Use of infliximab in a patient with pyoderma gangrenosum and rheumatoid arthritis

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Abstract Pyoderma gangrenosum (PG) is characterized by ulcerative skin lesions. Infliximab (IFX) may promote PG healing in patients with inflammatory bowel disease, but whether IFX is effective for treating PG in patients with rheumatoid arthritis (RA) has not reported. We report the case of a 53-year-old woman with PG complicated by RA who was treated using IFX therapy. This case suggests that IFX therapy might offer effective treatment for such patients.

Keywords Infliximab · Pyoderma gangrenosum · Treatment · Rheumatoid arthritis · Tumor necrosis factor α

Introduction

Pyoderma gangrenosum (PG) is an immune-mediated inflammatory condition characterized by chronic ulcerative skin lesions, commonly on the lower extremities [1–3]. The cause of PG remains unknown. PG reportedly occurs in approximately 1–2% of patients with inflammatory bowel disease (IBD) [4], such as Crohn’s disease (CD). Conversely, 36–50% of patients with PG have IBD [1, 3, 5]. However, cases of PG complicated by rheumatoid arthritis (RA) are rare. The mainstay of PG treatment remains immunosuppression, and the most commonly used medicines are corticosteroids and cyclosporine [2, 6]. Local treatments include dressing, debridement, and topical pharmacotherapy [7]. Infliximab (IFX), a monoclonal antibody against tumor necrosis factor (TNF)-α, has been approved for use in the treatment of moderate to severe CD [8, 9] and for RA when used in combination with methotrexate (MTX) [10]. IFX effectively blocks the inflammatory processes underlying CD and produces clinical and histological improvements. Recent case reports have suggested that IFX may promote healing of PG lesions in patients with IBD [11–14]. However, whether IFX is effective for treating PG in patients with RA has not been reported. We describe herein the case of a woman with PG complicated by RA and who was successfully treated using IFX.

Case report

A 53-year-old Japanese woman was referred to our hospital with joint tenderness and swelling in the wrists and fingers. She fulfilled the 1987 criteria of the American College of Rheumatology (ACR) for RA [15] at 35 years old in 1989. She had been treated with 4 mg/week of MTX and 6 mg/day of auranofin since 1997, and the condition of her disease had been stable. She had never taken prednisolone. The patient had a history of schizophrenia, but mental status was well-controlled by alprazolam (Constan; Takeda Pharmaceutical Co., Ltd., Osaka, Japan). Bilateral resection arthroplasty of the metatarsophalangeal joint had been performed for hallux valgus and crow toes in 2004, followed by partial arthrodesis of the left wrist in 2006. In April 2008, an ulcerous lesion
appeared on the left lower limb. This area gradually became larger, and RA activity increased at the same time. There was no trigger for RA exacerbation. MTX was not increased to \( \geq 4 \text{ mg} \) because she had a liver function disorder despite taking folic acid 5 mg/week. In the Steinbrocker classification, functional class was estimated to be class III and stage was assessed as stage III. In June 2008, she consulted a dermatologist regarding an ulcerous lesion (15 cm \( \times \) 9 cm) in which all layers of the skin were almost completely necrotic (Fig. 1a, b). Skin biopsy was immediately performed, and she was diagnosed with PG after histopathological identification of superficial and deep perivascular leukocytoclastic dermatosis (Fig. 2). No diarrhea, abdominal pain, or other digestive symptoms were present, so a diagnosis of IBD was excluded. Serological examinations showed positive result for rheumatoid factor (RF) (176 IU/ml), anticyclic citrullinated peptide antibody (ACPA) (>100 U/ml), and autoantibody to galactose-deficient immunoglobulin G (IgG) (CARF) (432.6 AU/mi); negative results of antinuclear antibodies (ANA), anti-CL \( b \) 2GP1 (<0.7 U/ml), myeloperoxidase–antineutrophil cytoplasmic autoantibodies (MPO-ANCA) (<1.3 U/ml), and PR3-ANCA (<3.5 U/ml).

The patient received 200 mg of IFX (4.8 mg/kg) at 0, 2, and 6 weeks, and every 8 weeks thereafter, in combination with 4 mg/week of MTX. She had been applying sulfadiazine silver cream (1% Geben cream) to the ulcer lesion once daily and had undergone a checkup by a dermatologist. Signs of improvement were observed after the second course of IFX, and the ulcer lesion was obviously reduced. The area of the ulcer lesion was 9 cm \( \times \) 4 cm at 3 months after initiating treatment with IFX (Fig. 1c, d). At the same time, swelling and tenderness of bilateral metacarpophalangeal, proximal interphalangeal, and ankle joints were decreased and disappeared. Before initiating treatment with IFX, laboratory evaluation revealed white blood cell count 13,200/\( \mu \text{l} \), C-reactive protein (CRP) 5.61 mg/dl, erythrocyte sedimentation rate (ESR) 57 mm in 1 h, matrix metalloproteinase 3 109 ng/ml, Disease Activity Score of 28 Joints-CRP4 (DAS28-CRP4) 5.24, and DAS28-ESR4 6.43 [16]. After 3 months of treatment, CRP had decreased to 0.26 mg/dl, DAS28-CRP4 to 2.78, ESR to 21 mm, and DAS28-ESR4 to 3.87. This patient was classified as a moderate responder according to European League Against Rheumatism criteria [17]. As of the time of this writing, 2 years after the first treatment with IFX, ulcers have completely disappeared (Fig. 1e, f) and RA remains very well controlled. Maintenance treatment with IFX in combination with MTX has been continued to control RA and PG activity.

**Discussion**

This case illustrates the benefits of IFX in healing RA-associated PG lesions. The etiopathogenesis of PG is still not well understood. However, the disease is associated with systemic diseases such as IBD and myeloproliferative diseases. TNF-\( \alpha \) is known to play an integral role in the development of such diseases. PG has frequently been reported to occur in patients with IBD [1, 3, 5]. However, cases of PG in patients with RA are rare. Clinically, PG is classified into ulcerative, pustular, bullous, and vegetative types [18]. The case reported here was typical of ulcerative PG. Diagnosis mainly depends on recognizing evolving clinical features and histopathological findings, as no specific investigations are available to reach the diagnosis. Other diseases such as occlusive vascular disease, vasculitis, infection, and drug-induced tissue damage must be excluded before a definitive diagnosis can be reached. In this case, the patient showed none of those diseases and was diagnosed with PG on the basis of characteristic skin findings. She also had no symptoms of IBD. Histopathological findings that may be useful to exclude other pathologies are not specific. With reference to findings in PG, perivascular dermal infiltrate of neutrophils is seen, generally extending to the subcutis and associated with a

![Fig. 1 Pyoderma lesion of the left lower limb.](image-url)
mixed interstitial infiltrate of lymphocytes and histiocytes [18].

Conventional PG management involves local and systemic therapy. The combination of both therapies is important in achieving PG control. Local treatment includes dressings, corticosteroid creams, topical sulfadiazine silver cream, and necrotic tissue debridement [7]. The mainstays of systemic treatment include corticosteroids and immunosuppressive agents. High-dose corticosteroids have been recommended in the acute phase [7] but are associated with significant side effects. Cyclosporine is commonly used in patients with steroid-resistant PG and has been reported as effective [6]. Other drugs such as azathioprine, tacrolimus, MTX, and cyclophosphamide have been used with success [2]. These drugs also show problematic side effects, including myelosuppression, nephrotoxicity, and hepatotoxicity.

A number of recent case reports have demonstrated good PG response to treatment with IFX [11–14] or etanercept [19]. In particular, IFX therapy has been shown to be effective and safe for IBD-associated PG in a retrospective study [20] and a randomized placebo-controlled trial [21]. However, whether biologics represent effective treatment for RA-associated PG remains unclear. Otherwise, IFX therapy has been a great advance in treating RA patients [10]. In Japan, several studies have shown the effectiveness of this treatment in terms of clinical [22] and radiographic results [23] and activities of daily life [24]. The typical IFX dose has been 5 mg/kg for IBD-associated PG, without combined MTX. In the case reported here, 200 mg of IFX (4.8 mg/kg) was used in combination with MTX at 4 mg/week. IFX dose was similar to that used in IBD-associated PG. This case study suggests that IFX might offer potential as an effective therapy for PG patients with RA.

TNF inhibitors have been reported to induce cutaneous vasculitis. Fujikawa et al. [25] recently reported three patients with anti-TNF therapy-induced cutaneous vasculitis. These patients developed a red rash on the extremities and fever. Skin biopsy of the rash showed leukocytoclastic vasculitis in two patients. The underlying mechanisms are unknown, but cutaneous vasculitis and ulcer may be worsened with the use of TNF inhibitors. Vandevyver et al. [26] presented a case of a patient with RA who developed PG under IFX and persistent cutaneous inflammation when switching to etanercept. Additional case studies and large prospective studies are needed to establish the appropriate use of IFX for PG patients with RA.

In conclusion, we report a case in which IFX therapy was successful for a patient with PG and RA. IFX administration may be useful not only for PG patients with IBD but also for PG patients with RA.

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