

Pyoderma gangrenosum associated with ulcerative colitis treated with infliximab

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Abstract

Pyoderma gangrenosum is an uncommon destructive and inflammatory skin disease of the neutrophilic dermatosis group. Of unknown etiology, it is possibly an immunological disorder. Infliximab is an anti-tumor necrosis factor alpha monoclonal antibody. We report 3 patients with ulcerative colitis and recalcitrant pyoderma gangrenosum not responsive to conventional therapies and treated with infliximab with favorable results. Seemingly, infliximab is an effective and well tolerated drug for the treatment of pyoderma gangrenosum associated with ulcerative colitis (*Dermatol Argent* 2009; 15(3):191-195).

Key words: anti-tumor necrosis factor alpha, inflammatory bowel disease, infliximab, pyoderma gangrenosum, ulcerative colitis.

Introduction

Pyoderma gangrenosum (PG) is an uncommon and destructive inflammatory disease of the neutrophilic dermatosis group.¹ This dermatosis may appear without other underlying disorders, or be associated with a systemic disease (17 to 74 percent).² It has been related to multiple entities, especially with inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and immunoglobulin A monoclonal gammopathy.³ Association of PG and ulcerative colitis (UC) is uncommon; prevalence ranges between 0.6 percent and 15 percent.¹ Clinically, it is characterized by the presence of nodules or sterile pustules progressing to painful ulcers with elevated crenated, erythematous and purplish borders, and an oozing necrotic base. Lesions are typically isolated. The ulcerated form is the most frequent clinical variant, and is generally associated with IBD, RA, and monoclonal gammopathy. Other less frequent forms are the pustulous variant usually related to IBD, the bullous form associated with myeloproliferative diseases, and the vegetating variety, usually idiopathic.⁴ The most frequent location of lesions is the legs.³ The etiology of PG is unknown. Although some immune regulation alterations have been reported, a specific pattern has not yet been detected.¹ The treatment of this disease is based on the use of immunosuppressive drugs. Systemic corticosteroids and cyclosporine are described in the literature as first choice drugs. However, numerous pharmaceutical drugs have been used for remission (azathioprine, cyclophosphamide, dapsone, thalidomide, etc.).^{2,5}

Infliximab is an anti-tumor necrosis factor alpha monoclonal antibody (TNF- α). Since it is effective for the treatment of va-

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Figure 1. Ulcer, 15 × 8 cm in diameter, with undermined erythematous-purplish borders and necrotic base on the external area of the lower third of the right leg.



Figure 2. Ulcer on the external area of the lower third of the right leg after the third infliximab infusion.

rious inflammatory pathologies involving multiple cytokines, its use in treating PG has been considered. Several retrospective studies and series of cases suggest that this monoclonal antibody may induce the cure of PG in IBD patients.⁶⁻⁹ Three patients with UC and PG treated with infliximab with favorable results are reported here in below.

Clinical cases

Case 1

A 41-year-old female patient with PG of an 11 years' evolution and episodes of partial remission in response to treatment with systemic corticosteroids and cyclosporine. Ten years after diagnosis of dermatosis she presented episodes of bloody diarrhea. Thus a videocolonoscopy (VCC) and a colon biopsy were performed, enabling a UC diagnosis; sulfasalazine treatment was instituted (4 g/day). Two months later, a 10 cm diame-

ter oval and painful blister with hemorrhagic content appeared, eventually evolving to a 15 × 8 cm diameter ulcer with undermined erythematous purplish borders and necrotic base, on the external area of the lower third of the left leg (**Figure 1**). A biopsy of the lesion was obtained and the histopathologic study revealed epidermal hyperplasia with severe spongiosis on the ulcer border, and a dense polymorphonuclear inflammatory infiltrate extending to the deep dermis. Upon diagnosis of PG, treatment with cyclosporine 3.33 mg/kg/day was started with little improvement, and prednisone was added to a maximum dosage of 120 mg/day. No response was detected, and infliximab treatment was decided on a 5 mg/kg EV dosage on weeks 0, 2, and 6. Previously, supplementary tests were performed, without evidence of alterations (**Table 1**). Patient referred pain alleviation 24 hours after the first infusion, and decrease of perilesional erythema was observed after second infusion. Nineteen days after treatment onset, the ulcer was superinfected with methicillin-resistant *Staphylococcus aureus*, and treated with vancomycin and trimethoprim-sulfamethoxazole, with good response. After 4 months, the ulcer showed complete reepithelization. Currently, control continues without relapses (**Figure 2**).

Case 2

A 34-year-old male patient with PG of a 10 years' evolution showing partial improvement with corticosteroid and dapsone treatment. At follow-up, he showed liver enzyme alterations; thus, liver biopsy and cholangioresonance were performed. Diagnosis was primary sclerosing cholangitis, and treatment with ursodeoxycholic acid was started. Subsequently, bloody diarrhea appeared and thus VCC with intestinal biopsy was performed, resulting in UC diagnosis. Three years earlier he developed two painful oval, 6 cm diameter ulcers with erythematous undermined borders and hemorrhagic base on the inner area of both legs (**Figure 3**). Biopsy was obtained and histologic study showed neutrophilic exocytosis, fibrinoleukocytic exudate, and polymorphonuclear inflammatory infiltrate throughout the dermis. Diagnosis of PG was established taking into account the clinical examination and the histologic data. Given the association of the three conditions, it is decided to begin with infliximab treatment. Supplementary studies were carried out before the first infusion, revealing anemia, abnormalities of liver tests (due to cholestasis) and positive PPD with normal chest X-ray, therefore 8-weeks isoniazid treatment was indicated be-

TABLE 1. PREVIOUS STUDIES TO INFLIXIMAB TREATMENT.

• PPD 2 UT.
• Blood cell count with leukocyte formula and platelet count.
• Serum level of total and fractionated bilirubin, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, leukocyte alkaline phosphatase, total cholesterol, prothrombin time, albuminemia, total proteins.
• Serum ionogram.
• Fasting glycemia.
• Serum urea and creatinine.
• Antinuclear factor.
• Complete urinalysis.
• Electrocardiogram.
• Chest X-ray.

TABLE 2. INFLIXIMAB PREPARATION AND INFUSION METHOD.

1. Calculation of total dosage to be infused (5 mg/kg/dose).
2. Careful dilution of total dose in 250 ml of 9% sodium chloride, without stirring the vessel, mixing with gentle movements.
3. Continuous intravenous infusion (with infusion pump) for 2 hours.
4. Control of vital signs every 30 minutes for the total infusion time and the 2 subsequent hours.

fore the infliximab treatment. The patient received intravenous infliximab on weeks 0, 2, 6 (**Table 2**). After the first infusion, the patient referred an important decrease in pain and diarrhea. After the second infusion, the ulcers reduced in size, and after the third infusion, the ulcer showed almost complete reepithelization (**Figure 4**). Since a small ulcer on the right leg persisted, a fourth infusion was administered.

Case 3

A 39-year-old female patient with UC history of a 5 years' evolution treated with mesalazine and methylprednisone. She consulted due to fever and a recent painful lesion on right ankle. Simultaneously, she started with bloody diarrhea and was hospitalized. Examination showed an oval, 5 cm diameter painful ulcer with purplish undermined borders and necrotic base on the external area of the right ankle (**Figure 5**). Biopsy was obtained for histologic study resulting in diagnosis of PG. Topical cures with methylprednisone 1 mg/kg/day and azathioprine 100 mg/day were started. After four weeks, the ulcer increased in size and the pain worsened, so treatment with infliximab was decided. Studies listed in **Table 1** were requested, and the results were all within normal parameters. Intravenous infliximab treatment was instituted on weeks 0, 4, 8. After the first infusion, the patient referred pain alleviation. After the second infusion, the lesion and the perilesional erythema reduced in size (**Figure 6**). Two weeks after the second infusion, the patient was hospitalized



Figure 3. Painful oval ulcers, 6 cm in diameter, with erythematous undermined borders and hemorrhagic base on inner area of the leg.



Figure 4. Ulcers on the inner area of the leg after the second infliximab infusion.

for pneumonia by *Streptococcus viridans*, thus receiving piperacillin-tazobactam treatment resulting in rapid clinical improvement. Two months after the third infliximab infusion the lesion showed complete reepithelization. No new lesions appeared in 2 years follow-up.

Comments

PG is a rare, inflammatory, and destructive disease. Treatment is still challenging. Both high dosage corticosteroids and cyclosporine have shown maximum efficacy in managing this disease. They may be used alone or combined with other immunosuppressive drugs (azathioprine, cyclophosphamide, etc.). However, patients receiving such associations have a higher risk of adverse effects, and the efficacy is controversial.^{2,10} TNF- α is a proinflammatory cytokine that induces other cytokine synthesis and release, and contributes in recruiting inflammatory cells in the skin by increasing adhesion molecule expression. TNF- α inhibition may reduce inflammatory response. Currently, two biological agents exist with



Figure 5. Painful oval ulcer, 5 cm in diameter, with purplish and undermined borders and necrotic base on the external area of the right ankle.



Figure 6. Ulcer on the external area of the right ankle after the second infliximab infusion.

action mechanism consisting in TNF- α inhibition: etanercept and infliximab. The former is a soluble TNF- α and TNF- β transporting protein.¹¹ The latter agent is an anti-TNF- α monoclonal antibody comprising a constant human fraction and a murine variable fraction that bind to TNF- α with higher affinity and specificity. It acts by neutralizing TNF- α soluble and transmembrane forms. In vitro, it has been proved that infliximab induces TNF- α expressing cell lysis through an antibody- or complement-mediated cytotoxicity mechanism.¹² In 1998, the Food and Drug Administration (FDA) authorized its use for treatment of Crohn's disease (CD).^{6,13} In 1999, its use was licenced together with methotrexate for refractory RA management.¹⁴ Psoriasis was the first dermatologic disease

where infliximab showed effectiveness. FDA has not authorized this use in spite of the satisfactory results in plaque psoriasis and psoriatic arthritis.^{4,15,16} As from 2000, several studies have been submitted on the use of infliximab in treating PG associated with IBD and evidencing satisfactory results.^{6,17,18} Infliximab was administered to our patients on weeks 0, 2, and 6, as described in published works on CD and PG treatment.^{6,15} We wish to point out that in our three reported patients the treatment with infliximab was chosen because of the presence of recalcitrant PG. A net alleviation of pain was detected 24 hours after first infusion, thus markedly improving quality of life of all patients. Throughout the treatment a gradual reduction of inflammatory signs in the lesion was found, together with the appearance of granulation tissue gradually covering the base of the ulcers. Infliximab has been well tolerated by our patients, with few adverse effects. Although the literature describes acute and delayed hypersensitivity reactions, we did not find them in these cases. At the onset of infliximab treatment, the physician in charge must be aware of the possibility of reactivating latent infections. Tuberculosis is the main condition to be taken into account in our setting. Thus, mandatory studies to be performed before treatment include PPD and chest X-ray. Other adverse effects that may appear with the use of this biological agent are optic neuritis, seizures and demyelinating diseases. The fact that the chronic use of infliximab may increase the incidence of lymphoproliferative disorders is still unknown. According to our experience, the use of infliximab in treating PG associated with IBD is efficacious in controlling symptoms and inducing clinical remissions of lesions and the gastrointestinal condition. It may be adequate for the recalcitrant form of the cutaneous disease, refractory to other treatments.

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