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Pyoderma Gangrenosum and Chronic Inflammatory Bowel Disease: About a Case Series and Review of the Literature

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Abstract: ***Pyoderma gangrenosum is one of the most widely described clinical pictures. It is a neutrophilic pustulo-ulcerous aseptic dermatosis of unknown cause which poses difficulties in management to this day. We report a retrospective series of 438 cases of chronic inflammatory bowel disease associated with extra-digestive manifestations, including fifteen cases of pyoderma gangrenosum, and we propose to analyse the diagnostic and therapeutic aspects. This is a retrospective observational study with a descriptive and analytical aim, involving a series of 438 patients followed for chronic inflammatory bowel disease in the hepato-gastroenterology department. The study was spread over 9 years, and included all cases of chronic inflammatory bowel disease whose diagnosis was retained on the basis of a set of arguments and who presented with cutaneous manifestations such as pyoderma gangrenosum. The average age was 35 years, with a slight female predominance. The skin and mucous membrane lesions found were mouth ulcers, erythema nodosum, pyoderma gangrenosum, and psoriasis. The average time to onset of skin lesions was 8 years after the diagnosis of the disease. Functional dermatological signs were skin redness, tingling, and atypical pain. Clinical examination often found one or more painful ulcerations with an inflammatory border. Skin biopsies were performed in 9 patients and histological examination revealed an inflammatory infiltrate with neutrophils and lymphocytes. In combination with the background treatment of their chronic inflammatory bowel diseases, all our patients received local care and seven patients received systemic corticosteroid therapy. All our patients had a favourable outcome with a mean follow-up of 5 years. Pyoderma gangrenosum is the second most common skin manifestation of IBD and the most severe, sometimes more disabling than the intestinal disease itself. Usually associated with extensive colonic involvement, Pyoderma Gangrenosum most often appears during a digestive flare. It can also occur independently in 30% of cases.***

Keywords: pyoderma gangrenosum, chronic inflammatory bowel disease, neutrophilic dermatosis, treatment

1. Introduction

The general consensus in the literature places mucocutaneous lesions as the second most common extra-intestinal manifestation of chronic inflammatory bowel disease[1]. Pyoderma gangrenosum is one of the most frequently described clinical pictures. A neutrophilic pustulo-ulcerous aseptic dermatosis of unknown cause, which to this day poses management difficulties [2].

We report a retrospective series of 438 cases of chronic inflammatory bowel disease associated with extra-digestive manifestations, including fifteen cases of pyoderma gangrenosum, and we propose to analyse the diagnostic and therapeutic aspects. The objectives of this work are to determine the main epidemiological characteristics of the occurrence of PG during IBD, to analyse their clinical and paraclinical expressions, to evaluate their prognosis as well as their therapeutic modalities.

Patients and Methods

This is a retrospective observational study with a descriptive and analytical aim, covering a series of 438 patients followed for chronic inflammatory bowel disease in the hepato-gastroenterology department. The study was spread over 9 years, from January 2011 to December 2019. We included in our study all cases of chronic inflammatory bowel disease whose diagnosis was retained on clinical, endoscopic, radiological and histological grounds and which presented extra-digestive manifestations. Thus, we excluded all files that could not be used and patients whose diagnosis of IBD was not certain. In the end, we were able to collect 15 cases of pyoderma gangrenosum.

2. Results

The average age was 35 years, with a slight female predominance (9 females / 6 males). The skin and mucous membrane lesions found in our series were mouth ulcers, erythema nodosum **(Figure 1)**, pyoderma gangrenosum **(Figure 2),** and psoriasis. The mean time to onset of skin lesions was 8 years (6 months - 20 years) after diagnosis of the disease. Functional dermatological signs were skin redness, tingling, and atypical pain.

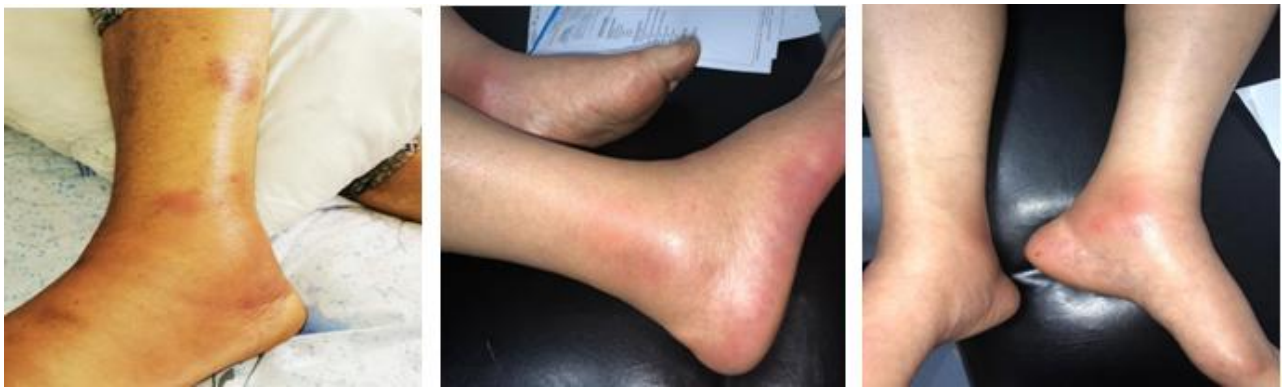

Figure 1: Erythema nodosum lesions of patients in our series

Clinical examination found one or more painful ulcers with an inflammatory border with purulent hutches. Skin biopsies were performed in 9 patients and histological examination revealed an inflammatory infiltrate of neutrophils and lymphocytes. In combination with the background treatment of their chronic inflammatory bowel diseases, all our patients received local care and seven patients received systemic corticosteroid therapy. All our patients had a favourableoutcome with a mean follow-up of 5 years.

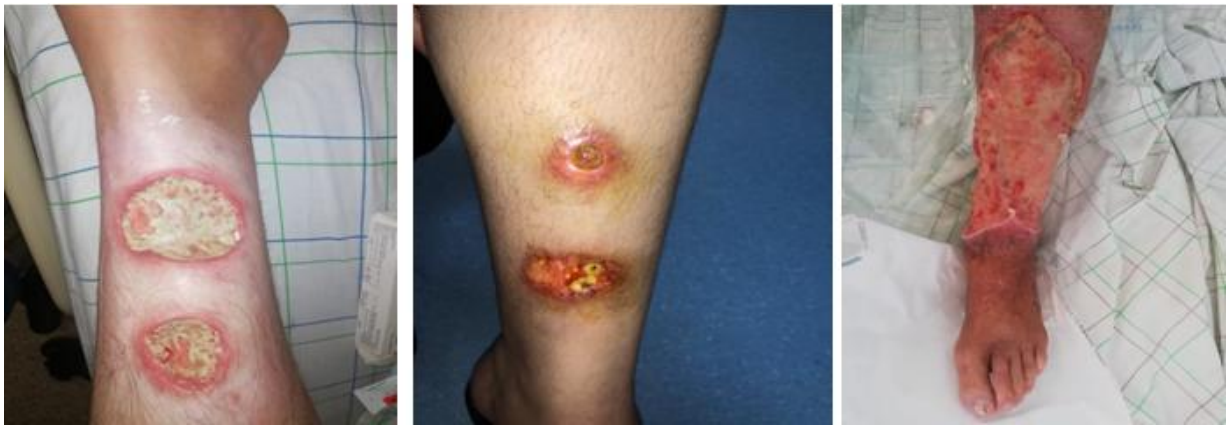

Figure 2: Pyoderma gangrenosum lesions in patients from our series

3. Discussion

PG complicates 2-3% of IBD, more common in ulcerative colitis (5%) than in Crohn's disease (2%) [1][3]. In our series, we collected 15 cases of PG out of 438 IBD patients followed up in the department, i.e. a prevalence of 3.4%. Conversely, IBD represents the first etiology of pyoderma gangrenosum (20 to 30% of cases) [4][5].

It usually appears after about ten years of evolution, which is consistent with our series (8 years). We noted an average age of 35 years for the first episode. This age is close to that of other series in which the age of diagnosis varied from 25 to 55 years [6][7][8].

We noted a slight female predominance (66%) in our series. The female predilection for PG is less clear in the literature and suggests a possible role for hormonal influences and some have suggested that oestrogen may have a modulating effect on MIE23 [8][9].

The pathogenesis of pyoderma gangrenosum is multifactorial and involves neutrophil dysfunction, inflammatory mediators, and genetic predisposition [6]. A number of loci associated with susceptibility to inflammatory bowel disease were significantly associated with pyoderma gangrenosum including IL8RA, MUC17, MMP24, WNK2, DOCK9, PRMD1 and NDIFIP1 [10][11][12].

The incidence of pyoderma gangrenosum appears to be higher in patients who have developed other extra-intestinal manifestations such as ocular or joint involvement [13]. This risk is also increased in cases of active smoking and colonic involvement in crohn's disease and in cases of a family history in ulcerative colitis[11].

The relationship between disease activity and PG is controversial. Several reports have suggested that the development of PG is closely related to disease activity, explained by immune complexes in the inflamed intestinal mucosa involving IL-15 and IL-8 and are responsible for skin lesions. In addition, other studies indicate that PG is not related to IBD activity and often occurs in patients whose bowel disease is in clinical remission [1][8][12].

The symptomatology is dominated by pain, often intense, found in all our patients [14][15]. The initial lesion, most often caused by trauma, initially presents as coalescing inflammatory pustules, which gradually fuse to form a necrotic ulcer with well-defined hypertrophic margins of purplish colour. The surrounding skin tissue is erythematous, infiltrated and frequently indurated. The base of the ulcer is often undermined, showing early

subcutaneous inflammatory extension, with secondary ulceration of the epidermis [16][3]This is often covered with yellowish deposits that falsely suggest pus, hence the name *Pyoderma*[17][18]. The lesions classically predominate on the lower limbs, but can be seen on the entire skin surface [7].

The development or aggravation of a lesion after trauma is a classic feature of PG and may be responsible for the high frequency of lesions in the leg, as this is a high-risk area for minor injuries. Peristomal localisation occurs in about 10% of cases, favoured by the various aggressions to which the peristomal skin is subjected, and appears on average two months after the stoma is made, but longer periods of up to three years have been observed [3].

The positive diagnosis is mainly clinical. No precise diagnostic criteria have yet been established and it remains a diagnosis of exclusion and elimination[5][4]. Biopsy of the lesion may aggravate it and should therefore only be done in case of diagnostic doubt. Histology is not specific and allows other diseases to be excluded. It reveals an inflammatory infiltrate with a predominance of poly-morphonuclears, localised thrombi and necrosis of the epidermis [19].

The differential diagnosis of ulcerated skin lesions includes vasculitis, arterial or venous insufficiency, infectious diseases, insect bites and neoplastic lesions. An angiological assessment, bacteriological smear and skin biopsy should be performed [6][19].

Appropriate treatment should be initiated as soon as possible to limit functional or cosmetic sequelae. It should be noted that there is no specific treatment, so different approaches can be taken simultaneously. In combination with standard wound treatments, topical antimicrobial agents are useful to decrease the bacterial load. Hyperbaric oxygen therapy has been successfully described. Local corticosteroids or intralesional injections have also been shown to be beneficial (approximately 40% complete responses) [20]. When local treatment is insufficient, systemic corticosteroid therapy can be started (0.5-1 mg/ kg/day). In case of corticosteroid resistance, treatment with immunosuppressive agents can be started: azathioprine, cyclophosphamide, chlorambucil, ciclosporin A or tacrolimus. Recently, immunomodulating agents have been successfully prescribed (thalidomide, infliximab) [21][14]. Surgical treatment should be avoided, as it may favour the progression of the disease due to the pathergic phenomenon [19][17]. Patients often develop a single episode but the lesions may recur in one third of cases [3].

The overall prognosis is good but extremely influenced by the underlying disorders[12]. Complete healing of the PG was achieved in all our patients. Smoking cessation should be presented as an essential associated measure, given the stimulating action of tobacco on neutrophils [21].

4. Conclusion

Pyoderma gangrenosum is the second most common skin manifestation of IBD and the most severe, sometimes more disabling than the intestinal disease itself. Generally associated with extensive colonic involvement, Pyoderma Gangrenosum appears on average after about ten years of IBD evolution, most often during a digestive flare-up. It can also occur independently in 30% of cases.

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