Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Case report and review of literature

Pyoderma gangrenosum and *Clostridium difficile* infection: an unfavorable association

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Abstract. Pyoderma gangrenosum is a chronic, neutrophil-mediated, recurrent skin disease that presents as a progressive ulceration, while being frequently associated with a systemic disease. We describe the case of a 58 year old woman previously operated for vulvar carcinoma, who developed pyoderma gangrenosum lesions at the site of subsequent lymphadenectomy and colitis with *Clostridium difficile*. The management plan included both immunosuppressive and antibiotic therapy. However, the patient did not present a favorable evolution.

Key Words: pyoderma gangrenosum, *Clostridium difficile*, lymphadenectomy, neutrophilic dermatosis

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Introduction

Pyoderma gangrenosum (PG) is a rare, chronic skin disease. The clinical evolution is characterized by a progressive ulceration that slowly responds to topical and systemic therapies, while the histopathological examination reveals neutrophilic infiltrates and consequent vessel destruction. PG is frequently associated with systemic diseases such as inflammatory bowel disease, arthritis, hematologic disorders such as IgA monoclonal gammopathy, acute myelogenous leukemia, myelodysplasia (Davis & Moschella, 2018). Initially, PG lesions are difficult to recognize and mistakenly considered to be infectious lesions; consequently, they are treated by surgical debridement and antibiotherapy. We describe the case of a patient with vulvar carcinoma, post-surgical PG at the site of lymphadenectomy, colitis with *Clostridium difficile* (C. difficile), that needed a challenging treatment including both immunosuppressive and antibiotic therapy.

Case report

A 58- year- old Caucasian woman was admitted for the investigation and treatment of bilateral, progressive, ulcerative plaques in the inguinal folds, which appeared 7 days after lymphadenectomy, performed as a follow-up treatment for vulvar carcinoma. Initially, two symmetrical, ulcerative lesions appeared around the excision scars and gradually extended over the course of 6 weeks on the thighs and abdomen, forming two large lesions (approx 15/5 cm on the left inguinal fold, approx 50/30 cm on the right lower abdomen) with necrotic deposits and an undermined, eritemato-violaceous border (Figure 1). The patient also presented around four diarrheic stools/ day. Previous treatments included local dressings to induce granulation, local debridement and a course of oral antibiotics that did not ameliorate the skin condition. Blood tests revealed an inflammatory syndrome, anemia and the presence of *C. difficile* in stool examination, while bacterial cultures from the ulceration were negative. A punch biopsy from the margin of the ulceration was obtained and sent for histopathology. The histology result was unspecific showing hypergranulosis, dermal oedema, vasodilation and mixed inflammatory infiltrate (Figure 2). A diagnosis of Pyoderma gangrenosum, *C. Difficil*e colitis was considered and both immunosuppressive treatment with Dexamethasone, Cyclosporine and antibiotic treatment with Vancomycin were initiated, in conjunction with anticoagulants, iron, hydroelectrolytic and albumine supplements. Local antiseptic solutions, neutral and alginate dressings were applied. The profuse diarrhea and C. difficile toxin positivity in the stool persisted. Consequently, oral metronidazole 500mg three times daily was added to vancomycin therapy (1g two times daily).

A positive evolution of PG was noted, with progression arrest of ulcer margins and the presence of granulation tissue; however, the general status of the patient worsened with abdominal bloating and abdominal pain, tachycardia, oedema, with an increase of the inflammatory markers, decrease of hypoalbuminemia, renal function impairment, thus raising the suspicion of toxic megacolon. The intensive care unit agreed to continue the therapy, but the patient solicited discharge, signed the informed consent that she understood the major risks for continuing the treatment at home and, unfortunately, died 2 weeks after discharge.

Discussion

Pyoderma gangrenosum is an uncommon, inflammatory, neutrofil-mediated disorder which may present bullous, pustular, vegetative lesions that usually progress into ulcerations. The adjusted incidence rate standardized to the standard European population is 0.63 per 100,000 person-years and the risk of death is three times higher compared to the general population (Langan et al 2012). Although the disease is idiopathic in

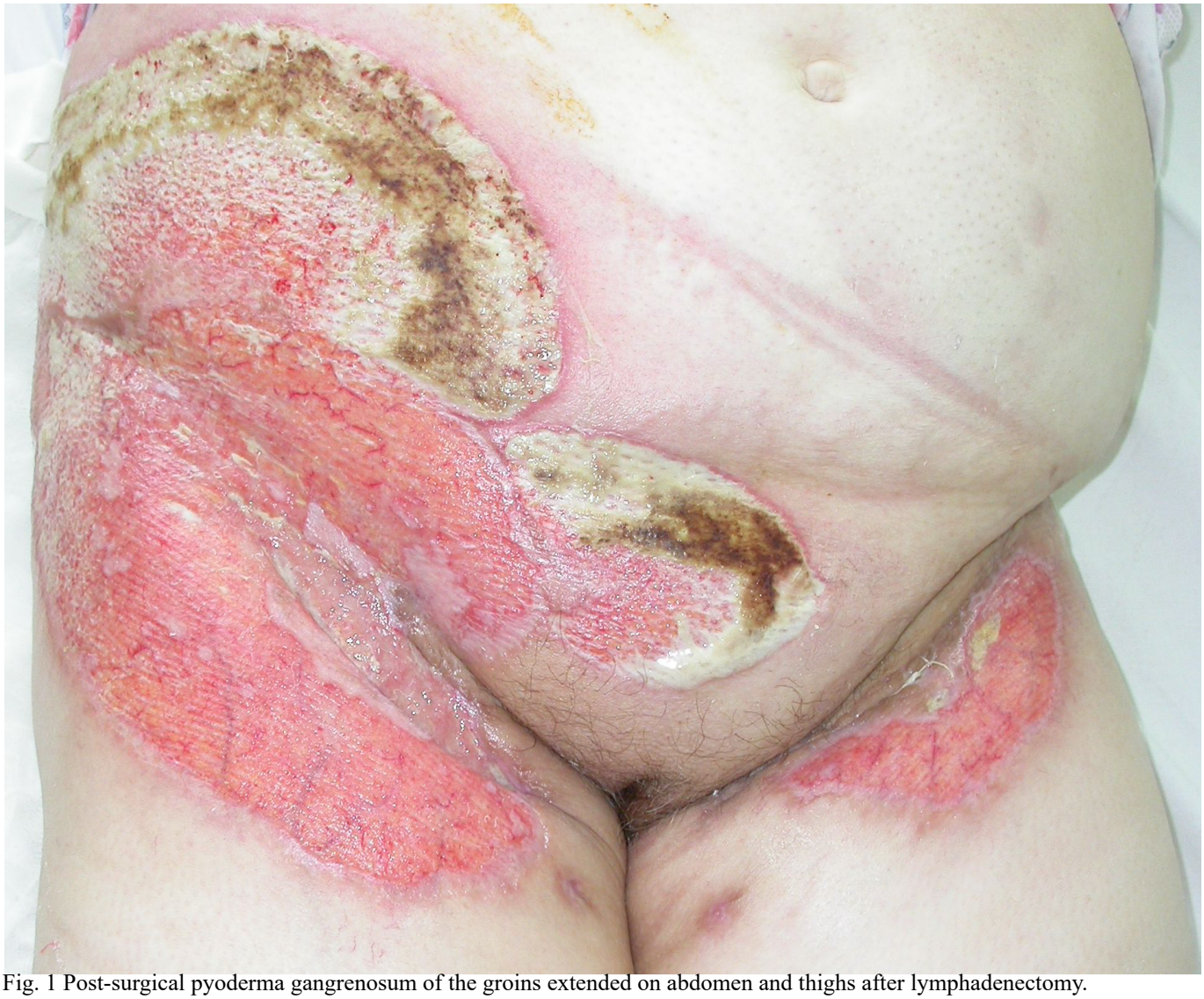

Fig. 1 Post-surgical pyoderma gangrenosum of the groins extended on abdomen and thighs after lymphadenectomy.

25-50% of patients, an association with a systemic disease or an underlying immunologic abnormality are currently considered (Davis & Moschella, 2018).

So far, no specific diagnostic criteria were validated. However, the clinician takes this diagnosis into consideration whenever faced with a progressive, painful, cutaneous ulcer with an eritemato-violaceous undermined border and when other causes were excluded (Su et al 2004). A retrospective review of the charts of 240 patients showed that 26% of patients that were initially treated for PG, proved to suffer of skin ulcerations of various etiologies, such as vascular occlusive disease, vasculitis, neoplasia, cutaneous infection, drug-induced or exogenous tissue injury, and other inflammatory disorders (Weenig et al 2002). The median time-frame between the initial diagnosis and the correct one was 10 months, the delay being higher in conditions such as vasculitis, antiphospholipid-antibody syndrome, or lymphoma where the treatment administered for the presumed PG ameliorated the disease. On the contrary, PG lesions, due to their aspect of deep ulceration with purulent base, frequently mimic cellulitis or soft tissue infection, determining a significant diagnosis delay.

The pathogenesis of PG is poorly understood. Neutrophil dysfunction, abnormal inflammatory exacerbations and genetic predisposition contribute to the formation of PG (Braswell et al 2015). Post-surgical PG define the pathergic formation of lesions in surgical incisions. A clinical review of 156 post-surgical PG cases found that 90% of patients received antibiotics and 73% underwent at least one debridement until the correct diagnosis was considered (Tolkachjov et al 2016). While useful in the case of bacterial infection and necrosis, or in order to prevent secondary bacterial infection of PG, surgical debridement of the wound may exacerbate the PG lesions due to a positive pathergy reaction (Reichrath et al 2005).

In this case, the patient associated the auto-inflammatory disease with an infectious pathology, colitis with *C. difficile*. *C. difficile* is a Gram-positive, anaerobic, toxin-producing bacillus and the leading cause of nosocomial diarrhea in industrialized countries, as the incidence of *C. difficile* infection is on the rise in Europe (Bauer et al 2011). Risk factors associated with the development of *C. difficile* infection include antibiotic use, age> 65 which also increases disease severity and mortality, inflammatory bowel disease, gastrointestinal surgeries, chronic kidney disease, transplantation, malignancy and immunosuppressant use (Czepiel et al 2019). Treatment regimens include administration of Vancomycin or Fidaxomicin, or Metronidazole, when the first two options are unavailable and an association of Vancomycin

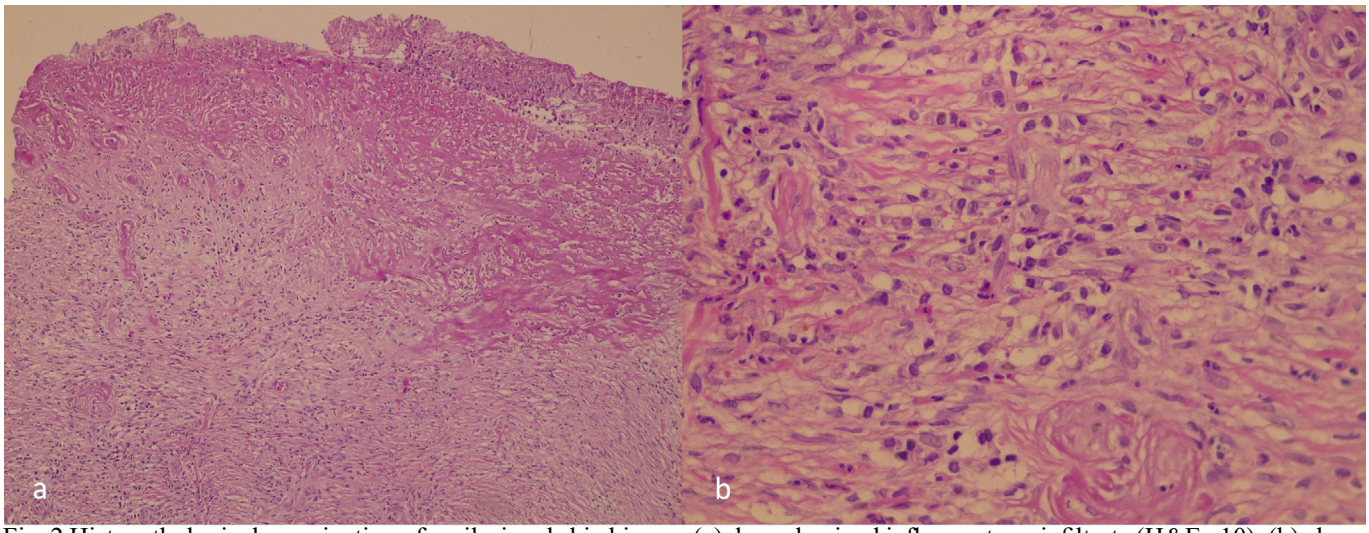

Fig. 2 Histopathological examination of perilesional skin biopsy: (a) dermal mixed inflammatory infiltrate (H&E x10); (b) abundant neutrophils without evidence of vasculitis or infection (H&E x40).

and Metronidazole for severe disease. While monoclonal antibodies such as Bezlotoxumab, that are directed against *C. difficile* toxins, prevent infection recurrence, fecal microbiota transplantation has very good resolution of *C. difficile* infection and the highest prevention rate for recurrent infection (van Nood et al 2013; Alonso & Mahoney, 2019). Fecal transplant may be performed during a lower gastrointestinal tract procedure such as colonoscopy, upper gastrointestinal procedure such as gastroscopy that delivers the material in the duodenum or via oral capsules, when available.

This patient had a number of factors that contributed to *Clostridium* occurrence: therapies with broad-spectrum antibiotics in the last months, age, neoplasia, hospitalizations post-operative status and immunosuppression. PG requires the administration of an immunosuppressive therapy, which does not help lower the *C. difficile* colonies but exacerbates them, posing the clinician in a difficult situation. Ideally, the immunosuppressive therapy should be continued in order to hinder the progression of PG, while administering antibiotic therapy and fecal microbiota transplantation to treat the *C. difficile* infection. The latter is especially useful since no surgical procedure is involved, therefore posing no risk for pathergy reaction.

In this case, the vulvar carcinoma, the surgeries, the general status of the patient, the age and the unfortunate decision to refuse medical care all contributed to the exitus of the patient.

Conclusions

Since PG may initially be difficult to recognize, a delay in the proper treatment is likely to occur. Antibiotherapy, underlying systemic diseases, hospitalisations and surgical interventions may favor the occurrence of C. difficile colitis, making the therapeutic strategy even more challenging.

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Citation	Candrea E, Danescu S, Vasilovici A, Baican C, Baican A. Pyoderma gangrenosum and Clostridium difficile infection: an unfavorable association. HVM Bioflux 2021;13(1):15-18.
Editor	Antonia Macarie
Received	6 September 2020
Accepted	20 December 2020
Published Online	7 February 2021
Funding	None reported
Conflicts/ Competing Interests	None reported