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Disseminated refractory pyoderma gangraenosum during an ulcerative colitis flare. Treatment with infliximab.

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Abstract

Background: Pyoderma gangraenosum is an immune-mediated, inflammatory, neutrophilic dermatosis of unknown etiology, which represents one of the extra-intestinal manifestations of inflammatory bowel disease. It is a rare disease that occurs in less than 1% of patients with inflammatory bowel disease and with the same ratio in patients with Crohn's disease and ulcerative colitis.

Main observations: A 36-year-old woman was diagnosed with ulcerative colitis 6 years before admission to our dermatology department with an acute disseminated pyoderma gangraenosum with mucosal involvement, during a flare of ulcerative colitis. Disease progression was interrupted by intravenous administration of the tumor necrosis factor-α inhibitor infliximab at 5mg/kg at weeks 0, 2, and 6 (1st cycle) and every 8 weeks thereafter. Improvement of intestinal, skin and oral manifestations was evident already after the 1st cycle of treatment and has been maintained since (at least 16 months).

Conclusions: This case report is one of very few on disseminated pyoderma gangraenosum with oral involvement complicating ulcerative colitis, where infliximab was shown to have a rapid efficacy on skin, mucosal and bowel symptoms. (*J Dermatol Case Rep*. 2015; 9(3): 62-66)

Introduction

Pyoderma gangraenosum (PG) is a severe ulcerating, primarily sterile, neutrophilic dermatosis. It can occur in association with systemic diseases in adults, the most common of which is ulcerative colitis (UC).[1] PG has been reported in 1-10% of patients with UC,[2] affecting equally men and women with a peak age incidence between 25 and 54 years. Approximately 50-78% of patients with PG have an underlying systemic disease[3] such as inflammatory bowel disease (IBD), myeloproliferative and rheumatological diseases.[4] PG has been reported to occur before, during, after or even independently of the onset of an underlying IBD.[5] Four clinical and histological variants of PG have been described: ulcerative, pustular, bullous, and vegetative.[4] We present here a female patient with severe, disseminated PG, refractory to conventional treatment, during a clinical flare of a previously diagnosed UC. Both entities responded to infliximab, a chimeric monoclonal antibody that inhibits tumor necrosis factor-α (TNF-α).

Case report

Medical History

A 36-year-old female was diagnosed with UC in 2005. The leading symptom was bloody diarrhea. Under treatment with mesalazine, remission was maintained for nearly 5 years. In October 2010, the patient relapsed with bloody diarrhea (at

least eight stools per day), fever and diffuse abdominal pain with increasing severity of the symptoms. She was admitted to an internal medicine department, where she was treated with antibiotics (levofloxacin and metronidazol), mesalazine, sulfasalazin and low-dose corticosteroids (20 mg prednisone daily). After two weeks of unsuccessful treatment and due to the simultaneous development of disseminated, painful ulcers of the oral mucosa the patient was admitted to our dermatology department. She declared having lost about 8 kg in the last two months. The treatment of the patient followed, in close cooperation with our gastroenterology department.

Clinical Examination

On admission the patient was in a reduced general status and had temperature of 38°C. The clinical examination detected two palpable masses in the right lower abdomen and tenderness in the left lower abdomen. Multiple, progressive, painful, large, violaceous nodules and plaques with central crusting necrotic ulceration, painful peripheral zone and undermined borders were present at the submammary and axillary areas, in mons pubis, face, trunk, outer ear and extremities. Furthermore, involvement of the oral mucosa was also present with shallow round ulcers, a central fibrinous membrane and erythematous halo on the edge of the patient's tongue and the buccal mucosa as well as a mild conjuctivitis (Fig. 1).

Diagnostic Procedures

Routine laboratory tests showed normal liver and renal function. A microcytic, hypochromic anemia with iron deficiency was diagnosed [erythrocytes 3.81×10^6 /μL (4.2-5.4); hematocrite 29.98% (37-47); hemoglobin 6.3 mmol/l (7.6-9.9); MCV 78.7 fl (81-99); microcytosis ++; hypochroma-

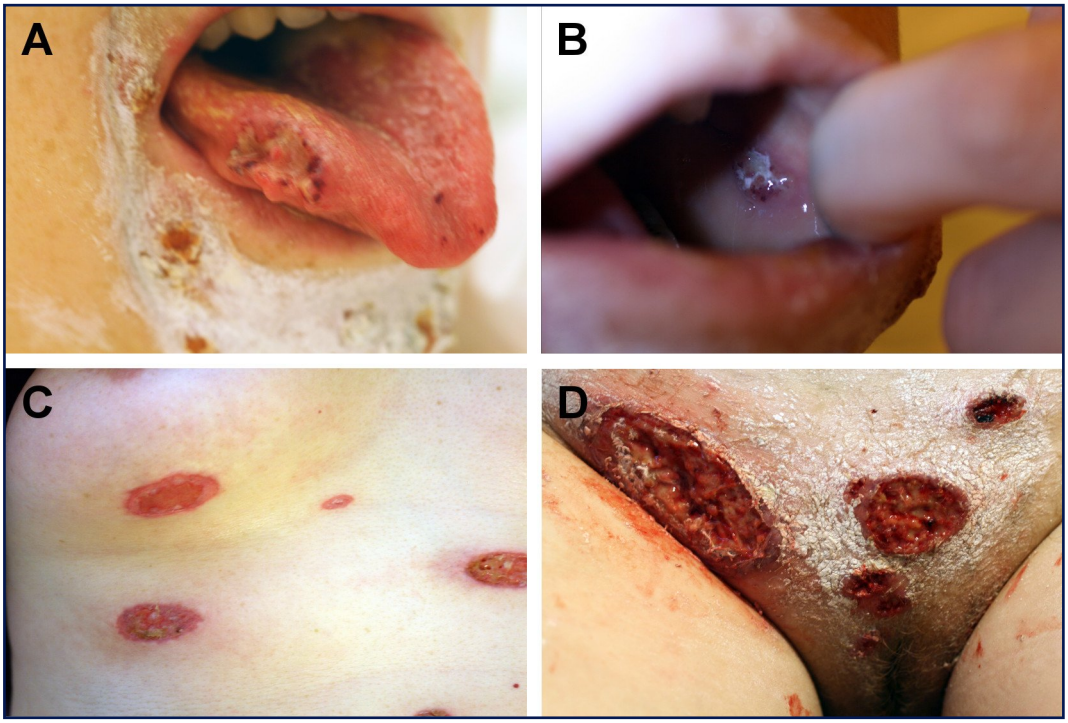

Figure 1

Multiple painful lesions of pyoderma gangrenosum located on the tongue (A) and oral mucosa (B), the submammary and abdominal region (C) and mons pubis (D).

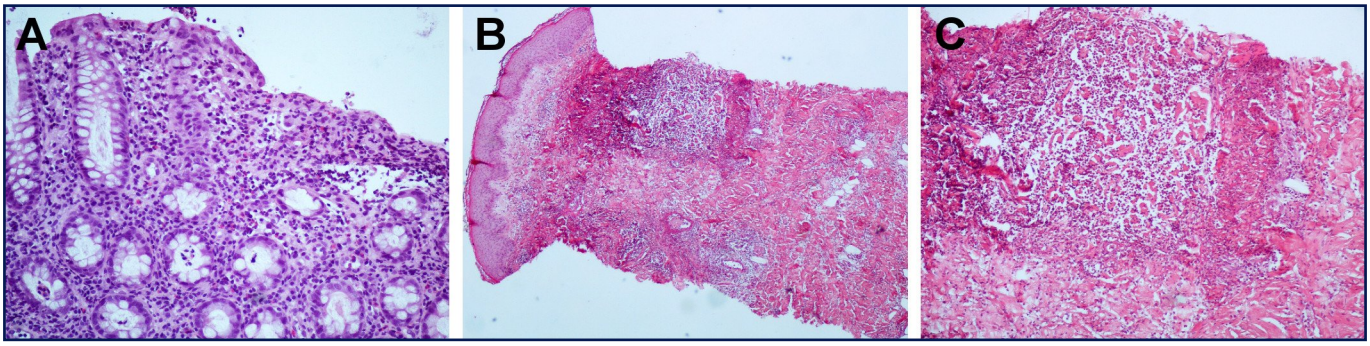

Figure 2

Bowel biopsy shows ulcerative proctocolitis with lymphocytic infiltration of the intestinal mucosa, distortion of crypt architecture, goblet cell depletion and frank crypt abscesses, HE staining (A). Biopsy of a skin ulcer shows lymphocytic and granulocytic infiltrates, single small abscesses, secondary vasculitis HE staining (B, C).

sia ++; iron 1.3 µmol/l (6.6-26); transferrin 1.6 g/l (2.0-3.6)]. The white cell and platelet counts were within the normal range, however the C-reactive protein was significantly elevated at 295 mg/l (0-5). The autoantibody screening test (ANA, dsDNA, ENA) revealed no immunologic abnormalities. Stool tests were negative for Clostridium difficile, Salmonella, Yersinia, Campylobacter, Shigella, parasites. Serological tests for antibodies against HIV1/2, Hepatitis A, B, C, HSV1/2, CMV, EBV, VZV and TPHA also proved negative. The smear tests of the ulcers' microbiology swabs (skin, outer ear, mouth, and eye) were negative for common bacteria. The abdomen sonography and gastroscopy revealed no pathological findings, however an MRI of the abdomen provided evidence of a long segment, circular KM-enhancing wall thickening in the sigmoid and rectal colon with no evidence of small bowel involvement or fistules. A sigmoidoscopy showed signs of severe ulcerative colitis, whereas the colonoscopy findings were compatible with a left-sided ulcerative colitis with macroscopic characteristics of pronounced activity.

Punch biopsies of the skin ulcers showed mild acanthosis of the epidermis, slight edema, lymphocytic and granulocytic infiltrates. Single small abscesses, secondary vasculitis and few eosinophils were also found. Neither fungal infection structures nor signs of dysplasia or malignancy were detected. The histological findings were not specific but compatible with the clinical picture of PG. A bowel biopsy was also conducted and confirmed the diagnosis of an ulcerative proctocolitis with lymphocytic infiltration of the intestinal mucosa, distortion of crypt architecture, goblet cell depletion and frank crypt abscesses (Fig. 2).

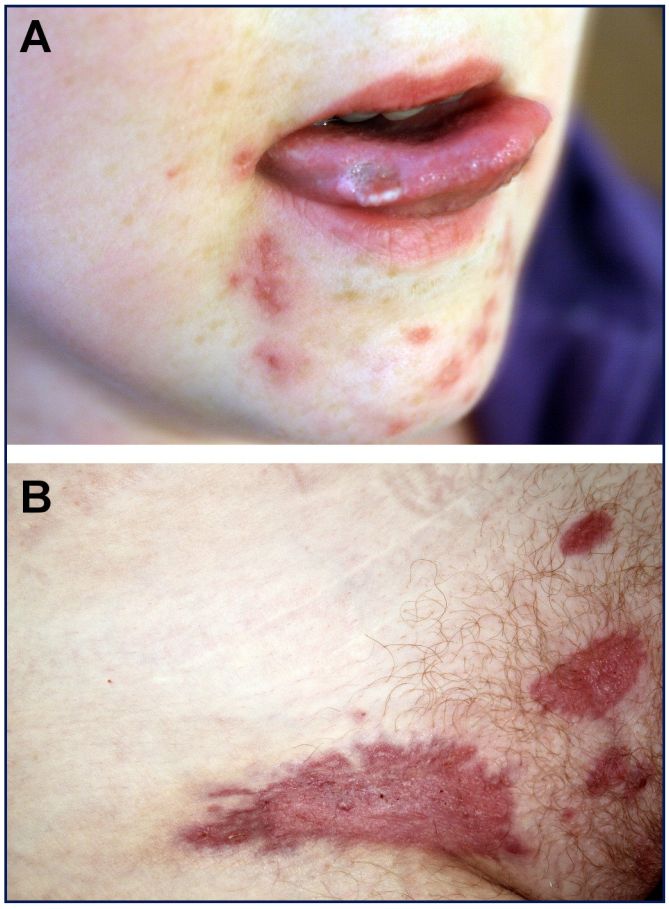

Figure 3

Lesions six weeks after infliximab therapy. Ulcer on the tongue edge (A) and lesions on mons pubis (B).

Therapy

The patient was initially treated with intravenous high-dose prednisolone 1 mg/kg per day in combination with antibiotics and mesalazine. Gastrointestinal symptoms and PG lesions persisted after ten days and showed no tendency of regression. Therefore, infliximab infusions were administered in a dose of 5 mg/kg at weeks 0, 2, and 6. Prior to the infliximab infusions, active tuberculosis was ruled out by a chest X-ray and the tuberculin skin test, which were both negative. Other active infections, such as hepatitis, were also ruled out by serology control. The therapy was completed with intensive topical antiseptic treatment of the lesions with polyhexamethylene biguanide (PHMB), chlorhexidine, oxytetracycline and ofloxacine eye drops for the management of the conjunctivitis. To accelerate wound healing, a hydrophilic polyurethane foam dressing in combination with a nanocrystalline silver-coated antimicrobial barrier dressing were also used. Infliximab infusions were well tolerated without any adverse effects.

Course of the Disease

Within a few days after the first infliximab administration a significant improvement was noted in stool frequency and cessation of hematochezia. The PG lesions showed a rapid healing tendency with granulation and epithelialization of all lesions. Four days after the first infusion, the patient was released from the hospital with no signs of active UC and the next two administrations of infliximab followed on an outpatient basis. Topical therapy was also continued after the discharge of the patient. Prednisolone was gradually reduced to discontinuation and the patient has since been closely monitored by our dermatology outpatient department and by the gastroenterology department of our hospital. Six weeks after the first infusion the PG lesions showed a fast healing tendency with some lesions having completely healed (Fig. 3). Infliximab infusions are currently still administrated at 8-week intervals with both UC and PG in complete clinical remission to date. The currently maintained therapeutic scheme consists of infliximab 5 mg/kg and mesalazine 3 x 1.0 g/day.

Discussion

The first reference of PG in the literature was in 1916 by Brocq,[3] whereas some years later Brunsting *et al*[4] in 1930 described the clinical features of PG in five different cases in adults. The incidence of PG has not been precisely determined, however it is estimated from 3 to 10 per million per year.[5] As already mentioned, approximately 50-78% of patients have an associated systemic disease, commonly IBD, arthritis, hematological and lymphoreticular malignancies,

or diseases known to be associated with significant immunocompromise.[6] Extracutaneous manifestations with neutrophilic infiltrates also exist (articular, ocular, renal, pulmonary, hepatosplenic, muscular), with lung involvement being the most common.[6,7] On the other hand, one third of patients with IBD develop cutaneous manifestations,[8] the most common of which are erythema nodosum and PG.[9]

The pathogenesis of PG remains still unknown, although a cell-mediated immunity defect has been suggested.[10] Since IBD is the most common underlying disorder, cross-reacting antigens in the bowel and the skin could be responsible for the cutaneous manifestation.[11] PG is thought to be related to immune dysregulation, including defects in neutrophil chemotaxis, neutrophil hyperreactivity and overexpression of cytokines such as interleukin-8.[12-14] Many of these effects may be mediated by the proinflammatory cytokine TNF-α.

The unusual feature in our patient was the severe manifestation of PG in a multilocular disseminated form, the tongue and the oral mucosa involvement and the rapid progress of the disease despite the high-dose corticosteroid therapy. The reported cases of severe disseminated multilocular PG in association with UC with concomitant painful oral involvement are extremely rare.[15-18] There have been some reports linking oral PG with IBD and hematological disorders,[19,20] however this was not the case in our patient where no hematological disorder was present.

Clinically, the oral lesions are usually painful, appear as irregular shaped ulcers 15 mm to 20 mm in diameter with rolled out margins and a grayish colored base[6,21] with most common sites of involvement being the tongue, palate, lips, buccal mucosa, gingiva and tonsillar fauces.[20,21] In our case, both tongue and buccal mucosa were severely affected.

Systemic corticosteroids are still suggested as the first line therapy for PG,[22] however there is no published algorithm for PG treatment.[23] The therapeutic approach currently depends on the severity of the skin manifestation, the general clinical condition of the patient as well as the underlying disease. In steroid refractory PG associated with UC, like in our patient, immunomodulatory therapy and biological response modifiers have been evaluated. Mycophenolate mofetil, dapsone, tacrolimus, thalidomide, cyclosporine, infliximab, adalimumab and more recently the recombinant human epidermal growth factor have been reported as successful agents in the treatment of PG.[22,24-29] Among biologics, infliximab was shown effective in classic PG in a randomized, double-blind, placebo-controlled study.[30] In a very recent systematic review the use of infliximab for PG was proposed as a first line treatment.[31]

Conclusion

There are only few case reports of infliximab treatment in disseminated PG with oral involvement associated with UC.[16,18,22,28,32] In our patient, infliximab was a rapidly effective treatment of PG associated with UC, both of which have been resistant to steroid therapy. This case report supports the use of infliximab as an alternative therapy for PG associated with UC and oral involvement when conventional treatment is ineffective.

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