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## Case report

# Biological therapy for pyoderma gangrenosum

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## ABSTRACT

**Introduction:** pyoderma gangrenosum (PG) is a rare and severe neutrophilic dermatosis associated with inflammatory bowel disease (IBD) and other systemic diseases such as rheumatoid arthritis and hematological malignancies. Diagnosis is based on clinical criteria and exclusion of other skin disorders. There is no gold standard for the treatment of PG; traditionally intravenous corticosteroids are used, but recently the use of drugs that inhibit tumor necrosis factor alpha (TNF-alpha) has changed the management of PG, showing great effectiveness.

**Case report:** female patient, 23 years old, diagnosed with severe nonspecific ulcerative colitis (UC) three years ago, undergoing treatment with oral mesalamine and azathioprine. She developed PG fourteen days after hospital discharge; hospitalization was due to worsening of intestinal disease symptoms. She was successfully treated using biological therapy after unfavorable evolution with corticosteroid therapy.

**Conclusion:** PG, a rare extraintestinal manifestation of IBD of difficult resolution that has significant impact on patient quality of life. The use of biological therapy for PG has higher efficacy in the treatment of patients decreasing wound healing time and return to daily activities.

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## Palavras-chave:

Doença inflamatória intestinal

Pioderma gangrenoso

Retocolite ulcerativa inespecífica

## Terapia biológica no tratamento do pioderma gangrenoso

## RESUMO

**Introdução:** pioderma gangrenoso (PG) é uma rara e grave dermatose neutrofílica associada a doença inflamatória intestinal (DII) e a outras doenças sistêmicas como a artrite reumatoide e neoplasias hematológicas. O diagnóstico é baseado em critérios clínicos e exclusão de outras desordens da pele. Ainda não há padrão ouro para o tratamento do PG, tradicionalmente usa-se corticoides endovenosos, porém recentemente o uso de fármacos inibidores do fator de necrose tumoral alfa (TNF-alfa) tem mudado o manejo do PG mostrando grande efetividade.

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**Relato do caso:** paciente feminina, 23 anos, com diagnóstico de retocolite ulcerativa inespecífica (RCUI) severa há três anos, em tratamento com mesalazina oral e azatioprina. Evoluiu apresentando PG quatorze dias após alta hospitalar, por internamento devido agudização dos sintomas intestinais da doença. Foi tratada com sucesso usando terapia biológica após evolução desfavorável com corticoide.

**Conclusão:** PG, uma rara manifestação extraintestinal das DII, é de difícil resolução e com significativa interferência na qualidade de vida dos pacientes. O uso de terapia biológica no PG vem mostrando melhor eficácia no tratamento desses doentes com diminuição do tempo de cicatrização das feridas e retorno às atividades diárias.

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## Introduction

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis in which painful nodules and later pustules, due to subsequent necrosis of the dermis, open up to form irregular and painful, with a granular base, commonly with purplish and undermined borders.<sup>1</sup> The lesions have distinctively an exudative, mucopurulent content, often sterile and eventually hemorrhagic.<sup>1-2</sup>

The lesions can be single or multiple, can appear in the site of prior trauma, but generally they affect the skin surrounding stomata and the extensor surface of the lower limbs and so they may be found in any part of the body. The anatomopathological analysis shows evidence of nonspecific neutrophilic dermatosis, however it has to be performed since PG diagnosis is based on clinical criteria and exclusion of other skin disorders.<sup>1-3</sup>

This severe dermatosis appears in 1% to 2% of patients with inflammatory bowel disease (IBD) and its correlation with disease activity, although it seems to coincide with the intestinal disease exacerbation, especially in the colon, is still controversial as it also occurs independently. PG seems to be more common in ulcerative colitis (UC) than in Crohn's disease (CD), occurring in approximately 5% of UC patients and just in 2% of those with CD.<sup>1,4-6</sup> This dermatosis is also described in association to other systemic diseases such as rheumatoid arthritis, hematological malignancies and solid tumors, as well as in the idiopathic form.<sup>7-8</sup>

There is no gold standard for the treatment of PG and there is no evidence that show different results of treatment effectiveness when it is intended for patients with or without IBD.<sup>1</sup> In general, immunosuppression is the mainstay of PG treatment and intravenous corticosteroids have traditionally been the first-line treatment.<sup>1</sup> Recently, the use of inhibitors of TNF-alpha has changed the management of PG in UC, showing significant effectiveness.<sup>1</sup>

In the present study we report a rare case of PG as extraintestinal manifestation of UC, successfully treated using biological therapy after unfavorable evolution with corticosteroids.

## Case report

Female patient, 23 years old, Brazilian mulatto, a resident in the city of Cuiabá, state of Mato Grosso, Brazil, diagnosed with severe UC three years ago with involvement of the

entire colon. She had been treated with oral mesalamine 4 g/day since diagnosis and had also been using azathioprine 2.5 mg/kg/day for the past year. She had a history of recurrent hospitalizations due to disease exacerbation, routinely treated with antibiotics and intravenous corticosteroids, followed by weaning and outpatient follow-up. She denied any extraintestinal manifestation of UC.

She sought treatment at the ER complaining of a non-monitored fever, malaise, myalgia and multiple painful sores all over her body when she was hospitalized. She reported at the time of hospital admission, a previous 14 days hospitalization due to the recent exacerbation of UC intestinal symptoms. At physical examination ulcers with undermined edges were observed with serosanguineous fluid and painful purplish pustules distributed over legs, ankles, and face (Fig. 1). She denied any gastrointestinal symptoms at admission. Laboratory assessment showed: mild anemia, absence of leukocytosis and elevated CRP (23.1 mg/dL). The patient declared that she had noticed the presence of small pustular lesions



**Fig. 1 - Before starting treatment with IFX. Notice ulcers with undermined edges and necro hemorrhagic background.**

on the lower limbs and at previous venous puncture sites at the time of her last hospital discharge, but lent no importance to it.

After admission, therapy with hydrocortisone 300 mg/day was promptly initiated, along with intravenous analgesics, and local care of the wounds with isotonic solution. Without significant response and with intense pain, on the third day of hospitalization it was decided to initiate biological therapy using Infliximab (IFX) at a dose of 5 mg/kg. After the first infusion, at week 0, it was noted a significant decrease of the local inflammatory activity and the patient also reported an important decrease in localized pain. After the second infusion, at week 2, the lesions decreased in size and the epithelialization process could be noticed. After the third infusion at week 6, the lesions showed almost complete re-epithelialization (Fig. 2) and after the fourth infusion at week 14, the lesions were at the advanced stages of healing with contraction of the edges (Fig. 3).

Even after completed treatment for PG, the patient continued using IFX regularly, which also resulted in a great impact on intestinal symptoms. Currently, she reports 1-2 daily episodes of bowel movement without mucus, pus or blood.



**Fig. 2 - After the third infusion of IFX. Ulcer is at the end of granulation phase, still reddish in appearance, showing almost complete epithelialization.**



**Fig. 3 - After the fourth infusion of IFX. Ulcer is shown at an advanced healing stage, with similar color to the surrounding skin, showing contraction of edges.**

## Discussion

Although the etiology of PG is partially unknown, the skin damage does seem to be immune-mediated.<sup>1,3</sup> Neutrophil dysfunction, together with defects in chemotaxis or hyperreactivity have been suggested as possible causes.<sup>9</sup> The goal of treatment is the rapid resolution of the lesions, as they may result in severe skin deformities.<sup>1</sup>

Tumor Necrosis Factor-alpha (TNF-alpha) is a potent pro-inflammatory cytokine present in patients with IBD and is reportedly expressed in skin samples from patients with PG; therefore, it is one of the key cytokines involved in this response, as it contributes to the recruitment of inflammatory cells to the skin and increase the expression of adhesion molecules.<sup>10</sup>

The safety, clinical effectiveness and capacity to reduce corticosteroid usage in patients with IBD undergoing therapy with IFX has been clearly proven by pivotal studies such as ACT 1, ACT 2<sup>11</sup> and SONIC.<sup>12</sup> However, although the effectiveness of IFX in PG lesions rapid healing has been described in recent case reports<sup>1,13-15</sup> studies comparing the efficacy of IFX with other immunosuppressive drugs are still lacking.<sup>1</sup> The largest multicenter, randomized, placebo-controlled trial involving IFX in the treatment of refractory PG included 30 patients, 19 of which had a diagnosis of IBD and 6 of UC. After 2 weeks, 46% of the IFX group showed improvement, in comparison to only 6% in the placebo group.<sup>16</sup>

Supported by the idea that the rapid and dramatic improvement of skin lesions is caused by the crucial role that TNF-alpha plays in the pathogenesis of PG, and that biological drugs have been able to decrease the healing time of skin and mucosal lesions, thus allowing an earlier return to daily activities, it is reasoned that drugs that inhibit TNF-alpha may be a promising therapeutic strategy for PG in patients with UC, in which case they are being already used with significant efficacy.

### Conflicts of interest

The authors declare no conflicts of interest.

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