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Mucocutaneous pyoderma gangrenosum: a case report and literature review

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Abstract

Pyoderma gangrenosum is an uncommon neutrophilic dermatosis that usually presents with rapidly growing, painful, undermined, and purulent ulcers that are more likely to develop at areas of trauma. It is associated with underlying systemic diseases in more than half of cases, most commonly with inflammatory bowel disease. Pyoderma gangrenosum has no specific clinical, histologic, or laboratory findings, and so the diagnosis is based on exclusion of all other diagnostic possibilities, especially infectious causes. Misdiagnoses are frequent, with systemic vasculitides representing one of the main imitators. Treatment of pyoderma gangrenosum usually requires a multidisciplinary approach, with infliximab emerging as the best treatment option for cases associated with inflammatory bowel disease. The prognosis of pyoderma gangrenosum remains unpredictable, and recurrences are common. Here, we report a case of mucocutaneous pyoderma gangrenosum as a preceding sign of ulcerative colitis that responded to treatment with methylprednisolone and infliximab.

Keywords: mucocutaneous pyoderma gangrenosum, inflammatory bowel disease, granulomatosis with polyangiitis, skin ulceration, nasal septal perforation

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Case presentation

A 57-year-old male patient presented to our clinic in September 2021 with five large painful ulcerated lesions on his lower back (Fig. 1), shoulder (Fig. 2), head, right hip, and nasal septum. The first lesions appeared a year earlier, as pustules, and in later months they grew and eroded, forming ulcers with a purulent discharge. He was prescribed various topical antibiotic and antimycotic creams by a general practitioner, which did not result in improvement. He was first referred to a dermatologist in November 2020. A bacterial swab of the ulcer was negative. A skin biopsy suggested the possibility of pyoderma gangrenosum (PG) due to extensive ulceration with undermined edges and suppurative inflammation with multinucleated giant cells in the ulcer base (Fig. 3). Bacterial and fungal stains were negative, but additional microbiological tests were performed to confirm or exclude the possibility of PG. He was prescribed topical antibiotics (mupirocin and clindamycin) and an antiseptic lotion.

After the biopsy, the wound initially healed completely, but after a few months two new growing papules formed under the scar, forming an ulcer larger than the previous one.

Nasal symptoms appeared simultaneously with skin lesions. First a clear nasal discharge was present, which then became green and partially bloody. Bumps formed on the nasal septum and turned into an erosion. He was referred to an otorhinolaryngologist in December 2020, who described an extensive perforation of the anterior nasal septum measuring 2.5 cm and some crusts in both nostrils. A biopsy of the lesion showed nonspecific granulations adjacent to the ulceration. A swab of the nasal erosion was positive for *Staphylococcus aureus*, sensitive to all antibiotics tested. He was prescribed a 2-week course of systemic ciprofloxacin.

In January 2021 he was referred to a rheumatologist. Clinical history for rheumatologic diseases was negative, except for brief morning stiffness, but he mentioned that he had unintentionally lost 4 kg in the previous 3 weeks. Routine laboratory tests showed only mildly raised C-reactive protein (CRP, 24 mg/l), erythrocyte

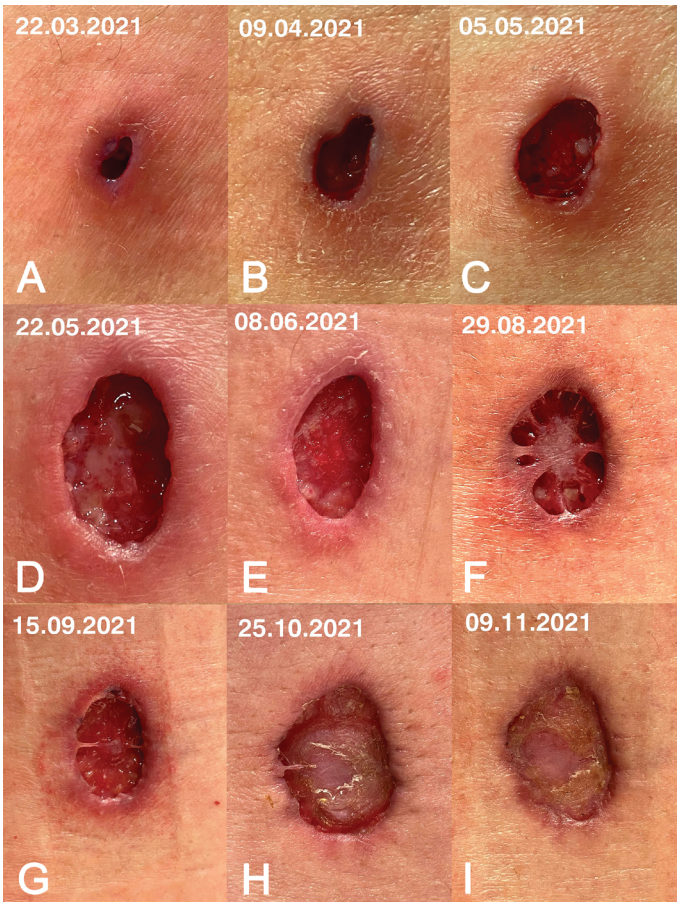

Figure 1 | Evolution of the ulcer on the left lower lumbar back: (a–e) growth, (f) reduction in size after initiation of treatment, (g) regrowth after discontinuation of methylprednisolone, and (h–i) healing of the ulcer.

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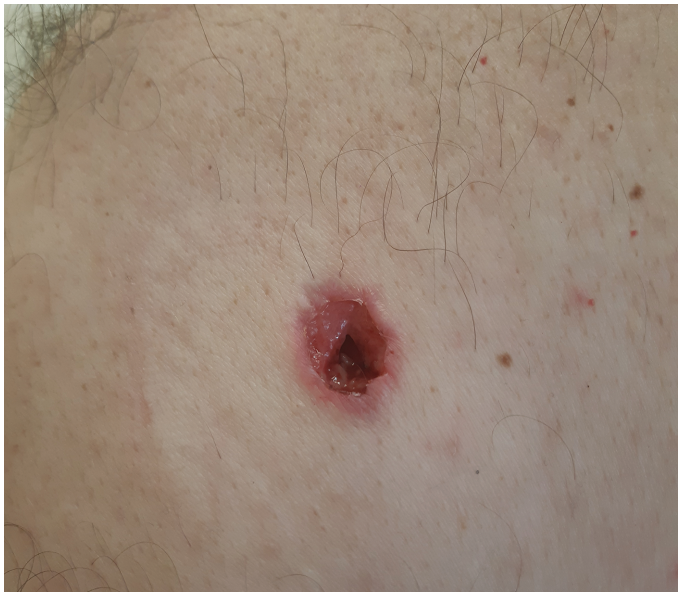

Figure 2 | Ulcer on the left shoulder at the time of presentation: 1.5 × 1 cm with infiltrated, slightly undermined edges and with surrounding erythema.

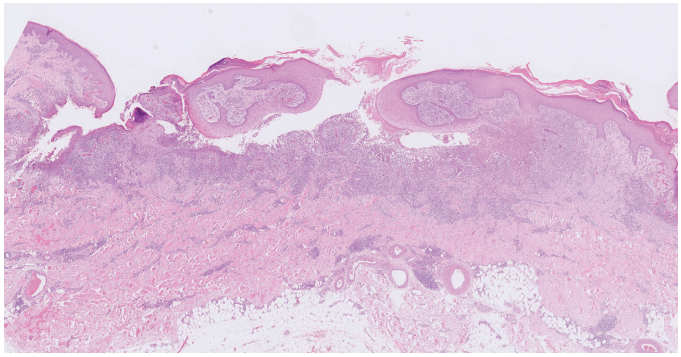

Figure 3 | Histopathologic changes, H&E 2×: extensive ulceration with undermined edges and neutrophil-predominant suppurative inflammation with multinucleated giant cells in the ulcer base.

sedimentation rate (ESR, 36 mm/hr), and gamma-glutamyl transferase (1.12 IU/l). Anti-nuclear antibodies (ANA), extractable nuclear antigen antibodies (ENA), antineutrophil cytoplasmic antibodies (ANCA), a QuantiFERON test, polymerase chain reaction (PCR) for leishmania, and serology for hepatitis, HIV, and syphilis were all negative. There were low levels of antiphospholipid antibodies (LA and aCL IgG) and cryoglobulins (480 mg/l). In May 2021, the rheumatologist repeated the skin biopsy, which showed similar changes to the first one: suppurative and granulomatous folliculitis and perifolliculitis. Stains for bacteria and fungi were negative. There were no changes suggestive of vasculitis or primary thrombotic disease. Again, correlation with microbiologic tests was suggested to rule out infectious etiology. A direct immunofluorescence study was unspecific.

In June 2021, the patient was hospitalized in the gastroenterology department because of dehydration, weight loss, malaise, and loss of appetite. Laboratory tests showed elevated CRP (118 mg/l) and ESR (78 mm/hr), and elevated fecal calprotectin (> 1,000 µg/mg). Ultrasound of the abdomen, chest X-ray, CT of the thorax and abdomen, and gastroscopy were all normal. CT of the sinuses showed destruction of the nasal septum and lateral wall of the left maxillary sinus with thickened mucosa of the sinuses. Colonoscopy showed multiple chronic erosions and inflammation across the entire colon with sparing of the terminal ileum, and the histopathologic changes were consistent with the diagnosis of ulcerative colitis (UC). Treatment was initiated with the systemic corticosteroid methylprednisolone at an initial dose of 56 mg per day, which was tapered down 8 mg every week until the end of July, and with the tumor necrosis factor-alpha (TNF-α) inhibitor infliximab: 450 mg initially every 2 weeks, then 4 weeks, then 6 weeks. The level of infliximab was measured at 11.97 µg/mg, which was above the therapeutic range. Inflammatory bowel disease (IBD) and mucocutaneous lesions improved with treatment, but discontinuation of methylprednisolone resulted in worsening of the mucocutaneous lesions (Fig. 1). Because of this and newly discovered hematuria, the fourth application of infliximab was omitted. Hence, treatment with methylprednisolone at 20 mg per day was reintroduced, but it did not result in any noticeable improvement.

In August 2021, gastroenterology specialists discovered growth of the nasal erosion (2.5 cm), describing necrotizing mucosa with purulent discharge of the entire frontal part of the nasal mucosa with saddle nose deformity. At that time, CT of the sinuses showed growth of the nasal septal defect with thickened mucosa of the left maxillary sinus without orbital and intracranial involvement. Repeated biopsy of the nose erosion showed unspecific necrotizing, chronic, and suppurative inflammation. These changes were nonspecific but potentially compatible with granulomatosis with polyangiitis (GPA) in the correct clinical context. Systemic antibiotic treatment was initiated with amoxicillin with clavulanic acid and several analgesics.

On the day of the first examination at our clinic in September, the patient stated that his skin lesions had not been healing and had been painful, with the nose erosion causing the most pain, not alleviable with a combination of analgesics. He had no fever, cough, dyspnea, nausea, vomiting, diarrhea, chest or abdominal pain, dizziness, leg swelling, or painful urination.

The patient had no prior chronic diseases and allergies, and his family history was negative for dermatological diseases. His mother has an unknown rheumatic disease. He was taking methylprednisolone, pantoprazole, calcium, and paracetamol with ibuprofen.

On examination, there was an erythematous livedoid infiltrate measuring 4 × 2 cm with a superficial erosion on the right hip. On the left lower lumbar back was a 2 × 3 cm ulceration with infiltrated, slightly undermined edges and a base covered with yellow fibrin (Fig. 1). There was a similar but smaller (1.5 × 1 cm) ulceration on the left shoulder; this one lacked a base covered with fibrin and had surrounding erythema (Fig. 2). In the left frontotemporal recess there was a 1.5 × 2 cm shallower ulceration without surrounding erythema and fibrin. On the right forearm there was a thin atrophic scar measuring 1.5 × 1 cm. The nose was soft and tender, and had a saddle deformity.

We decided to present the patient's case at a consensus expert council of dermatologists. In the meantime, his condition worsened, the nose pain became unbearable, and he noticed a new skin lesion on the left thigh with purulent discharge on pressure. He was admitted to the rheumatology department. The dermatology expert council proposed PG and GPA as the two most plausible diagnoses with further diagnostic tests, including repeated skin biopsy, needed.

Rheumatologists repeated routine laboratory tests, serum protein electrophoresis, tumor markers, immunoserologic tests, thyroid hormones, coagulopathy panel, HIV and hepatitis serologic tests, and chest X-ray, which were all without significant abnormalities. Calprotectin was low (31 µg/mg), and the level of infliximab was 2.11 µg/mg. A swab of the nasopharynx was positive

for *S. aureus* and negative for SARS-CoV-2 and pathogenic fungi. A wound swab and blood cultures were negative. The patient's clinical status remained unchanged on control gastroenterology examination. An ophthalmologist reported bilateral blepharitis with no signs of scleritis, episcleritis, or intraocular inflammation. Re-evaluation of the biopsy of the colon showed changes consistent with the diagnosis of IBD, without any signs of vasculitis or granulomas. Because of hematuria, the patient was examined by a urologist. Clinically there were no abnormalities, and PSA and urine culture were normal, but cystoscopy showed a necrotic growth on the left side of the prostatic urethra. He is scheduled for transurethral resection of a bladder tumor at the time of writing.

Ultimately, the diagnosis of IBD-associated mucocutaneous PG was made based on clinicopathologic correlation. Gastroenterologists were consulted, and they recommended optimization of the infliximab dose (to 10 mg/kg every 4 weeks) and high doses of methylprednisolone for the treatment of PG.

He was started on intravenous methylprednisolone 250 mg pulse therapy daily for 3 days followed by oral methylprednisolone 60 mg daily with tapering of 4 mg every week and infliximab 800 mg intravenously every 4 weeks. He received sulfamethoxazole and trimethoprim 80/400 mg daily for *Pneumocystis jirovecii* pneumonia prophylaxis and as therapy for *S. aureus*, which was isolated from the nasal mucosa. He was also prescribed pantoprazole, vitamin D, calcium, and local therapy for blepharitis.

In November, the gastroenterologist increased the dose of infliximab to the maximum dose of 900 mg every 4 weeks. Control laboratory tests were without significant abnormalities, and clinically IBD was in remission.

On dermatological control examination in early November, we observed healing of all skin lesions. Previous ulcerations had evolved into atrophic scars with no signs of inflammation (Fig. 1). A small erosion persisted in the left frontotemporal recess. No new lesions appeared. The distinct saddle nose deformity remained.

Discussion and literature review

PG is a rare neutrophilic dermatosis characterized by painful necrotic ulceration (1). It can affect all age groups, with a peak between 40 and 60 years, and it has a slight female predominance (2).

It is characterized by neutrophil-predominant infiltrates in the affected skin. To this day, the exact reason for the development of inflammation remains unknown. Although called pyoderma, PG is neither an infectious nor gangrenous condition. Abnormalities in neutrophil function, genetic variations, and dysregulation of the innate immune system are considered to be involved in the pathogenesis (1).

PG has many manifestations, but it usually starts as an inflammatory tender papule, pustule, vesicle, or nodule that quickly enlarges and erodes to a painful ulcer with sharply marginated, undermined, violaceous borders surrounded by erythema and a purulent necrotic base. Pain that is greater than expected, based on the clinical appearance, is a characteristic feature. Ulcers heal with thin atrophic cribriform scars. Lesions are often multiple and recurrent, and they can occur or worsen at areas of trauma (1). This process, called pathergy, is present in approximately one-third of cases (3).

The clinical manifestations of PG vary, and there are currently four major subtypes. The most common is ulcerative (classic) PG, which represents the vast majority of cases. The lower extremities are most commonly involved. Other variants include bullous (atypical), pustular, and vegetative PG. There are also some special presentations of PG linked to certain locations such as peristomal, genital, and extracutaneous PG (4).

More than 50% of patients with PG have an associated systemic disease. The most common is IBD, followed by inflammatory arthritis, hematologic disorders, and malignancies and other neoplasms. PG usually follows the diagnosis of an associated disorder, but it can also be the presenting sign of an underlying disease. PG may or may not follow the course of the systemic disease (1). In our case, PG preceded IBD. Mucocutaneous manifestations are the most common extraintestinal manifestations of IBD, appearing in 22 to 75% of patients with Crohn's disease (CD) and 5 to 11% of patients with UC (5). The mucocutaneous manifestations of IBD are classified into five categories according to their pathophysiology: 1) specific, 2) reactive, 3) associated, and 4) malabsorption manifestations, as well as 5) adverse effects of IBD therapy (6). PG is considered a reactive manifestation, and it is the second-most common cutaneous manifestation after erythema nodosum. It is more common in UC than in CD (5).

There are no pathognomonic or specific clinical, histologic, or laboratory findings of PG. Its diagnosis can usually be made only after other diagnostic possibilities have been ruled out (1). In 2018, new diagnostic criteria for ulcerative PG were published using a Delphi consensus of international experts. The diagnostic model includes one major criterion and eight minor criteria. The major criterion and at least four minor criteria are needed for diagnosis (7).

When PG is suspected, the clinical assessment should include a detailed history, physical examination, and biopsy (1). Histologic features are nonspecific and vary depending on the site of the biopsy and stage of the lesion. Specimens should incorporate the inflamed border, ulcer edge, and subcutaneous fat. Microbial special stains should be performed on histopathologic examination, and specimens should also be sent for culture, including for atypical mycobacteria. Biopsies of early lesions often show dermal neutrophilic abscess formation, whereas late-stage lesions show epidermal and superficial dermal necrosis and ulceration with an underlying dense mixed inflammatory cell infiltrate with abscess formation. Giant cells may be seen on the edge of the lesions. Direct immunofluorescence studies are nonspecific and are usually performed only when diagnoses of vasculitis, bullous disorder, or lupus are suspected (8).

There are no specific laboratory studies for PG, and recommendations for work-up vary. Based upon clinical suspicion, laboratory tests are most useful for identifying PG-associated diseases and to narrow down the list of differential diagnoses. Nonspecific common laboratory findings in PG include leukocytosis, elevated ESR, and elevated CRP (1).

Because the diagnosis of PG is one of exclusion, misdiagnoses are common. One study showed that 10 percent of patients were later found to have a different diagnosis. The most confounded disorders include antiphospholipid antibody syndrome, venous stasis ulcers, GPA and other vasculitides, cutaneous infections, factitial ulcers, vascular occlusion disorders, malignancies, and other ulcerative inflammatory disorders such as metastatic CD (9). In our case, the main differential diagnosis was GPA. Skin lesions occur in up to 50% of patients with GPA, often at the same time with systemic signs and symptoms, but they can also be the presenting sign of the disease (10). The actual incidence of PG-like ulcerations in GPA remains controversial (11). We should think of GPA

in patients that have pyoderma-like lesions with facial involvement, when there are no typical PG features such as surrounding erythema or clearly evident undermined violaceous borders, with positive ANCA serologic test results, with systemic signs and symptoms of GPA, or without any typical PG disease associations (12). Long-term follow-up and reconsideration of the diagnosis of PG are recommended for all patients with PG, especially when lesions are unresponsive to standard treatment. The need to rule out other diagnoses and initiate proper treatment should overrule the concern of exacerbating PG by biopsy-induced pathergy (9).

There are no definitive guidelines for treatment of PG. Usually a combination of optimization of wound healing, suppression of inflammation and disease activity, treatment of secondary infections and associated diseases, and pain management is needed. If the lesion is solitary and small, topical treatment with corticosteroids, tacrolimus, or special dressings may suffice. In multiple or large lesions, systemic treatment is mandatory. Oral corticosteroids (methylprednisolone or prednisone), cyclosporine, and biologic agents such as infliximab and adalimumab are traditionally used for several months (1, 3, 13). It usually takes months, even years, for ulcers to completely heal, and relapses are present in more than half of cases (1).

In conclusion, we present a case of PG associated with IBD with rare involvement of not only the skin, but also of the nasal mucosa, mimicking a localized variant of GPA that presented before IBD.

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