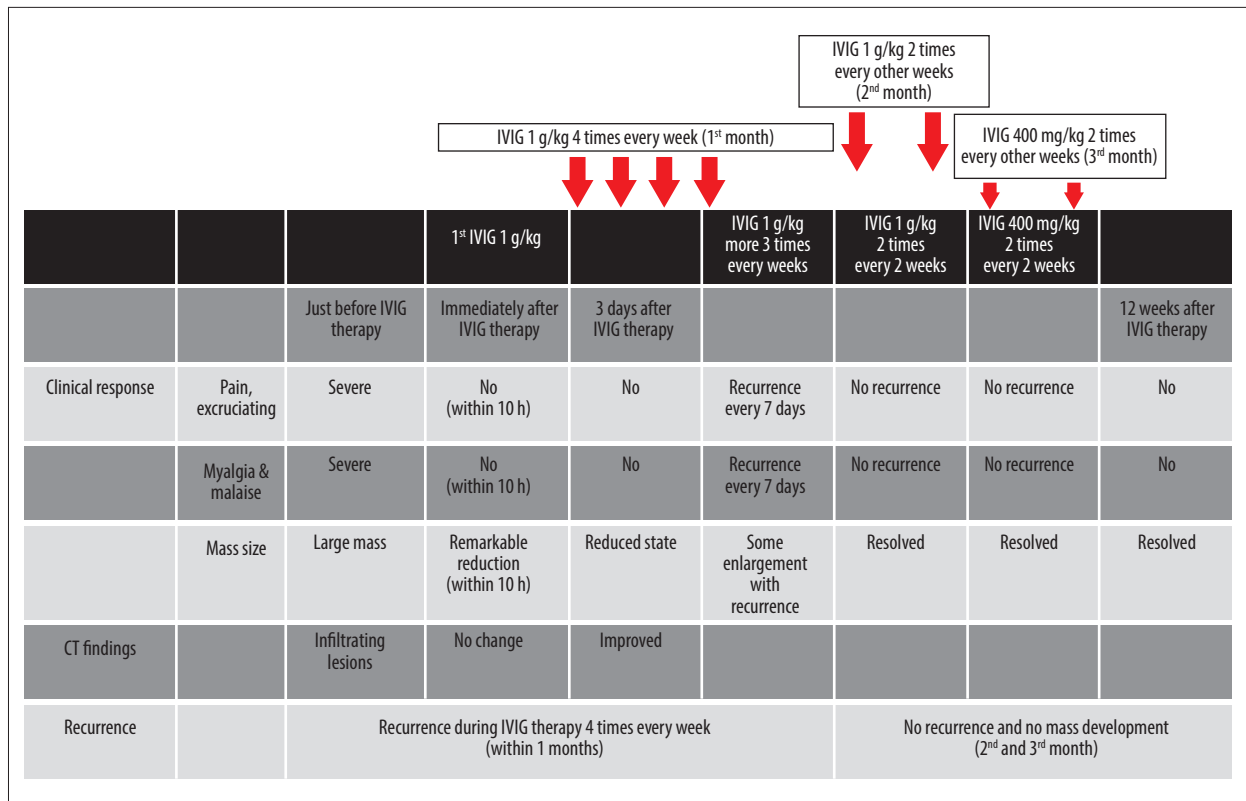
**Figure 2.** Pathologic findings. A biopsy of the left anterior chest mass and lymph nodes in the left axillary area was performed. The biopsy findings showed angiocentric lymphoid infiltration with necrosis. A final pathologic diagnosis considering the clinical history and presentation was diffuse necrotic panniculitis with multifocal reactive lymphoid hyperplasia.

previously noted subcutaneous infiltrative lesion involving the left anterior upper abdominal wall in the follow-up CT immediately after the first IVIG administration. Immediately after the first IVIG administration, mild diffuse edematous changes in the lesion sites were observed. There was no remarkable interval change in the previously noted subcutaneous infiltrative lesion, with some heterogeneous enhancement involving the left anterior wall in the follow-up CD 3 days after IVIG therapy. However, some resolution of the previously noted subcutaneous infiltrative lesion with heterogeneous enhancement involving the left anterior chest wall, especially involving the sternal region, was observed 1 week after the first IVIG administration. In the follow-up CT 2 weeks after the first IVIG administration, there was no remarkable change from the CT 1 week after IVIG therapy. In the follow-up CT 8 weeks after the first IVIG administration, much resolution of the previously noted subcutaneous infiltrating lesion involving the anterior chest wall was observed. There was a difference between the clinical response and the radiologic change on CT.

Clinically, general signs and symptoms, such as fever, malaise and myalgia, were absent, and the masses had nearly subsided, with several very small hard nodules remaining for 3 months until the time of this report. There was no further aggravation of the disease, in particular no development of pain or enlargement of masses based on the menstrual cycle. The patient remained clinically stable for 12 weeks after the fourth IVIG administration (16 weeks after the first IVIG injection).

## Discussion

IVIg was effective in a patient with PWCD who was unresponsive to standard treatment, including corticosteroid and cyclosporine A. A trial of IVIG for PWCD was reported in 1980 [10]. In the report, IVIG was added to basic corticosteroid therapy in 2 children with PWCD. However, the IVIG effects could not be evaluated because the combination of IVIG and the corticosteroids was not described in the report. This study is the



**Figure 3.** IVIG therapy protocol and the progression of the clinical presentations and radiologic findings.

first report concerning IVIG monotherapy in PWCD. Moreover, IVIG responses are rapid and dramatic.

The patient presented to our institution due to severe and long-lasting allergic rhinitis and atopic dermatitis. Histobulin™ therapy is a treatment for allergic rhinitis and was recently reported to be effective in atopic dermatitis [11], and the patient received Histobulin™ therapy. Interestingly, with Histobulin™ therapy, the lesions surprisingly began to decrease in size, and the signs and symptoms, including chills and myalgia, improved. Histobulin™ is a histamine-fixed immunoglobulin preparation that is composed of 0.15 µg of histamine dihydrochloride and 12 mg of IgG [12]. There are no reports that histamine itself is related to the pathogenesis of PWCD. Additionally, it is not suspected that the histamine contained in Histobulin™ possibly improved PWCD. The effects of Histobulin™ were strongly suspected to be due to the small quantity of immunoglobulin contained in Histobulin™. Although the previous response to Histobulin™ therapy was favorable, new lesions developed. Subsequently, high-dose IVIG therapy was considered to confirm the effects because of the clinical urgency of the patient's status and the necessity of rapid clinical improvement.

PWCD is basically an inflammatory disease of unknown etiology. The effects of IVIG are basically anti-inflammatory effects [13]. A steroid-unresponsive patient with PWCD responded

to a nonsteroidal anti-inflammatory drug (NSAID) [14]. The anti-inflammatory effects of IVIG may have worked in this case of PWCD by improving inflammation. The rapid responses of IVIG in this case also support the anti-inflammatory effects of IVIG.

PWCD has been suspected as a disorder of the immune system [15], and immunologic abnormalities have been described [16]. The patient in this case maintained an improved status with IVIG therapy. IVIG also has effects on autoimmune diseases through immunologic mechanisms, including ITP [13]. Considering the remission in this case with the autoimmune aspects of PWCD, IVIG may have effects on the autoimmune pathogenesis of PWCD.

The serum levels of soluble interleukin-2 (IL-2) receptor, interferon gamma, IL-1 beta, IL-6, and tumor necrosis factor alpha were found to be elevated in the active state [17], and a T cell immune response was suspected to be involved in the pathogenesis of PWCD [18]. IVIG decreases these cytokines [19] and downregulates T cell effector responses through regulatory T cells [20]. In some patients with PWCD, elevated levels of circulating immune complexes have been noted [21]. From a report of PWCD with immune complex glomerulonephritis, immune complexes seem to be relevant [22]. IVIG may have effects on immune complex-mediated inflammation [23].

The participation of autoimmune mechanisms in the etiopathogenesis of PWCD is suspected [14]. In a specific form of panniculitis, an unusual antibody to extractable nuclear antigen, and, sometimes, antinuclear antibodies, were present [24]. PWCD is associated with lupus anticoagulant and anticardiolipin antibodies [25]. The patient in this report was rheumatoid factor (+), and her mother had rheumatoid arthritis. IVIG is well known to be effective in treating autoimmune diseases by neutralizing autoantibodies [19].

Safety is the most important issue in medical treatment. PWCD during pregnancy and in neonates [26] has been reported. Therapeutics for PWCD, including immunosuppressive drugs such as high-dose steroids and cyclosporine A, carry a high risk to the mother and fetus during pregnancy. IVIG is safe for use in pregnancy based on conditions such as recurrent spontaneous abortion [27]. PWCD has also developed in newborns [28]. IVIG can be safely used in neonates. The use of safe therapeutics, especially in pregnancy and newborns but also in general patients with PWCD, is highly significant and important.

PWCD is a classic skin condition that features recurring inflammation in the subcutaneous fat layer of the skin [10,29]. The involved skin areas manifest as recurrent crops of erythematous, sometimes tender, edematous, subcutaneous nodules. This case is compatible with the skin type of PWCD as previously described. The lesion distribution of PWCD is reported to be symmetric, and the thighs and lower legs are frequently affected most. However, this case showed unilateral lesions on the breast. This case did not present arthralgia, nausea, vomiting, abdominal pain, weight loss, hepatomegaly, or additional systemic features that may also occur. A case of PWCD with polymorphonuclear leukocyte infiltration in the earliest lesions was reported [30] and this case met the key pathologic finding on microscopy of a nodular inflammatory pattern of fat lobules.

High-dose corticosteroid treatment is the first-choice treatment according to the literature and reports [31]. However, the patient in this case did not show any improvement with corticosteroid treatment and rather showed several severe adverse effects, including hypertension, generalized edema, and severe insomnia. Steroid-resistant PWCD has been reported [7].

The current trend is that the second-choice treatment is cyclosporine A [32], and cyclosporine A was attempted according to a report on successful treatment of steroid-resistant PWCD [33]. However, the patient was substantially aggravated with the use of cyclosporine A. Nodular panniculitis following the sudden withdrawal of corticosteroids was reported as poststeroid nodular panniculitis [34] and poststeroid panniculitis [35]. The aggravation of the patient may have been due to abrupt withdrawal of the high-dose steroid. Considering poststeroid panniculitis, steroids may not be appropriate for the treatment of Pfeifer-Weber-Christian disease (PWCD), as the core disease entity is panniculitis.

Until now, the treatment choices recommended were azathioprine, cyclophosphamide, mycophenolic acid, methotrexate, and infliximab as well as high-dose steroid and cyclosporine A for the standard treatment [5]. IVIG therapy has not been included. IVIG is comparably safe and the clinical responses were rapid and very effective in this case. Further clinical data and basic studies of the mechanisms of action may be necessary.

## Conclusions

IVIG is effective in PWCD. This report has shown that PWCD is a rare condition that is difficult to diagnose, but the histopathology of nodular panniculitis supports the diagnosis. In cases that do not respond to standard immunosuppressive therapy, including corticosteroids and cyclosporine A, IVIG therapy may lead to a favorable response with rapid symptomatic relief. The pathogenesis of PWCD and the relevant mechanisms of action of IVIG need to be further investigated.

## Ethics approval

IVIG therapy in this case was approved by the IRB of Cheju Halla General Hospital (IRB No. 2020-L05-01).

## Conflict of interest

None.

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