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Pioderma Gangrenoso Orbitário Fatal com Envolvimento do Sistema Nervoso Central

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RESUMO – O pioderma gangrenoso é uma doença inflamatória crónica que se caracteriza pelo desenvolvimento de uma úlcera dolorosa e profunda com bordos mal delimitados. Cabeça e pescoço são regiões anatómicas raramente atingidas e geralmente associadas a um pior prognóstico. A corticoterapia é a base do tratamento desta dermatose, embora as opções disponíveis não sejam específicas nem inteiramente eficazes no pioderma gangrenoso. Relatamos o caso de um doente de 46 anos com pioderma gangrenoso orbitário de caráter agressivo, com extensão progressiva ao sistema nervoso central e resposta insuficiente ao tratamento, que culminou na morte do doente.
PALAVRAS-CHAVE – Doenças Orbitárias; Doenças do Sistema Nervoso Central; Pioderma Gangrenoso.

Fatal Orbital Pyoderma Gangrenosum with Central Nervous System Involvement

ABSTRACT – *Pyoderma gangrenosum is a chronic inflammatory disease characterized by the development of a painful deep ulcer with undermined borders. Head and neck are rarely affected regions of the body and also usually associated with a worse prognosis. Corticosteroids are the mainstay of treatment although available options are not specific nor completely effective in pyoderma gangrenosum. We report the case of a 46-year-old patient with an aggressive orbital pyoderma gangrenosum with progressive extension to the central nervous system and insufficient response to treatment, ultimately leading to patient's death.*
KEYWORDS – *Central Nervous System Diseases; Orbital Diseases; Pyoderma Gangrenosum.*

INTRODUCTION

Pyoderma gangrenosum (PG) is a rare chronic inflammatory dermatosis of unknown etiology (1-4). It usually starts as a pustule or a nodule that progressively enlarges, developing central necrosis and culminating in a painful deep ulcer with raised and undermined borders.[1-3,5] There is frequently a purulent and hemorrhagic discharge.[1]

CASE REPORT

A 46-year-old male with a history of alcoholic liver disease presented with an extensive and friable ulcer of the right upper eyelid with exuberant periorbital edema (Fig. 1). The lesion was present for two years with progressive growth. Prior to our observation, he had been submitted to five surgical interventions, in Ophthalmology and Plastic Surgery, due to malignant suspicion, which was excluded in all histologic exams. Infectious causes were ruled out through immunohistochemistry assays (Warthin-Starry, PAS, PAS-D, Giemsa, Grocott) and bacterial, mycobacterial and fungal cultures of affected tissue. Screening for HIV and viral hepatitis as well as immunologic study, including antinuclear antibody titer, anti-neutrophilic cytoplasmic antibodies, antiphospholipid antibody and rheumatoid factor, were negative. Computed tomography scan showed

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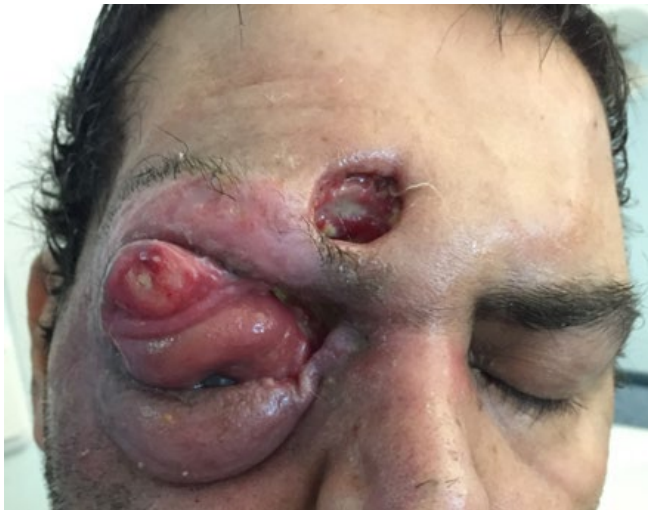

Figure 1 - Extensive ulcer of the right upper eyelid with periorbital edema.

an expansive orbital lesion with invasion of the eye globe (Fig. 2). Due to this dramatic evolution, the hypothesis of a pyoderma gangrenosum was placed and corroborated by revision of the histological specimens (Fig. 3). We initiated prednisolone 1 mg/kg/day with slight clinical and radiological improvement after a few days. Treatment was maintained during one month, but after prompt response, the lesion progressed, reaching the right forehead and eyebrows. At this time, the patient was hospitalized for clinical stabilization. He had a positive interferon-gamma release assay (IGRA), making immediate biologic treatment unfeasible. Therefore, we started oral cyclosporine 300 mg/day in combination with oral corticosteroid. Imaging control through magnetic resonance imaging showed progression to the frontal sinuses and central nervous system, causing a mass effect without consequences in patient´s neurological state. Dexamethasone 4 mg three times daily was started

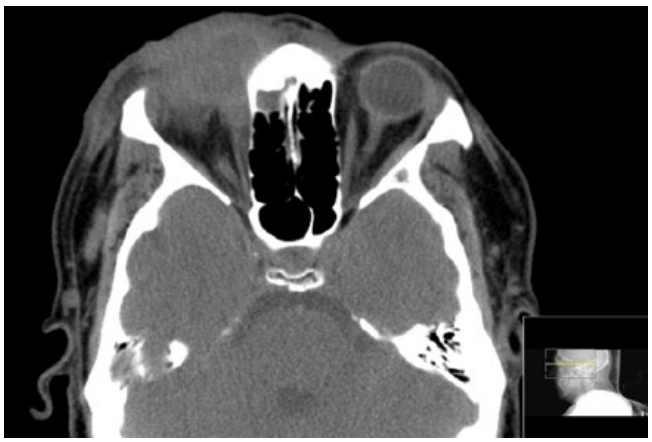

Figure 2 - CT scan showing expansive orbital lesion with invasion of the globe of the eye.

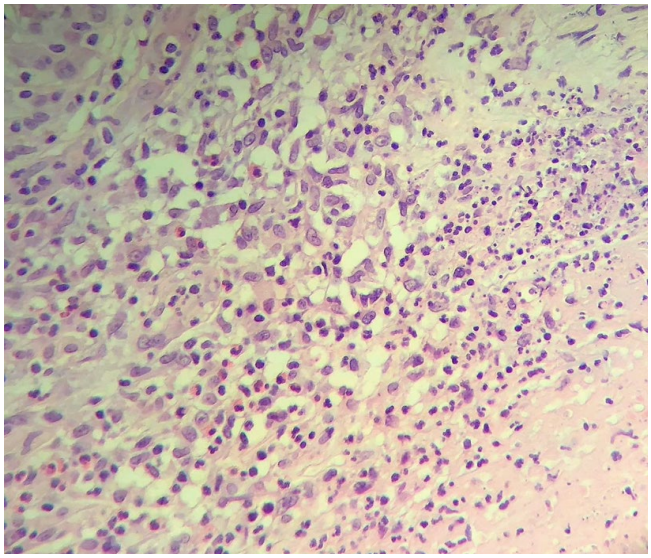

Figure 3 - Histological findings showing a predominantly neutrophilic infiltrate in the dermis (HE, 400x).

and cyclosporine was increased to 350 mg/day, with negligible benefit (Fig. 4). Cyclosporine was discontinued after one month due to a *Pneumocystis jiroveci* pneumonia, treated with trimethoprim/sulfamethoxazol. Patient's consciousness had a rapid deterioration due to progressive cerebral edema, unsuccessfully treated with mannitol. Pneumonia evolved with septic shock and multi-organ dysfunction. The infectious complication in association with the evolution of the lesion ultimately led to patient's death.

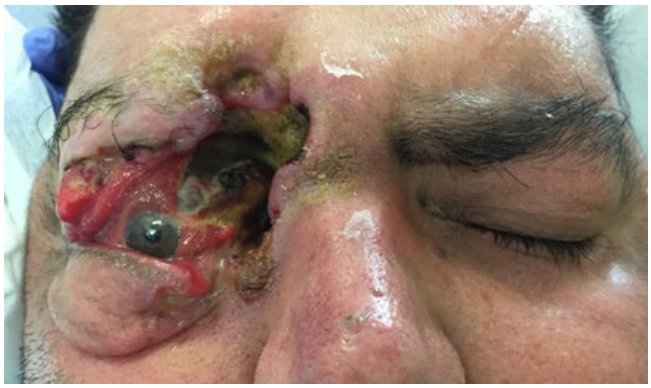

Figure 4 - Deep ulcer of the right upper eyelid with irregular borders and a necrotic center.

DISCUSSION

PG usually affects adult patients, with a female predominance and a peak incidence between 30 and 50 years.[6] The disease may develop in association with systemic diseases as inflammatory bowel disease (IBD), polyarthritis, and lymphoproliferative disorders, but can also rise in the absence of an underlying disease,[1,3,4,6] as in the present case.

The most frequently affected anatomic regions are the trunk and lower extremities but PG can develop in other areas.[1,7] There are a few previous case reports of central nervous system involvement in patients with PG, although usually representing independent foci of attainment.[8,9] Malignant pyoderma is a term used to describe a rapidly evolving ulcer in the head and neck without previous history of systemic disorders, which is considered by many authors to be a rare subtype of PG.[5,10,11] This variant may show some particularities, namely the absence of undermined borders, worse response to treatment and more frequent relapses.[5,11] The designation seems appropriate since it highlights the rapidly invasive nature of PG making crucial both an early diagnosis and aggressive treatment.

PG is a neutrophilic dermatosis and its pathophysiology is probably multifactorial.[4,10] Defects in neutrophil chemotaxis were classically linked to PG development, although altered neutrophil structure and abnormal integrin-endothelial interactions may also contribute to the increased migration of the inflammatory cells.[4,10] Previous studies suggest that T cells are also abundant in PG lesions but specific antigen responsible for T-cell activation is still unknown.[4,10] More recent theories classify this entity as an auto-inflammatory disease due to dysregulation of the innate immune system.[4,10]

Pathergy, a phenomenon where minor trauma leads to the development of a new lesion or aggravation of existing ones, is a feature in 20% to 30% of the patients with PG.[1,4,12] This patient's surgical interventions prior to a definitive diagnosis, may have been partly responsible for the progressive worsening of the disease.

PG is no longer a diagnosis of exclusion, according to a recent consensus.[13] Authors consider a skin biopsy with neutrophilic infiltrate a major criteria for the diagnosis although a mixed infiltrate or the presence of leukocytoclastic vasculitis do not exclude the disease.[13] Eight clinical and laboratorial findings are considered minor criteria (exclusion of infection; pathergy; personal history of IBD or arthritis; history of a papule, pustule or vesicule with subsequent ulceration; perilesional erythema, undermining borders and local tenderness; multiple ulcerations; cribriform or wrinkled scars in healed skin; response to immunosupressive therapy).[13] Our patient presented 1 major and 4 minor criteria for PG according to these newly proposed criteria.

The clinical course of PG is unpredictable, with some patients experiencing a rapid development of the skin lesions whereas others have a more protracted evolution.[1] The mortality rate may be up to 30% with male sex, older age, bullous PG and association with hematological malignancy being considered poor prognostic factors.[1,11]

Treatment is not specific nor consistently effective.[1,6] Proper wound care and pain management are crucial to increase patient comfort.[3] Topical drugs may be useful in mild cases while systemic treatments should be considered in more aggressive and extensive lesions.[1,5] A previous review suggests that combination therapy seems to be more effective than monotherapy.[6] Although there are no systematic analyses on systemic drugs used in PG, corticosteroids, dapsone, cyclosporine and other immunosuppressive drugs are commonly used.[1,5,7] Infliximab is an option for refractory PG.[1,3]

In our patient, refractory PG along with a rarely described central nervous system involvement contributed to his earlier death although infectious intercurrence had a predominant role in this outcome. Despite our several therapeutic options, the disease revealed resistant probably due to a significant delay in the diagnosis. Patient's comorbidities also limited our decisions throughout the clinical evolution. Therefore, this case wants to emphasize that dermatologists should be highly alert to unusual sites of involvement and atypical clinical presentations of PG, which may otherwise lead to delays in diagnosis and adequate treatment, with possible fatal outcomes. Moreover, surgeons should be alert to avoid repeated surgical procedures in this disease.

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Confidencialidade dos dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.
Direito a privacidade e consentimento escrito: Os autores declaram que pediram consentimento ao representante legal para usar as imagens no artigo.
Protecção de pessoas e animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.
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Protection of persons and animals: *The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).*
Patient consent: *Obtained.*

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