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SPECIAL REPORT

The diagnostic tangle of pyoderma gangrenosum: a case report and review of the literature

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ABSTRACT

This report describes a 55-year-old patient with the rare inflammatory dermatosis pyoderma gangrenosum. It is an often misdiagnosed condition of unclear origin and pathogenesis. There is an association with underlying systemic disorders such as inflammatory bowel disease, haematological disorders, rheumatological disease or solid malignancies, although this last association is still under investigation. The diagnosis can be challenging and treatment depends upon the severity of the lesions. The long-term prognosis is unpredictable.

KEYWORDS

Pyoderma gangrenosum, ulcerative dermatosis, sterile necrosis

What was known on this topic?
Pyoderma gangrenosum is a rare, non-infectious and painful ulcerative disease, belonging to the spectrum of neutrophilic dermatoses, which is often mistaken for an infection. It can be associated with a variety of severe comorbid conditions.

What does this add?
This well-illustrated case aims at increasing the physician's awareness for this condition. The diagnostic features and current therapeutic recommendations are briefly reviewed.

INTRODUCTION

Pyoderma gangrenosum is a rare inflammatory neutrophilic dermatosis with poorly understood aetiology and pathogenesis. In up to 50% of cases, the disorder is associated with an underlying systemic disease. It presents as an inflammatory papule rapidly evolving into an ulcer with undermined borders with a necrotic and mucopurulent base. It is an often misdiagnosed condition.[1-3]

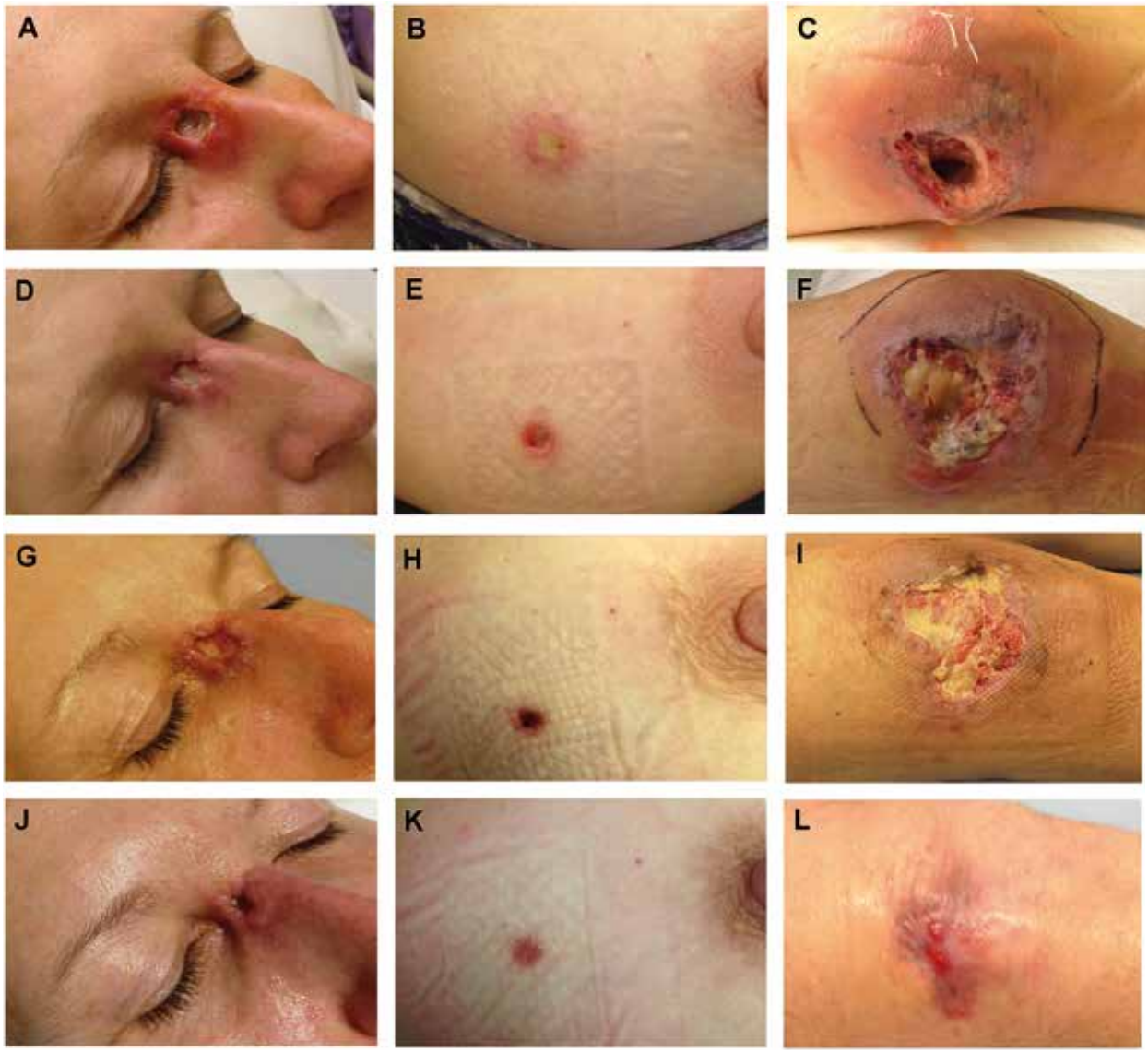
This report describes a 55-year-old patient with pyoderma gangrenosum, illustrated with sequential clinical pictures spanning the complete disease course towards resolution. We briefly review the current understanding, diagnosis, and management of this disease.

CASE REPORT

A 55-year-old woman with a history of ulcerative colitis was admitted to hospital because of suspected arthritis of the right knee starting 14 days earlier. She had taken NSAIDs with only temporary relief. Three days before admission a synovial fluid aspiration was performed because of persistent pain and swelling of the right knee. The aspirate contained few leukocytes, no crystals and bacterial cultures remained negative. Given the lack of clinical improvement and the inconclusive results of the aspiration, she was admitted to hospital. Temperature at admission was 37.3 °C. On clinical examination, her right knee was red, swollen, and tender. In addition, a small red furuncle-like nodule was observed on the nasal bridge.

The haemoglobin was 10.5 g/dl, leukocyte count 7.4 x 10^9/ml without left shift and C-reactive protein was 340 mg/l. The laboratory values for liver and kidney function as well as the electrolyte panel were unremarkable. There were no bone lesions visible on X-ray of the right knee. Ultrasound examination showed a significant amount of intra-articular fluid and a new puncture was performed. The differential diagnosis at that time included gout, rheumatological systemic disorder and infectious causes such as septic arthritis, *Borrelia burgdorferi* or gonococcal infection. Also, on account of a recent flare-up of underlying ulcerative colitis, inflammatory bowel disease-associated arthropathy was considered. Because of the limited response to paracetamol and NSAID so far, an empirical therapy with cefuroxime 1.5 g three times a day intravenously (TID IV) was started immediately after the puncture. Again the aspirate yielded no crystals, a negative Gram staining and 2250 leukocytes per µl. Bacterial cultures remained negative. One day later, a blister of 3 cm developed at the puncture site, spontaneously draining purulent haemorrhagic fluid. Within a few hours a necrotic ulcer developed with blue edges (*figure 1C*). Underneath the ulcer there was a large zone of subcutaneous fat necrosis reaching the fascia. On suspicion of fasciitis necroticans, cultures were taken from the wound and the antibiotic therapy was switched to meropenem (1g TID IV) and clindamycin (600 mg TID IV). Meanwhile, the lesion on the nasal bridge had enlarged and yielded a large amount

Figure 1. *Consecutive clinical pictures of the three lesions*



Clinical presentation of the pyoderma gangrenosum lesions of the nasal bridge (left), right breast (middle) and right knee (right) three days after admission (A-C), and one week (D-F), two weeks (G-I) and four weeks (J-L), respectively, after starting high-dose corticosteroid treatment. Informed consent was obtained from the patient for the use of these clinical photos.

of pus at incision (*figure 1A*). Shortly thereafter a new lesion developed on the right breast (*figure 1B*).

Given the negative blood, tissue and synovial fluid cultures and the lack of clinical and biochemical improvement despite broad-spectrum antibiotics, the development of a new plane ulcer on the right breast and the underlying inflammatory bowel disease, the diagnosis of pyoderma gangrenosum was considered. High-dose methylprednisolone (1 mg/kg) was administered intravenously after which progressive healing of the ulcers ensued (*figure 1D-L*). The anatomopathological examination of a punch biopsy of the knee lesion sampled before the administration of corticosteroids showed an infiltrate with a mixed composition, associated with signs of vasculitis and subepidermal oedema. These were compatible with the diagnosis of pyoderma gangrenosum.

DISCUSSION

Initially described as painful enlarging necrotic ulcers by Brunsting and colleagues in 1930, pyoderma gangrenosum was believed to be the spread of a bacterial infection leading to cutaneous gangrene.[4] According to current insights, it is a rare inflammatory skin disorder and part of the spectrum of neutrophilic dermatoses. Up to 50-70% of cases are associated with an underlying systemic disease such as inflammatory bowel disease, haematological disorders, rheumatological disease or solid malignancies, although some debate remains on the last-mentioned association.[3,6,10,11] The incidence is estimated at 3-10 patients per million population per year, with a peak incidence between 20-50 years and a slight female predominance.[2,3,5,6] Patients can present with a sterile inflammatory papule, pustule or vesicle, either 'de novo' or after (minimal) trauma or surgery. Often these lesions remain unrecognised as pyoderma gangrenosum because they look unimpressive at first sight.[7-9] The lesions expand and form an ulcer, producing a purulent and haemorrhagic exudate. The ulcers show an irregular necrotic or mucopurulent base with an erythematous radiance. Patients have mostly single and rarely multiple lesions, all in different stages of development.[3,5-7] An exacerbation of pyoderma on sites of trauma such as biopsy, surgery, insect bites, or injections is commonly known as *pathergy*. This phenomenon is seen in 20% of patients.[3,5-9]

Our patient presented with a nodule on the nasal bridge draining pus on incision, mimicking a furuncle but rapidly evolving into a widening ulcer. Development of the large ulcers after puncture, as well as the development of a new lesion on the breast, together with sterile cultures eventually led to the diagnosis.

Pyoderma gangrenosum is a diagnosis of exclusion. There is no specific biochemical test available to confirm the diagnosis. Diagnostic criteria have been proposed (*table 1*). The diagnosis can be supported if two major criteria and at least two minor criteria are present.[3,10] Biopsy is indispensable in ruling out alternative diagnoses and this outweighs the risk of possible local disease progression (pathergy).[3,5,10]

The treatment of pyoderma gangrenosum is challenging since no randomised controlled trials are available to guide therapy (*table 2*). In milder forms, topical treatment with corticosteroid or tacrolimus ointment may suffice.[6,11,12] In more severe cases systemic treatment is necessary and will depend on the associated underlying disorder. Current recommendations state high doses of corticosteroids (e.g. methylprednisolone 0.5-1.5 mg/kg orally per day) to induce remission, with gradual tapering over 4-6 weeks.[3,10,12,13] Cyclosporine A has become an accepted treatment for widespread pyoderma gangrenosum after initial steroids or in combination with steroids, starting at 4-5 mg/kg/day orally. The drug induces an early response but has no impact on the incidence of recurrences.[12,13] Azathioprine (100-150 mg/day) in combination with steroids for induction therapy has to be considered when the underlying disease is ulcerative colitis or Crohn's disease.[12,13] Complete withdrawal of therapeutics may be possible, but a low-dose maintenance therapy is often required and the long-term outcome is unpredictable.[11-14] Sulpha drugs are useful in milder cases: the combination of steroids with dapsone up to 200 mg daily has been

Table 1. *Diagnostic criteria for pyoderma gangrenosum (adapted from Su et al. and Al Ghazal et al.[3,10])*

Major criteria
1. Sterile pustule or ulcer with a violaceous and undermined border
2. Other relevant differential diagnoses have been excluded (this usually involves skin biopsy).
Minor criteria
1. History suggestive of pathergy
2. Histopathological findings showing sterile dermal neutrophilia and/or mixed inflammation and/or lymphocytic vasculitis
3. Underlying systemic disease associated with pyoderma gangrenosum
4. Response to systemic immunosuppressive therapy
5. Extremely painful ulcer (out of proportion to size of ulceration, VAS > 4)
Major and minor diagnostic criteria which can be used to support the diagnosis of pyoderma gangrenosum. Two major criteria and at least two minor criteria are required. VAS = visual analogue score.

Table 2. *Current treatment recommendations for pyoderma gangrenosum*

Disease stadium dose	Treatment	Recommended dose
Limited disease	Topical corticosteroid	Clobetasol 0.05% ointment
	Topical tacrolimus	Tacrolimus 0.03-0.1% ointment
Extensive disease	*First-line induction therapy*	
	Systemic glucocorticoids	Prednisone 0.5-1.5 mg/kg/day
	± Cyclosporine	4-5 mg/kg/day
	± Azathioprine	100-150 mg/day
	Second-line	
	Cyclosporine	4-5 mg/kg/day
	In conjunction with corticosteroids:	
	Thalidomide	
	Dapsone	200 mg/day
	Methotrexate	
	Infliximab	5 mg/kg single dose
	Anakinra	

Overview of the current treatment regimens for different stages of pyoderma gangrenosum. When available, the recommended dose is mentioned.

described.[13,14] Methotrexate and thalidomide have been used as well but are generally more effective as adjunctive therapy rather than first-line agents.[13-15] Recent studies show favourable results with anakinra, an IL-1 receptor antagonist and single-dose infliximab, etanercept and adalimumab, monoclonal chimeric antibodies against tumour necrosis factor alpha, although worsening of pyoderma gangrenosum has been described after the use of the last two as well.[13-15]

CONCLUSION

This case shows that pyoderma gangrenosum is a challenging condition which needs to be considered in patients with unusual skin ulcerations and sterile necrosis not responding to systemic antibiotic treatment. The pathogenesis is poorly understood and validated diagnostic tests are lacking. Clinicians should be aware of this condition in order to improve recognition and treatment. Abstaining from surgical debridement results in optimal chances of healing without residual scarring.

DISCLOSURES

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