

Generalized Pyoderma Gangrenosum Associated with Ulcerative Colitis: Successful Treatment with Infliximab and Azathioprine

Pyoderma gangrenosum (PG) is a rare ulcerative skin disease, part of the spectrum of neutrophilic and auto-inflammatory dermatoses. Its pathogenesis is unknown, although immune pathways have been implicated. Lesion biopsies show a predominantly neutrophilic infiltrate. The incidence of PG is uncertain, but it is estimated to be 3-10 per million per year, occurring at any age but most commonly between 20 and 50 years with a possible slightly higher incidence in women. Approximately 50% of patients with PG also have another disease associated with PG. The most common is inflammatory bowel disease (IBD), particularly Crohn's and ulcerative colitis (UC). Local treatment may be sufficient for mild cases, while for severe cases systemic immunosuppressants are the mainstay (1,2). We report the case of a patient with bullous PG and UC successfully treated with infliximab and azathioprine.

A 32-year-old male Caucasian patient presented with painful violaceous vesicles and enlarging bullae

of various sizes and with acute onset, located on the trunk and bilaterally on both the lower and the upper extremities. Lesions on the trunk were composed of hemorrhagic pustules with a surrounding erythematous overhanging border. Some of the lesions had undergone central necrosis and ulceration (Figure 1, a-d). The patient reported of the lesions had appeared one week ago, simultaneously with the exacerbation of a known inflammatory bowel disease with hemorrhagic mucoid diarrhea and fever of up to 38.5°C. The patient's medical history included UC affecting the whole colon (pancolitis), diagnosed 5 months prior to the onset of the epidermal lesions, for which the patient was receiving treatment with oral prednisolone 10 mg/day and mesalazine granules.

Blood tests showed severe anemia, leukocytosis, and increased inflammatory markers (C-reactive protein, erythrocyte sedimentation rate). Antinuclear antibodies (ANA), anti-double stranded DNA (anti-dsDNA) antibodies, antineutrophil cytoplasmic an-



Figure 1. Large, rapidly progressing lesions of pyoderma gangrenosum on the lower extremities (a-b) and on the trunk (c-d) before treatment.

tibodies (cANCA), perinuclear neutrophil antibodies (p-ANCA), antiphospholipid antibodies, and tumor markers were within normal limits. The patient was negative for cryoglobulins, viral hepatitis (B, C) and human immunodeficiency virus (HIV). Blood cultures were negative. Microscopy and cultures for mycobacteria and fungi gave negative results. Stool samples tested negative for infections agents. The Mantoux skin test was negative. Colonoscopy showed severe pancolitis, and biopsies from the rectum and sigmoid colon were consistent with chronic ulcerative colitis. Abdominal ultrasound and chest and abdominal X-rays did not result in significant findings. Because of severe anemia, the patient received 2 blood transfusions. The histopathologic examination carried out on the erythematous border of a lesion on the lower leg showed a neutrophilic infiltrate, confined to the dermis. On the basis of clinical findings, the diagnosis of PG was established.

Topical wound care consisted of local wound care and a topical corticosteroid. Systemic therapy was initiated with 40 mg/day methylprednisolone for 7 days, 30 mg/day for 7 days, then 25 mg/day, and then tapered down further. The patient received an infusion of infliximab 7.5 mg/kg at weeks 0, 2, and 6 and every 8 weeks thereafter. After week 2, oral azathioprine 2.5

mg/kg daily was added to the treatment. The patient also received mesalazine tablets (2 g \times 2/day) and mesalazine enema (1-2/day). The patient showed good response to treatment, with clinical remission of skin lesions. Lesions healed with characteristic thin, atrophic scars (Figure 2, a-d). At 7-month follow-up the patient was continuing with infusions of infliximab 7.5 mg/kg and azathioprine 2.5 mg/kg and was still in remission.

We reported our experience with a case of generalized bullous pyoderma gangrenosum associated with ulcerative colitis. Generalized pyoderma gangrenosum is very rare. Bullous or atypical PG was first described by Perry and Winklemann in 1972 (1). Brunsting *et al.* coined the term pyoderma gangrenosum (PG) to describe a series of patients with recurrent ulcerations (3). The incidence of this disease is uncertain. Its pathogenesis is unknown, but an immunological background has been suggested. In approximately 50% of patients, an underlying immunological disease is present, commonly inflammatory bowel disease (IBD) (4-6). In larger series of patients with PG, approximately 50% present with a primary disorder. Ulcerative colitis is found in 10-15% of cases. Crohn's disease is associated with PG closed than UC. Less than 3% of patients with Crohn's disease or UC develop PG (6).

PG is characterized by cutaneous ulcerations with mucopurulent or hemorrhagic exudate. It begins as an inflammatory pustule with a surrounding halo that enlarges and begins to ulcerate. These very painful ulcers present with undermined bluish borders with surrounding erythema. The lesions of PG most commonly occur on the legs, but they may occur anywhere on the body. The clinical picture of PG is very characteristic. Therefore the diagnosis of PG is based firstly on clinical signs and on the patient's history of underlying diseases and then supported by biopsy. PG has four distinctive clinical and histological variants. Some have morphological and histological features that overlap with other reactive neutrophilic skin conditions. There are no diagnostic serologic features (6,7).

There is no evidence that the efficacy of treatment strategies for PG differs between IBD and non-IBD patients. For patients with a diffuse disease or rapidly progressive process, systemic treatment is essential. Immunosuppression is the mainstay of treatment. Traditionally, the most commonly used drugs with the best clinical experience are systemic corticosteroids. Corticosteroids have been considered as first line treatment (6,8). As reported by the European Crohn's and Colitis Organisation (ECCO) in 2008, an



Figure 2. Clinical remission of skin lesions on the lower extremities (a-b) and on the trunk (c-d) after treatment with 4 infliximab infusions and azathioprine.

evidence-based consensus on the management of special situations in patients with ulcerative colitis, systemic corticosteroids are recommended (9). Treatment with corticosteroids (e.g. prednisolone 1-2 mg per kg/day or pulse therapy with 1 g of methylprednisolone) aims to prevent progression and rapidly stop inflammation (6). Additional mesalamine and corticosteroids may be effective in patients with bowel disease (10).

In recent years, tumor necrosis alpha (TNF- α) inhibitors, such as infliximab and adalimumab, were reported to be effective for PG associated with IBD. These drugs block the biological activity of TNF- α , which effects regulatory T cells, restoring their capacity to inhibit cytokine production. The TNF- α inhibitors thus suppress the inflammatory processes that is involved in the pathogenesis of PG (11). Infliximab, a chimeric monoclonal antibody, is given by infusion at weeks 0, 2, and 6 and then every 8 weeks, usually at a dosage of 5 mg/kg.

UC of patients with frequent disease relapse or those that are resistant or dependent on corticosteroids is often treated with purine antimetabolites, such as azathioprine (AZA) (10). AZA, a purine antimetabolite (2.5 mg per kg/day) is administered for its steroid-sparing effects. The response occurs after 2 to 4 weeks (6, 10). Infliximab can be combined with AZA. Patients with UC treated with infliximab plus AZA were more likely to achieve corticosteroid-free remission at 16 weeks than those receiving either monotherapy (10,12).

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