Familial Pyoderma Gangrenosum: About 2 cases

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Abstract Pyoderma gangrenosum occurrence in a familial pattern is extremely rare. We report pyoderma gangrenosum in two Tunisian siblings with onset respectively at 28 and 26 years old. The initial lesion was a pustule that breaks down to form an ulcer with an erythematous border. Treatment with oral corticosteroids induced an excellent clinical response. This familial clustering suggests a possible genetic role in the development of pyoderma gangrenosum in some cases.

Keywords Pyoderma gangrenosum; Heredity; corticosteroids

Introduction

Pyoderma gangrenosum (PG) is an inflammatory, ulcerative skin condition that occurs in all age groups. Its occurrence in a familial pattern is extremely rare. As far as we could ascertain, only four reports indicating genetic predisposition have been published earlier (1-4). We describe familial pyoderma gangrenosum in two Tunisian sisters with unaffected parents.

Clinical presentation

Case 1

A 28-year-old female patient, born to non consanguineous parents, with past medical history of tuberculosis and Crohn’s disease complicated with parotid enlargement and interstitial lung disease, presented with skin ulcers, high temperature, and swollen joints. She reported that during 2 week period the skin lesions started as erythematous pustule in her back. Physical examination showed multiple ulcers with undermined violaceous margins and indurated bases on posteriorly faces of both thighs and in the lumbar region. The oral mucosa was unaffected. The rest of the clinical examination was unremarkable. Biological investigations showed biological inflammatory syndrome. Cell blood count, serum protein electrophoresis, liver and renal tests, glucose and electrolytes were normal. Immunological investigations including antinuclear antibodies (ANA), antiphospholipids antibodies, anti-neutrophil cytoplasmic antibodies (ANCA) were negative. Blood culture, skin swabs, urine analysis, BK sputum examination, and HIV serology were all negative. The patient was initially treated with intravenous antibiotics (pristinamycine 3 g/day, metronidazole 1.5 g/day, and gentamicin 160 mg/day) associated to surgical resection of the necrotic tissue. Despite this first line treatment, skin lesions rapidly progressed and the patient was pyrexic. Histopathologic examination of the excised tissue showed extensive ulceration and necrosis of epidermis and dermis down to subcutaneous fat. A mixed cell infiltrate extended from the papillary and reticular dermis down the subcutis, and was composed of neutrophils, lymphocytes, and prominent reactive histiocytes. There was no evidence of vasculitis, infection, or granuloma formation. Immunological stain ruled out lymphoproliferative syndrome. The histopathologic findings and the clinical picture were considered consistent with pyoderma gangrenosum. Treatment was commenced with oral prednisone (60 mg/day) and daily dressings with topical fusidic acid and betamethasone valerate. The area of ulceration ceased to enlarge and became less inflamed. The patient was afibrile but required transient morphine analgesia. Oral prednisone was tapered slowly after 6 weeks of full doses. After 12 months of treatment, the lesions have completely healed and the patient was well and thriving.

Case 2

A 26-year-old female patient, born to non consanguineous parents, with past history of deep venous thrombosis of
lower limbs due to protein S deficit and treated with acenocoumarol since 2 years, presented with an anal pain and superficial ulceration of the right buttock with temperature. She denied a history of hematologic, gastrointestinal, or arthritis disease. Physical examination showed 3x2 cm ulcer in the right gluteal region and anal abscess. It started as a painful papule which progressed to a pustule and then an ulcer with a yellowish serous discharge and irregular violaceous swollen edges. The rest of the physical examination was normal. Laboratory data showed neutrophil leukocytosis and high CRP rate. Other laboratory tests including blood glucose level, liver and renal function tests, serum electrophoresis, ANA, ANCA and urinalysis were reported as normal. Tuberculin test was negative. Ulcer swab culture for aerobic, anaerobic pathogens was positive for E. Coli. Surgical flattering of the abscess was performed and intravenous antibiotics (amoxicilline 3 g/day) were administered. Skin lesions progressed to the lumbar region and right flank, and other ulcers appeared in the neck. Bacteriological swab remained this time negative and skin biopsy concluded to epidermal ulceration with an inflammatory infiltrate of neutrophils and mononuclear cells. Based on the clinical and histologic features, a diagnosis of familiar PG was retained and the patient was started with oral prednisone (55 mg/day). Complete reepithelialization of the ulcers occurred in 8 weeks leaving behind puckered scars.

Discussion:
Pyoderma gangrenosum is a rare, chronic ulcerative skin disease. The overall incidence of PG is estimated at 6/million in the population (Langan et al., 2012). No specific laboratory or histologic tests confirm the diagnosis. Pyoderma gangrenosum is a diagnosis of exclusion, after ruling out other etiologies of cutaneous ulceration such as infectious, malignant, vasculitic, and factitial, and favorable response to steroid therapy. PG ulcers can occur anywhere in the body. The earliest lesion is a pustule that typically persists and develops into a large painful ulcer, with erythematous-violaceous undermined, rolled borders. Four distinct clinical variants of pyoderma gangrenosum have been described: ulcerative (classic), pustular, bullous, and vegetative (Kikuchi et al., 2015). Although pyoderma gangrenosum has been reported in otherwise healthy people, 50% of the cases are associated with underlying hematologic, gastrointestinal, and arthritic disorders as it is illustrated in the case no 1 in which the patient had a past history of inflammatory bowel disease (Von den Driesch, 1997).

To our best knowledge, only four reports of about familial predisposition in PG have been published earlier in English literature (Miller and Dooley, 1973; Al Rimawi et al., 1996; Khandpur et al., 2001; Boussofara et al., 2013). This is the second report of familial PG in Tunisia.

The first Tunisian report was about siblings, male and female, born to nonconsanguineous parents who developed at the age of 9 and 19 years old with a subsequent diagnosis of CVID and atypical clinical presentation showing oral involvement mimicking a pyostomatitis vegetans.

In our cases, the patient was not siblings, both female and was born to consanguinous parents. In both reports, the parents were uninvolved which suggests autosomal recessive mode of inheritance.

Our observations were remarkable through the spontaneous occurrence of the skin lesions. In fact, a unique feature of PG is pathergy that is defined as an inflammatory reaction in the skin induced by trauma, and reportedly seen in 50% of PG patients (Satoh and Yamamoto, 2013). No trigger factor was found in our cases.

In the case no2, the patient developed skin ulcers while she was treated with oral anticoagulant (OAC) for deep venous thrombosis. Other than the classic skin necrosis induced by OAC in patients with protein C and/or S deficiencies, recurrent pyoderma gangrenosum (PG)-like ulcers induced by OAC was previously reported and was the principal differential diagnosis in this case. But, the chronology of the events and the favorable outcome on steroids treatment and the absence of recurrence while OAC was not discontinued allowed a diagnosis of idiopathic PG (Pralong et al., 2014).

The etiopathogeny of PG is still unclear. Its association with a variety of immunologic disorders and reports of family cases suggests an underlying immunogentic defect. In fact, this was documented in PAPA’s syndrome (Pyogenic sterile arthritis,
Pyoderma gangrenosum and acne, a rare clinical subtype of PG, which is a hereditary, autosomal dominant, auto-inflammatory disease caused by mutations in the PSTPIP1 gene. The proline-serine-threonine phosphatase interacting protein 1 is involved in immune regulation (Zeeli et al., 2015). Likewise, genetic studies on PG associated with crohn’s disease have suggested association with PSTPIP1, PTPN6, and TRAF3IP2 genes (Weizman et al., 2014).

If left untreated, PG may last for months to years. Due to the lack of randomized controlled trials, treatment is empirical and consists of a combination of topical and systemic drugs (such as corticosteroids, immunosuppressants, analgesia) and local wound care. In our series, corticosteroids were considered as the first line treatment for this two disseminated PG. It has demonstrated its efficiency for acute and rapidly progressive forms. Furthermore, in the case n°1, we administered intralesional corticosteroids. Both patients were good responders and we did not add immunosuppressant agents.

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