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Development of pyoderma gangrenosum during therapy with infliximab

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Abstract

Background: Pyoderma gangrenosum is a rare inflammatory disease of unknown etiology and a poorly understood pathogenesis. Its clinical presentation is variable and a large percentage of cases are associated with inflammatory bowel diseases. Peristomal pyoderma gangrenosum represents a variant of the diseases, occurring in patients with colostomy. Multiple cases demonstrate efficacy of infliximab and other anti-TNF-alpha drugs in treatment of pyoderma gangrenosum.

Main observations: A 47-year-old male with ulcerative colitis and proctocolectomy with ileal pouch reconstruction protected by ileostomy in the course of diseases received infliximab therapy together with azathioprine for his inflammatory bowel diseases. Six months after initiation of infliximab therapy the patient developed multiple pyoderma gangrenosum lesions on the trunk, abdomen, genitalia, gluteus, extremities, left preauricular region and peristomal area. After systemic corticosteroid therapy, combined with topical tacrolimus, the lesions slowly improved. Seven months later, during ongoing infliximab therapy, the patient developed a sepsis with fatal outcome.

Conclusion: Constant trauma generated by colostomy may be a contributing factor to the development and persistence of pyoderma gangrenosum. It may be hypothesized that this patient developed pyoderma gangrenosum despite infliximab or that pyoderma gangrenosum may represent a rare adverse effect of the drug.

Introduction

Pyoderma gangrenosum (PG) is a rare inflammatory disease of unknown etiology and a poorly understood pathogenesis.[1] Its clinical presentation is variable and a large percentage of cases are associated with inflammatory bowel diseases.[1-5] Several case report and studies of short series demonstrated the efficacy anti-tumor necrosis factor therapy in pyoderma gangrenosum.[6] We report the case of a patient with ulcerative colitis who developed PG during therapy with infliximab.

Case Report

A 47-year-old hispanic male with a history of ulcerative colitis. He had evidence of high grade dysplasia, requiring proctocolectomy with ileal pouch reconstruction protected by ileostomy. The patient developed an abdominal collection with suprapubic skin drainage that recurred two times. He was treated with antibiotics and percutaneous drainage guidesd by tomography.

He continued presenting manifestations of pouchitis, demonstrated by rectosigmoidoscopy, and a perianal fistulae of difficult management, having multiple local infections needing medical and surgical treatment.

Because of the resistance to medical and surgical treatments, infliximab was started (3 doses of 5 mg/kg, at 0, 2 and 6 weeks, followed by 5 mg/kg every 8 wks) together with azathioprine, obtaining a good response of the intestinal symptoms. During infliximab therapy, six months

after the first dose, the patient developed multiple erythemato-violaceous lesions that became ulcerated. Painful ulcers, with an erythemato-violaceous border and a seropurulent base were present on the trunk, abdomen, genitalia, gluteus, extremities, left preauricular region and peristomal area. Despite multiple antibiotic treatments there was no improvement. New lesions continued to appear (Fig. 1 and 2). Patients never reported arthralgia or fever associated with dermatologic lesions.

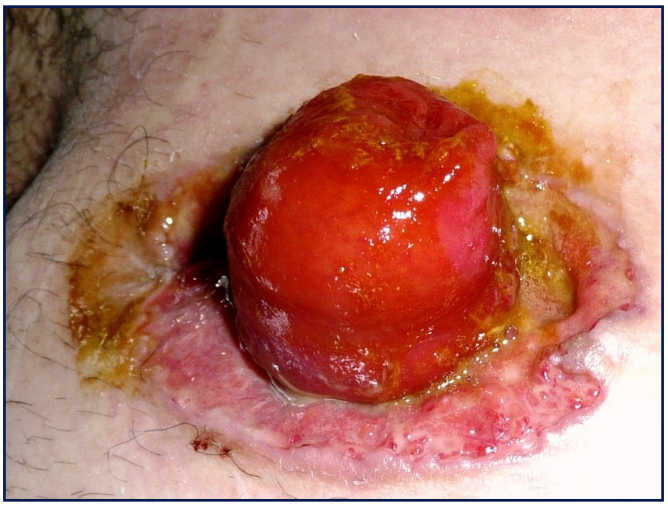

Figure 1

Peristomal pyoderma gangrenosum.

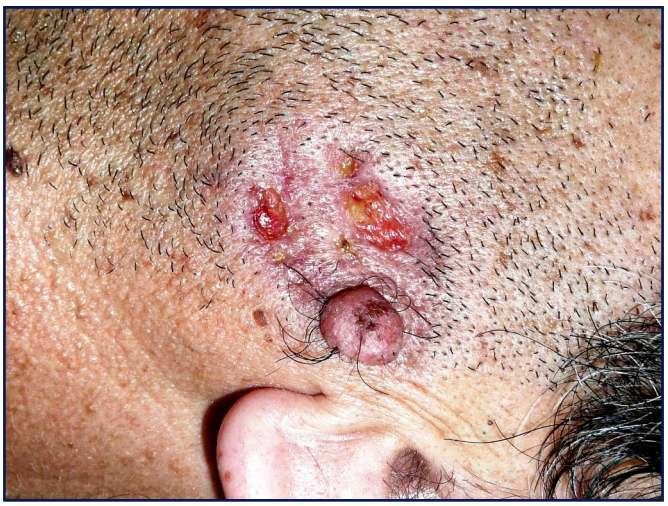

Figure 2

Ulcer with irregular violaceous border on left preauricular region with partial scarring.

Biopsy showed an ulcerated epidermis with a dense cell infiltrate; compose of giant cells, plasmatic cells and lymphocytes, as well as neutrophils abscesses. These changes were non-diagnostic but raised the possibility of a pyoderma gangrenosum (Fig. 3).

Aerobic, anaerobic and fungal cultures were negative.

The patient had normal baseline chest radiography before infliximab therapy. Chest radiography was not repeated thereafter.

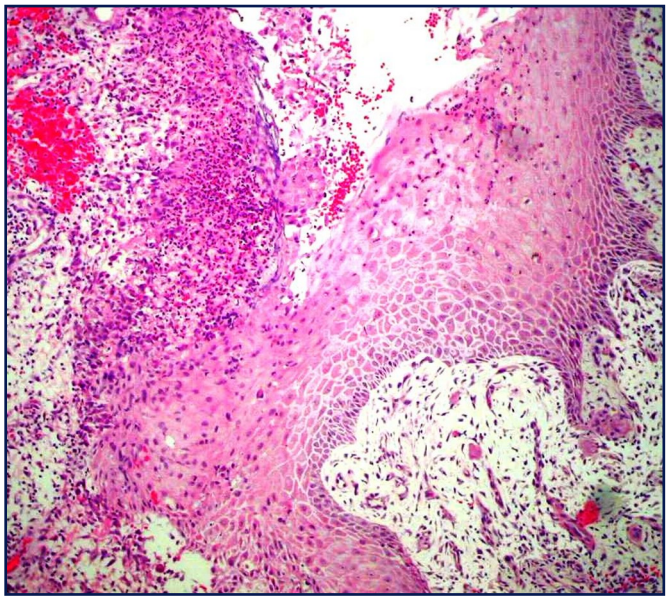

Figure 3

Histopathology of a lesion. Skin with ulceration, giant cells, plasmatic cells and lymphocytes, as well as neutrophils abscesses.

Methylprednisolone was administered at a dose of 100 mg IV tbd, for 5 days. At day three oral prednisolone was initiated at 1 mg/kg/d and topical tacrolimus 0,1% twice a day was introduced. Slow improvement of the ulcers, except the peristomal lesion, was observed.

The patient was discharged with topical tacrolimus 0,1% bid and oral prednisolone (1mg/kg/day). Two months later the skin ulcers continue to improve and prednisolone was tapered 5 mg per week until was discontinued. Infliximab therapy was continued. After an observation period of 7 months the patient developed a fatal sepsis.

Discussion

Pyoderma gangrenosum (PG), is a rare inflammatory disease of unknown etiology.[1-4] Although in about 40% of cases a systemic disease is not detectable (idiopathic PG), more than half of cases are associated with systemic disease, especially inflammatory bowel disease, either ulcerative colitis or Crohn disease.[5] Other diseases that have been associated with pyoderma gangrenosum are: rheumatoid arthritis, seronegative polyarthritis, myelocytic leukaemias, hairy cell leukaemia, myelofibrosis, myeloid metaplasia; monoclonal gamopathy. Rarely reported associations include spondylitis, osteoarthritis, psoriatic arthritis, chronic active hepatitis, hepatitis C viral infection, primary bliary cirrhosis, myeloma, polycythemia rubra vera, paroxysmal nocturnal haemoglobinuria, lymphomas, systemic lupus erythematosus; C7 complement deficiency, hypogammalgobulinaemia, hyperimmunoglobulin E syndrome. HIV infection, sarcoidosis, Takayasu's arteritis, hidradenitis suppurativa, acne conglobata, solid tumours and chronic obstructive pulmonary disease iatrogenic im-

munesuppression, malignancy, Grave's disease or primary antiphospholipid syndrome.[4-7]

Cutaneous lesions of PG are classified according to their morphology (ulcerative, bullous, pustular and vegetant). Even though one variant predominates, some patients could present with more than one type (frequently pustular and ulcerative PG).[1-4] Frequently, clinical presentation of PG is variable and does not have a histological pathognomonic finding.[3,4]

Peristomal PG could be considered a variant of PG, found around colostomies. This variant was first described by O'Loughlin and Perry, as characterized by multiple sterile pustules surrounded by an erythematous halo and accompanied by with fever and arthralgias.[8] Since then, multiple cases have been reported.[2,9-11] Lyon *et al* estimated that the incidence of peristomal PG is 0.6% among all patients will colostomies.[10] Poritz *et al*[11] observed that peristomal PG occurs an average of 18.4+/-7.5 months after stoma creation. The majority of cases reported have occurred in patients with inflammatory bowel disease, particularly Crohn's disease, probably because these patients require more frequently colostomies.[11] This variant of pyoderma gangrenosum, in addition to pain and discomfort related to ulceration, impairs patient's social live due to related to weakened adhesion of the stomal appliance and leakage of faeces. In our case peristomal pyoderma gangrenosum was accompanied by widespread lesion in various locations.

There are no unified guidelines for an uniformly effective treatment for pyoderma gangrenosum.[11,12] Drugs being used in therapy of pyoderma gangrenosum include systemic corticosteroids, and immunosuppressive drugs, such as cyclosporine, azathioprine, cyclophosphamide, chlorambucil, cyclosporin, tacrolimus, mycophenolate mofetil, methotrexate and cyclophosphamide or intravenous immunoglobulins. Pyoderma gangrenosum can respond to sulfones (sulfasalazine or dapsone), clofazimine, and wide spectrum antiobiotics, including minocycline and rifampicin.[11,12]

Recently anti-TNF-alpha biological drugs have widened the therapeutic options for several diseases, including inflammatory bowel disease, rheumatoid arthritis, psoriatic arthritis and psoriasis. There are several case reports and randomized trials demonstrating a favorable response to anti-TNF-alpha drugs infliximab[12-18] etanercept[19-22] and adalimumab[23-26] used in pyoderma gangrenosum, associated with inflammatory bowel diseases or applied off-label in idiopatic PG.

Although there is generally a good response to therapy in general and particularly to anti-TNF-alpha biological drugs in most cases of pyoderma gangrenosum,[12] peristomal PG remains difficult to treat. Poritz *et al*[11] carried out a retrospective study (1997-2007), identifying 16 patients with peristomal PG, of whom 6 received infliximab, being effective just in two of them. Single case reports of favorable course of persomal PG treated with another anti-TNF-alpha drug, adalimumab, were published in 2009.[23,24]

In our case infliximab therapy was applied for inflammatory bowel disease. Development of pyoderma gangrenosum six moths after therapy introduction must be considered a paradox reaction. Lesions had a wide distribution, including trunk, abdomen, genitalia, gluteus, extremities, left preauricular region and peristomal area. The presence of peristomal PG in this patient may contribute to the general observation that this a variant of PG, which requires an individual therapeutic approach.

In these patients, constant trauma generated by the colostomy may be a contributing factor to the development and persistence of pyoderma gangrenosum. The best PG treatment in these cases would be the closure of the colostomy, yet this is not always possible. Thus, peristomal PG, usually do not show a good response to therapy.[11]

It may be hypothesized that in our patient the development of pyoderma gangrenosum despite infliximab therapy may reflect the severity of the intestinal disease, or the opposite, and less probable, it is an adverse effect of the drug.

More data are needed to determine the efficacy and safety of these anti-TNF-alpha agents, especially in patients with a colostomy.

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