Case Report

Bullous pyoderma gangrenosum and myelodysplastic syndrome*

*Pioderma gangrenoso bolhoso e síndrome mielodisplásica**

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Abstract: Pyoderma gangrenosum can present as a cutaneous manifestation of paraneoplastic syndromes. A case of bullous pyoderma gangrenosum associated with bicytopenia is described. During the complementary investigation, myelogram, bone marrow biopsy and karyotype were performed, and showed a pattern consistent with myelodysplastic syndrome. The patient was treated with dapsone with improvement. Pyoderma gangrenosum can be a manifestation of systemic diseases. The possibility of myelodysplastic syndrome should always be considered in patients with pyoderma gangrenosum associated with cytopenia. Pyoderma gangrenosum could indicate poorer prognosis in patients with systemic diseases.
Keywords: Autoimmune diseases; Dapsone; Myelodysplastic syndromes; Pyoderma gangrenosum

***Resumo**: O pioderma gangrenoso pode apresentar-se como manifestação paraneoplásica. Relata-se um caso de pioderma gangrenoso, da variante bolhosa, acompanhado de bicitopenia, em que foi evidenciado, por meio de mielograma, biópsia de medula óssea e cariótipo, padrão compatível com síndrome mielodisplásica, subtipo citopenia refratária com displasia de multilinhagens. Foi tratado com dapsona, obtendo cicatrização das lesões. O pioderma gangrenoso pode associar-se a doenças sistêmicas, devendo a síndrome mielodisplásica ser considerada nos casos acompanhados de citopenias. Portanto, o pioderma gangrenoso pode ser um marcador cutâneo de doença sistêmica de prognóstico reservado.*
Palavras-chave: Dapsona; Doenças auto-imunes; Pioderma gangrenoso; Síndromes mielodisplásicas

INTRODUCTION

Pyoderma gangrenosum (PG) is an uncommon inflammatory disease, first described in 1930,[1] that begins with an erythematous nodule or hemorrhagic pustule, evolving progressively to necrosis and painful ulcer with violaceous, undermined and irregular borders, surrounded by an erythematous halo. There can be single or multiple lesions, which typically present cribriform scarring pattern.[2] The pathergy phenomenon has been frequently described associated to the infection, in regards to the development of new lesions or worsening of pre-existing lesions after different types of trauma, such as debridement, intradermal injections, vaccinations, or surgical scars. This phenomenon is found in up to 50% of patients.[3]

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Atypical clinical forms of the disease were also described, such as chronic vegetative, bullous, peristomal and vulvar lesions.[4] Bullous pyoderma gangrenosum (BPG) is characterized by aggressive, painful lesions with superficial vesicles that rupture to form typical ulcerations with undermined borders.[5] While classical PG is more frequently located on the lower limbs, the bullous variant occurs chiefly on the upper limbs.[3]

The diagnosis of PG is made by exclusion, and it is necessary to investigate other causes of ulcerous diseases, such as bacterial infections, mycobacterioses, vascular insufficiency, vasculitis, halogen-derived dermatosis, neoplasms and factitial dermatitis.[6] Histopathological findings of PG are not specific, encompassing areas with abscess, areas with neutrophilic and lymphocytic infiltrate, and with moderate vasculitis with fibrinoid necrosis.[7] In BPG, there is diffuse neutrophilic dermatosis without primary vasculitis.[3] Direct immunofluorescence showed positive perivascular pattern for antiC3 antobody in 83% of cases, for antiIgM in 78%, for antiIgA in 14% and for antiIgG in 11% of cases.[4]

The association between PG and systemic diseases occurs in 50 to 75% of patients. The most frequently associated diseases include inflammatory bowel diseases, hematological neoplasias and rheumatoid artritis.[7]

PG associated to hematological disorders can present atypical clinical characteristics, and the association with leukemia and myelodysplastic syndrome (MDS) in the bullous form is frequently described.[5] Up to 54% of the reported cases of PG associated with leukemia were of the bullous subtype.[8] The outbreak of BPG can be an indication of reserved prognosis in these diseases.[5]

The case reported shows the association between PG, especially the bullous variant, and MDS, of the refractory cytopenia with multilineage dysplasia subtype (RCMD). In these cases, PG is the cutaneous marker of the systemic disease with unfavorable diagnosis.

CASE REPORT

A male patient, 60 years-old, mullato, born and living in the city of Campos Sales, State of Ceará, married, farmer, was refered to the Dermatology Service of Hospital Sao Paulo in March 2003, complaining of skin lesions for one year. He complained of mild pain on the lesion site. According to the patient, the lesions were intermittent, and they receded spontaneously leaving a scar. He denied fever, nocturnal sudoresis and gastrintestinal symptoms, as well as the use of drugs. The dermatological exam showed lesions in different phases: erythematous papules, pustules, vesicles containing blood, ulcerative and vegetative lesions with undermined borders (the largest measuring five centimeters in diameter) and irregular scars. The lesions were located on the chest and upper limbs (Figures 1 and 2), including the palms. He presented no adenomegaly or hepatosplenomegaly upon examination.

A biopsy of the lesion was performed, and the pathological examination was characterized by diffuse chronic dermatitis in acute phase (Ziehl-Neelsen, PAS and direct immunofluorescence were negative), which was compatible with unspecific chronic ulcer. Another biopsy was perfortmed and the outcome was ulcerated suppurative chronic inflammatory process with granulation tissue (absence of granulomas, and Leishmania test was negative) (Figure 3).

With a suggestive clinical picture and ruling out differential diagnoses by pathological examination and other tests (serology for syphilis, HIV, HTLV, leishmaniasis, bacterioscopy for mycobacteria on the lesion and acid-fast bacilli in lymph – all tests were negative), the presumptive diagnosis was bullous pyoderma gangrenosum. The patient was submitted to neoplasm screening since pyoderma gangrenosum is usually present as paraneoplastic syndrome.

In May 2003, the investigation was interrupted because the patient suffered an acute myocardial infarction and underwent left ventricular aneurysmectomy. The cardiac condition evolved satisfactorily but he developed a crusty erythematous lesion on the upper portion of the thoracotomy scar.

Resuming the investigation, general tests were conducted, including complete blood count, which showed bicytopenia (normocytic/normochronic anemia and leukopenia), and proteinogram that showed dysproteinemia (immunoglobulins A, G and M above

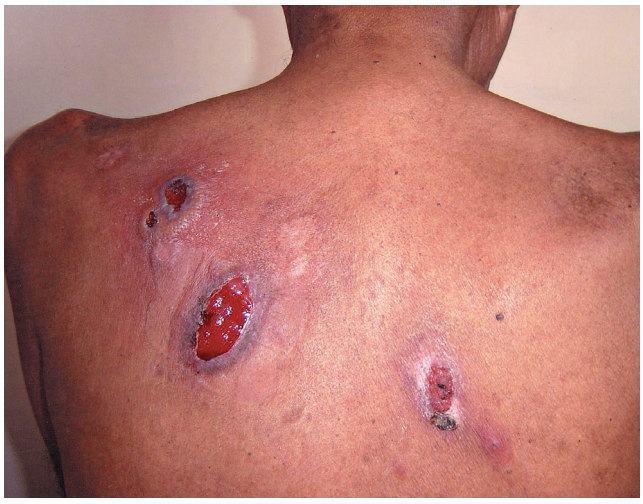

Figure 1: Ulcers with granulation tissue and undermined borders on the chest

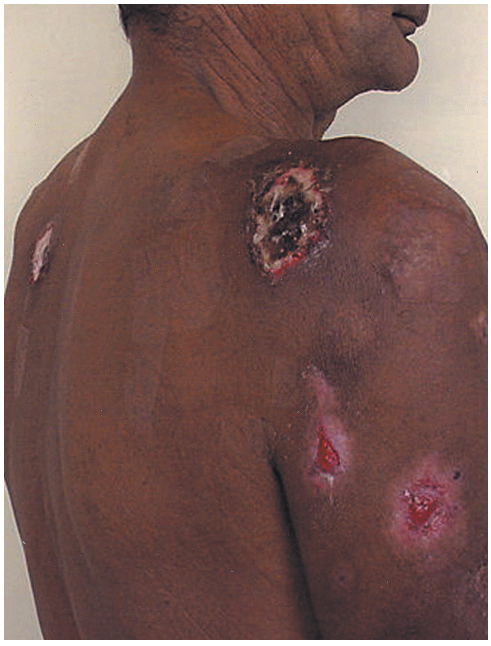

Figure 2: Lesions at different development stages: ulcerative and vegetative lesions with undermined borders, ulcerative and crusty lesions and irregular scars on the chest and upper limbs

normal limits). The myelogram showed hypercellular bone marrow with dysplasia in over 50% of cells from the erythrocytic and granulocytic series, which is compatible with RCMD, according to the World Health Organization (WHO) classification.[9] A biopsy of the bone marrow revealed dysplastic alterations and increased early granulocytic cells in the center of intercellular spaces (Figure 4), associated to increased CD34 expression in the immunohistochemical test (Figure 5). A G-band kariotyping showed 46 XY [20][?]. The patient initiated treatment for the skin condition with dapsone, 100mg per day, and the lesions healed 45 days later. A multidisciplinary follow-up will be conducted due to the risk of evolving to myeloid leukemia.

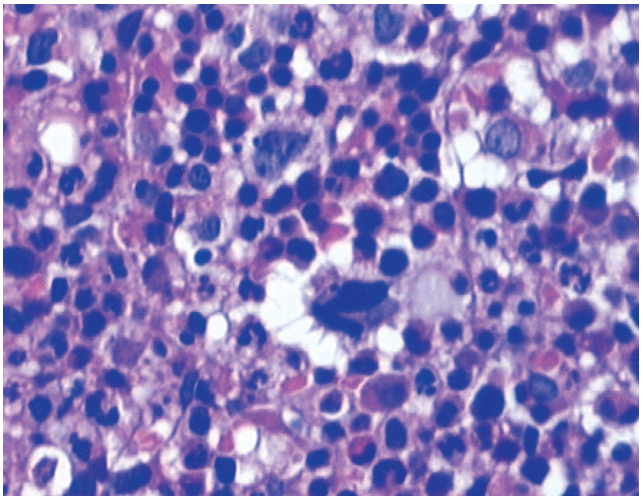

Figure 4: Photomicrography of histological section of bone marrow displays atypical megakaryocyte, some precursor granulocytic cells and decreased erythroblastic series, with a left shift. Stroma shows edema and fibrosis (HE 400X)

DISCUSSION

Myelodysplastic syndromes (MDS) are clonal hematological disorders clinically and morphologically characterized by ineffective hematopoesis. They can present chronic course, lasting a few years, or suffer leukemic transformation, which occurs in 40% of cases.[10] They are associated with auto-immune manifestations, such as thrombocytopenic purpura, vasculitis, chronic inflammatory demyelinating polyneuropathy and PG, which occurs in 10 to 13.6% of cases. These auto-immune manifestations represent a significant cause of morbidity and mortality, and are associated with poorer prognosis.[11] The average survival after diagnosis of MDS is 25 months; if auto-immune manifestations occur, it drops to nine months. Auto-immune manifestations respond to immunosuppres-

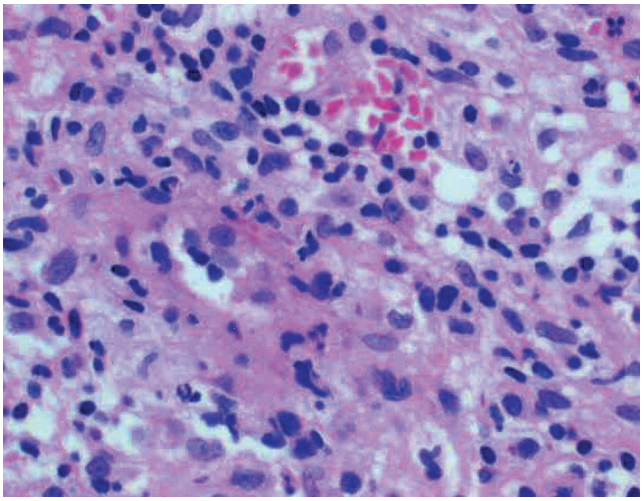

Figure 3: Photomicrography of histological section of skin shows diffuse infiltrate with polymorphonuclear lymphocytes, histiocytes and fibrinoid degeneration of the vascular wall (HE 100X)

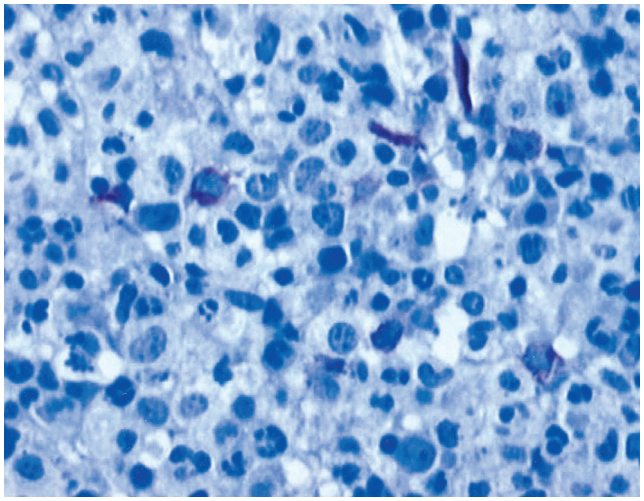

Figure 5: Photomicrography of histological section of bone marrow. Immune-histochemical reaction with antibody CD34 showing increased number of cells positive to antibodies (peroxidase 400X)

sant therapy; however, the clinical response is generally not sustained requiring progressively higher doses of immunosuppressants.[12]

The case reported presents MDS of the RCMD subtype.[9] In an comprehensive literature review through Medline, no descriptions were found on the association with this subtype with PG.

The pathogenesis of the relation between PG and hematological disorders remains unclear. MDS would cause alterations in antigen presentation, in T-cell response or in the interaction between T and B cells, leading to an immune system imbalance,[12] which would lead, in turn, to production of auto-antibodies against cutaneous antigens with perivascular immune complexe deposition.[13] PG can occur concomitant to the hematological disease or, during its evolution, as marker of the malignant transformation of a previously stable disease.[8]

As in the case reported, PG can be the cutaneous manifestation of a systemic disease. The possibility of MDS should always be considered in patients with pyoderma gangrenosum presenting by mono-, bi- or pancytopenia. ❑

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