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Multifocal pyoderma gangrenosum secondary to subclinical diverticulitis: case report and brief literature review

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Abstract

Pyoderma gangrenosum is characteristically associated with inflammatory bowel disease. However, the association between this neutrophilic dermatosis and diverticular disease is scarcely mentioned in the literature. Diverticulitis should be included in the differential diagnosis in patients with pyoderma gangrenosum and gastrointestinal complaints, or even in asymptomatic patients, particularly in the elderly. Misdiagnosis can lead to inadequate treatments and serious complications.

Keywords: pyoderma gangrenosum, diverticulitis, colonic, diverticular disease, inflammatory bowel disease, prednisone

Introduction

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis that can occur as an idiopathic disease, in association with systemic conditions or as part of an inherited inflammatory syndrome [1]. The association between PG and colonic diverticulitis is poorly described in the literature. We present a case of PG that preceded the diagnosis of diverticulitis.

Case Synopsis

An 88-year-old woman presented with a 7-day history of multiple cutaneous abscesses on her chest and left leg. Surgical drainage was performed and multiple samples were taken for microbiological culture. In addition, amoxicillin/clavulanate 875/125mg every 8 hours was initiated. However, cutaneous lesions worsened during the next days, whereas swab cultures were negative. The patient was otherwise asymptomatic but significantly, she had a recent lower gastrointestinal bleeding attributed to hemorrhoids.

A month later, the patient was admitted to the hospital because of fever up to 40ºC, weight loss, and gastrointestinal bleeding of 48 hours of evolution, without abdominal pain or vomiting. Physical examination revealed an inflammatory cribiform ulcer on her lower left leg, with violaceous borders and 12 cm in diameter (**Figure 1A**). In addition, multiple smaller ulcerative lesions were seen proximally (**Figure 1B**), whereas some pustules were present on her presternal region.

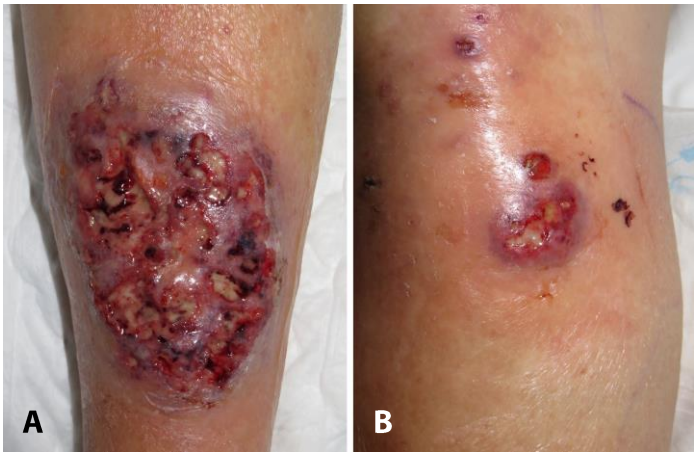

Figure 1. ***A)*** *Lower left leg. Inflammatory and necrotic cribriform ulcer with violaceous border.* ***B)*** *Upper left leg. Small ulcerative lesion with similar characteristics.*

Skin biopsy of a violaceous edge of the largest ulcer revealed a dense inflammatory infiltrate mainly composed of neutrophils affecting dermis and subcutaneous tissue, with associated edema and interstitial hemorrhage (**Figure 2**). Microbiological cultures of skin biopsies for bacteria, mycobacteria, and fungi were negative. Laboratory work up showed normocytic anemia (hemoglobin 9.5g/dL), 10.900 leukocytes/mm3, and C-reactive protein of 117g/dL. Antinuclear antibodies (ANAs), anti-neutrophil cytoplasmic antibodies (ANCAs), and serological tests (HIV, hepatitis B and C viruses) were negative. Fecal occult blood test was positive and colonoscopy revealed inflammatory signs with mucopurulent discharge of sigmoid colon, suggesting acute diverticulitis. Computed tomography scan showed sigmoid colon diverticulosis with increased density of adjacent fat tissue, as well as regional lymphadenopathy. Histopathological analysis of intestinal biopsy revealed non-specific inflammation without ulcers, erosions, fissures, or granulomas.

The endoscopic and radiological findings, along with the absence of histopathological data suggesting inflammatory bowel disease (erosions, ulcers, granulomas) led to the diagnosis of acute diverticulitis. Therefore, a diagnosis of PG and associated diverticulitis was rendered. The patient started treatment with prednisone in a dose of 60mg daily, in addition to intravenous clindamycin and metronidazole. The skin lesions began to improve rapidly and prednisone was continued on a slowly tapering dose over 5 months. The patient experienced progressive clinical improvement of her skin lesions, which were completely resolved three months after introduction of corticosteroid therapy. After 12 months of follow up, the patient remains completely asymptomatic.

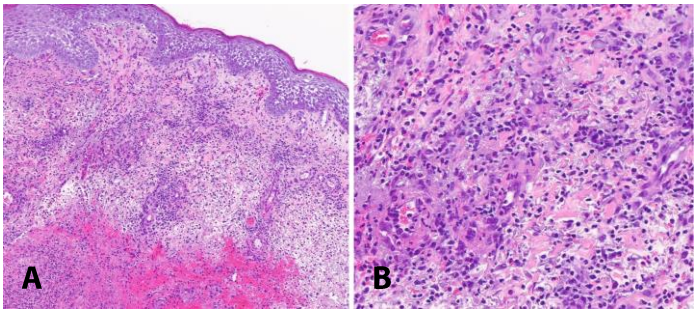

Figure 2. ***A)*** *Dense inflammatory infiltrate in dermis and subcutaneous tissue composed mainly of neutrophils. Edema and marked interstitial hemorrhage can be observed. H&E, 100×.* ***B)*** *Dense mixed-inflammatory infiltrate with abundant neutrophils. H&E, 400×.*

Case Discussion

Pyoderma gangrenosum is classically considered a diagnosis of exclusion, as there are no definitive laboratory tests or pathognomonic histopathological findings [2]. Nevertheless, international experts have recently proposed diagnostic criteria that facilitate its diagnosis. In addition to skin biopsy demonstrating a dense neutrophilic infiltrate (major criterion), patients must have at least four minor criteria: exclusion of infection; pathergy; personal history of inflammatory bowel disease or inflammatory arthritis; peripheral erythema, undermining border, and tenderness at ulceration site; multiple ulcerations, at least one on an anterior lower leg; cribriform or "wrinkled paper" scar at healed ulcer sites; and decreased ulcer size within one month after initiating immunosuppression [3]. Our patient therefore fulfilled the major criteria as well as five minor criteria. Once a PG diagnosis has been made, it is important to look for underlying systemic conditions, mainly inflammatory bowel disease (IBD), rheumatoid arthritis, or hematological malignancies or paraproteinemia [1]. Indeed, the most common of systemic associations of PG is IBD, with some studies suggesting that ulcerative colitis is more frequent than Crohn disease [4].

Diverticulitis is an inflammatory disorder of the gastrointestinal tract that affects colonic mucosal herniations. It is common among the elderly and presents generally as left-sided abdominal pain, fever, and leukocytosis [4]. Although the majority of patients can be managed with systemic antibiotics, some patients require surgical intervention because of complications.

Klein et al. first reported three patients with diverticulitis, arthritis, and pyoderma gangrenosum. Misdiagnosis of IBD led to unsuccessful medical therapy, whereas colon resection resolved both cutaneous and intestinal symptoms [5]. To our

knowledge, only eight more cases have been published to date [5-9], (**Table 1**). The patients were mostly elderly (range from 56 to 88 years in our case; mean: 72 years; median 69 years) and there was no difference between sexes (4 men/5 women). Five patients presented with multiple lesions, whereas four presented with a single lesion. Concomitant articular involvement was documented in four of nine patients.

As occurred in our case, diverticulitis can be asymptomatic, leading in some cases to advanced disease with abscess formation and need for surgical treatment [6-8]. Overlap between bowel-associated dermatosis arthritis syndrome and pustular pyoderma gangrenosum has also been reported in a patient with diverticulitis and sigmoid stenosis [9]. Pyoderma gangrenosum associated with diverticular disease is often recalcitrant to standard therapies and complete resolution has been achieved with bowel resection in all cases, except one in which the patient died from surgical complications [4-9]. In fact, in previous reports, no response was obtained with medical therapies such as systemic corticosteroids, cyclosporine A, antibiotics, dapsone, hyperbaric oxygen therapy, and intralesional or topical corticosteroids. In our case, however, combined therapy with antibiotics and high-dose corticosteroids led to a complete resolution of both gastrointestinal and cutaneous symptoms, without subsequent recurrences. To our knowledge, there are no previous reports in which medical combined therapy achieved complete and sustained response of both diverticulitis and PG.

Pyoderma gangrenosum generally follows a course independent to that of IBD. In this sense, cutaneous lesions could appear at any stage of the disease, even when it is controlled. However, in most of the few reported cases associated with diverticular disease, PG evolved in parallel with diverticulitis [5-8]. Surgical treatment with excision of the affected bowel segment led to a favorable evolution and without recurrence of the dermatosis.

The pathophysiology of PG is complex and not fully understood [2]. Both innate and cellular immunity play a role in the pathogenesis of PG although it remains unclear which is the trigger of this immune dysregulation. Immune alterations in PG are complex, and involve neutrophils, T-cells, and inflammatory mediators such as IL1β, IL8, IL17, and TNF [1]. In diverticulitis, colonic inflammation may provide an antigenic stimulus that would trigger an inflammatory cascade. Bacterial antigenic stimuli could result in PG through deposition of circulating immune complexes in the skin [8].

The management of PG is based on reducing inflammation through anti-inflammatory and immunosuppressive drugs [2]. As occurred in our case, it is important to recognize and treat any underlying systemic disease [1]. For localized PG, topical and intralesional corticosteroids can be effective; for more severe or recalcitrant disease, systemic corticosteroids and immunosuppressive medications such as cyclosporine may be used [2]. In addition, adequate wound care is required to improve healing, minimize pain, and decrease the risk of secondary infections.

Conclusion

One of the most common systemic associations of PG is IBD. Because of clinical similarity between IBD and diverticulitis, misdiagnosis can occur. Acute diverticulitis should be added into the differential diagnosis in patients with PG and gastrointestinal disease or even in asymptomatic patients, particularly in the elderly. An early diagnosis and adequate medical therapy could prevent serious complications and need for surgical intervention.

Potential conflicts of interest

The authors declare no conflicts of interests.

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Table 1. *Published cases of pyoderma gangrenosum related to colonic diverticulitis.*

Refer-ence	Number of patients	Age /Gender	Number of skin lesions	Articular involvement	Medical treatment for PG	Surgery	Intestinal biopsy	Evolution
Klein et al. [5], 1988	N=3	56/F 65/M 67/M	One One One	Recurrent arthritis (lower limbs) Recurrent arthritis (ankles) Recurrent arthritis (left knee)	PRD; ilCS PRD; ilCS; hyperbaric O_2 PRD	Yes Yes Yes	Diverticulitis with ruptured diverticula and pericolic abscesses	No recurrence after surgery
Kurgansky et al. [6], 1993	N=1	75/F	Multiple	Previous seronegative arthritis	Vancomycin/ Gentamycin → Ceftriaxone/ Clindamycin	Yes	Diverticulitis with perforation, fistula formation, chronic serositis with fibrous adhesions	No recurrence after surgery
Brouard et al. [9], 2004	N=1	78/F	Multiple	Arthralgia (elbows, wrists, knees, ankles)	Topical betamethasone	Yes	Numerous foci of inflammation and abscess formation in the mucosa, submucosa and intervening bowel wall	Death due to surgical complications
García-Morales et al. [7], 2005	N=1	69/M	One	Not mentioned	CsA, PRD, ilCS	Yes	Not mentioned	No recurrence after surgery
Fongue et al. [8], 2015	N=2	83/M 63/F	Multiple Multiple	Not mentioned Not mentioned	No PRD, Dapsone	Yes Yes	Diverticulitis complicated with abscess formation	No recurrence after surgery
Current case	N=1	88/F	Multiple	No	PRD	Not necessary	Non-specific inflammation without ulcers, erosions or granulomas	No recurrence after PRD + antibiotics

PG, pyoderma gangrenosum; M, male; F, female; PRD, prednisone; ilCS, intralesional corticosteroids; O_2, oxygen; seroneg, seronegative; CsA, cyclosporine A.