SHORT REPORT

A case of pyoderma gangrenosum with ulcerative colitis treated with combined approach:
Infliximab and surgery

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Abstract

Pyoderma gangrenosum (PG) is an ulcerating noninfectious disease of the skin seen in 1–2% of patients with inflammatory bowel disease (IBD). The pathogenesis of PG has yet to be determined, but may be related to abnormal T cell responses and the production of TNF-α, a pathway also involved in IBD pathogenesis. Infliximab, a chimeric monoclonal antibody to TNF-α, is used to treat moderate to severe IBD and several case reports and studies suggest the efficacy of infliximab in the treatment of PG. The surgical approach to PG is reserved to a few selected cases. We report here the case of a patient with ulcerative colitis (UC) and PG localized on the left breast, treated with a simultaneous combined medical and surgical approach.

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1. Introduction

Pyoderma gangrenosum (PG) is an immune-mediated inflammatory condition that belongs to a group of neutrophilic dermatoses. PG usually begins as painful, hemorrhagic pustules, red papules, plaques, or nodules growing rapidly and generating ulcers with undetermined purple-colored borders commonly on the lower extremities. It occurs approximately in 1–2% of patients with inflammatory bowel disease (IBD) and may have no relation with the clinical activity of the underlying intestinal disease, but sometimes coincides with disease exacerbation or treatment failure. Conversely, 36–50% of patients with PG have IBD. The pathogenesis of PG has yet to be determined, but may be related to abnormal T cell responses and the production of TNF-α, a pathway also involved in IBD pathogenesis. Infliximab, a chimeric monoclonal antibody to TNF-α, is used to treat...
moderate to severe IBD and several case reports and studies show the efficacy of infliximab in the treatment of PG.\textsuperscript{5,6} Selected cases of PG treated with two different surgical techniques have been reported so far: the simultaneous application of free anterolateral thigh fasciocutaneous flaps after radical debridement\textsuperscript{5} and split-thickness skin graft.\textsuperscript{6} We herein report the case of a patient with PG and ulcerative colitis treated with the simultaneous and combined approach of therapy with infliximab and surgery.

2. Case report

A 76-year-old patient presented with a painful, itchy, ulcer on the left trunk (Fig. 1). The skin lesion had developed 2 months before the onset of abdominal complaints: bloody diarrhea (5 to 6 bowel movements per day), fever 37.4 °C, abdominal pain and weight loss. He had been diagnosed with ulcerative colitis 3 years before. He was suffering from hypertension and diabetes and treated with oral hypoglycemic and antihypertensive drugs. He had been treated with mesalazine (2.4 g daily) for ulcerative colitis and systemic/topic corticosteroids in case of relapse, until June 2010, when he first visited our clinic. On physical examination, the patient was slim and slightly pale. He had painful ulcer. The ulcer measured about 10 cm×6 cm in diameter, with a violaceous undetermined border and a necrotic ground covered with purulent exudate. The lesion was located in the lower half of the left breast (Fig. 1), however spared areola and nipple. Oral mucosa was dry. No adenopathy was appreciated on palpation in the cervical chain. He had a normal cardiac examination and clear lungs. His abdomen was flat, with normal bowel sounds. His abdominal examination showed diffuse tenderness to palpation but no rebound or guarding. We performed blood tests that showed: elevated white blood cell count of 12.0×10\textsuperscript{9}/L [range: 4.3 to 10.8×10\textsuperscript{9} cells/L], an increased C-reactive protein (CRP) (34.5 mg/L [range: 1–3 mg/L] and absolute number of neutrophils (10,200 cells/\mu L) [range 1500–7800 cells/\mu L]. Stool culture and \textit{Clostridium difficile} toxin were negative. We performed ileocolonoscopy that revealed moderate–severe pancolitis: the mucosa from rectum till mid transverse colon and beyond showed some superficial ulcers, loss of vascular pattern and friability (Fig. 2). The histologic workup showed distortion of crypt architecture, cryptitis with frank crypt abscesses, and inflammatory cells in the lamina propria. Histopathology of the skin biopsy taken from the ulcer of the chest showed perivascular and perifollicular mixed infiltration of neutrophils and lymphocytes from the epidermis to the subcutis and no bacterial organism was identified by culture. According to the lesion’s histological features, there was an evidence of neutrophilic infiltration in the absence of leukocytoclastic vasculitis. With malignancy and infective causes excluded, the skin lesions were diagnosed as PG. He was treated for 5 days with 6-methylprednisolone (1 mg/kg/day i.v.). However, his bloody diarrhea still persisted and the skin ulcer showed no improvement. Therefore, we decided to treat the cutaneous lesions with a skin graft technique. There are three main types of skin grafts: 1) \textit{split-thickness graft} is the most commonly used type of skin graft. It removes only the epidermis and part of the dermis. This allows the source site to heal more quickly; 2) \textit{full-thickness graft} removes the epidermis, the dermis, and the hypodermis in their entirety. Cosmetically, the outcome is usually better, which is why full-thickness grafts are usually recommended for the face; 3) \textit{composite graft} can entail the removal of skin, fat, muscle, and cartilage. These grafts are typically used in areas that require three-dimensional reconstruction. In our patient a split-thickness skin graft was used. In particular, the outline of the wound on the skin of the donor site was marked, enlarging it by 3–5% to allow for tissue shrinkage. We used a dermatome to remove a split-thickness graft from the left thigh, and spread on the bare area to be covered. We applied gentle pressure and used stitches to hold the graft in place (Fig. 3). A sterile non adherent dressing was then applied to the raw donor area to protect it from infection (Fig. 3). After the surgical procedure we immediately started infliximab therapy at 5 mg/kg body weight at weeks 0, 2, and 6 and every 8 weeks after that.

Both the skin lesion and intestinal symptoms significantly improved after infliximab induction regimen: one to two bowel movements per day with no blood and marked improvement of breast pain and itch. Complete healing with scarring was achieved after 6 months of treatment (Fig. 4). Moreover, one-year colonoscopy showed mucosal healing with rare pseudopolyps (Fig. 5).

Figure 1  An ulcer 10 cm×6 cm in diameter on the lower half of the left breast, with a violaceous undetermined border and a necrotic ground covered with purulent exudate.

Figure 2  The mucosa of transverse colon with superficial ulcers, loss of vascular pattern and friability.
3. Discussion

The pathogenesis of PG is uncertain, but likely involves similar immune-mediated processes underlying Crohn’s disease (CD) and UC. PG rarely involves the breast. A published work survey disclosed almost 400 reported cases up to date. In most of the cases the lesions were related to previous surgical interventions, probably as the result of a pathergy phenomenon. As most of the lesions healed with significant scarring, early recognition and treatment of PG located on the breast are important to prevent serious physical and psychological morbidities.7–9 Several case reports and reviews on efficacy of anti TNF-α in the treatment of PG have been reported (Table 1).10–34 Brooklyn et al.10 conducted a randomized, double blind, placebo-controlled trial. Thirty patients were enrolled. The primary end-point was clinical improvement at week 2, with secondary end-points being remission and improvement at week 6. At week 2, more patients in the infliximab group had significantly improved [46% (6/13) as compared to the placebo group 6% (1/17); P = 0.025]. Overall, 29 patients received infliximab with 69% (20/29) demonstrating a beneficial clinical response. Remission rate at week 6 was 21% (6/29). There was no response in 31% (9/29) of patients. Reguiero M. et al.3 performed a multicenter retrospective study of 13 patients with IBD and medically refractory PG treated with infliximab. Three patients had a complete response to induction infliximab therapy and did not required additional treatment. Ten patients responded to infliximab induction and maintained pyoderma gangrenosum healing with infusions every 4–12 weeks. Few cases of PG treated with surgical approaches5,16,35,36 have been reported so far, in particular with the skin grafting technique adopted to promote the healing of the wound and provide an acceptable cosmetic result. However, skin grafting is normally avoided because of the potential risk of pathergy in the skin area damaged by trauma. In addition, few cases of PG treated with combined therapeutical and surgical approaches have been reported. Pomerantz RG et al.16 presented a case report of a 61-year-old woman, in which PG lesions on both pretibial areas were treated with skin grafts and then with etanercept, but the PG lesions progressed in number and severity. In the past she had been treated with infliximab for her arthritis and PG, with rapid improvement of PG lesions, but infliximab use was discontinued when the patient developed a systemic reaction at the second dose. Therapy with adalimumab was then initiated, and 5 months after the beginning of therapy, the patient was completely healed. Imus et al.37 presented a case report in 2001 in which PG was stabilized with cyclosporine and wound healing was promoted with allogenic cultured human skin.

Figure 3  Split thickness skin graft. A) The graft from the left thigh. B) The graft spread on the bare area with sutures to hold the graft in place.

Figure 4  Complete healing with scarring after 6 month of combined treatment.

Figure 5  Mucosal healing with rare pseudopolyps after one-year of infliximab therapy.
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<th>Author</th>
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<td>All patients demonstrated complete healing of the skin lesions. Three patients had a complete response to induction infliximab therapy and did not require additional treatment. Ten patients responded to induction infliximab and have maintained pyoderma gangrenosum healing with infusions every 4–12 weeks. After randomisation, 13 patients received infliximab and 17 patients received placebo. At week 2, significantly more patients in the infliximab group had improved (46% (6/13)) compared with the placebo group (6% (1/17); P=0.025). Overall, 29 patients received infliximab with 69% (20/29) demonstrating a beneficial clinical response. Remission rate at week 6 was 21% (6/29). There was no response in 31% (9/29) of patients.</td>
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<td>Patients 2 and 3, who had previously responded to infliximab, albeit with recurrence, were successfully treated with adalimumab at a dose of 40 mg once a week. Patient 1 initially responded to adalimumab, but after 7.5 months failed to show wound bed improvement at a dose of 80 mg/week subcutaneously. This patient had not previously been treated with infliximab.</td>
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skin (Grafskin, Organogenesis, Canton, MA). Zakhireh et al. reported 3 cases of PG treated with cyclosporine and skin graft, but it was performed once the wound bed showed healthy granulation tissue and minimal fibrous exudates. Deok-Woo K. et al. presented a case of PG in patients with Behcet's disease treated with split-thickness skin graft, in which, they decided to start cyclosporin to promote healing 7 days after debridement, because no proliferation of the tissue occurred. Lamet S et al. reported the case of PG associated with acute leukemia, treated with corticosteroids and after stabilization of skin lesion was treated with split-thickness skin graft approach. As reported in the literature, the use of skin thickness grafts is related to a final cosmetic result considered to be superior to wound healing by secondary intention and concomitant use of immunosuppressive therapy seems to decrease the risk of pathergy developing. Our patient represents a case of PG on the breast treated with a simultaneous combined approach: infliximab and surgery. This approach was chosen because of the presence of a large ulcer, the relapse of the underlying UC and the refractoriness to systemic glucocorticoid treatment in a suffering elderly patient with comorbidities. n conclusion, here we report for the first time a combined and simultaneous approach with infliximab and split-thickness skin graft in the treatment of both refractory PG and UC. The benefit of this approach is the prevention of possible complications by closing a chronic wound and dampening the UC flare, reduction of hospital stay and, finally, reduction the suffering of the patient.

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Conflicts of interest

There are no competing interests.

Contributorship

GA, GL, AP, AEP, DC and AA: conception and drafting the article, revising it critically for important intellectual content and final approval of the version to be published.

References


Table 1 (continued)

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