Institute of Experimental Morphology and Anthropology with Museum
Bulgarian Anatomical Society

Acta morphologica et anthropologica, 15
Sofia • 2010

Pyoderma Gangrenosum – Morphological Challenge

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Pyoderma gangrenosum (PG) is an uncommon, ulcerative skin disease usually included in the group of vasculitic disorders. We discuss four patients with the diagnosis PG and define morphological substrate of their skin lesions. These findings we juxtapose to those reported in the literature. Based on the clinical and histopathological characteristics we make some aspirations for the pathogenesis of the disease and search the relation with vasculitis.

Key words: Pyoderma gangrenosum, vasculitis, neutrophilic infiltrate, histopathology.

Introduction

Pyoderma gangrenosum (PG) is an uncommon, ulcerative skin disease usually included in the group of vasculitic disorders with distinctive cutaneous clinical characteristics first described in 1930 [3]. It is associated with underlying conditions in up to 50% of cases, the most common of which are inflammatory bowel disease, rheumatoid arthritis, and hematological malignancies [6]. The pathogenesis of PG has remained obscure even as an ever-widening array of systemic diseases described in association with it. Clinically it starts with sterile pustules that rapidly progress and turn into painful ulcers of variable depth and size with undermined violaceous borders. Course can be mild or malignant, chronic or relapsing with remarkable morbidity. PG has four major clinical types – ulcerative, pustular, bullous, and vegetative [4] and mainly affects the skin of lower limbs, but rarely atypical bullous variant seems to affect upper limbs [2]. Correct diagnosis relies on clinical signs first and is supported by biopsy for histopathology. Knowledge of the patient's history for possible underlying disease and specific investigations based on that background are necessary. Therefore diagnosis is made by exclusion of other possible disorders. No laboratory parameter for PG is available. The histopathology is nonspecific and remains speculative in most patients. The pathology includes necroses and ulceration of the epidermis and dermis, particularly in follicular zones, heavy infiltration of acute inflammatory cells at the base. In ulcerative PG the histopathological picture shows central neutrophilic abscess formation with distal lymphocytic angiocentric infiltrate. We have followed 4 very interesting patients with the rare diagnosis PG which varied both in clinical and histological picture.

Materials and Methods

Case1 is a 45-year-old woman suffered from a painful and deep ulcerative lesion that appeared after a minor trauma on the flexural part of her right lower limb. Her medical history is complicated with chronic hepatitis.

Case 2 is a 40-year-old woman with ulcerative lesions on her forearms and hands, following successful surgery for Quervain's disease. She had pain and a moderate increase of the temperature.

Case 3 is a 28-year-old woman who developed in a short time two painful but not so deep ulcers on her left thigh.

Case 4 is a 67-year-old lady that had pustular lesions and erosions of long duration on the skin of her legs, treated with topical therapy without effect. She had also arthralgia and hypertonia.

Routine laboratory examinations, immunological investigation including anti-nuclear, antideoxyribonucleic, antineutrophilcytoplasmic and anticardiolipin (aCL) antibodies, X-ray, thermometry and Doppler ultrasound studies were done. Specific stains and cultures for fungal and bacteria were performed. Skin biopsy specimens taken from the lesions and direct immunoflourescense of all the cases were examined.

Results and Discussion

Having in mind the clinical characteristics of the lesions, confirmed by the laboratory and histopathological findings we put the diagnosis PG in all four cases. The disease has a variety of conflicting microscopic descriptions. This is the reason we want to illustrate our morphological findings and compare them to precious descriptions.

Clinical examination of case 1 corroborated leg ulcerative lesion with deep and crusted appearance and underminded borders. Histopathological findings of skin specimen showed a dense neutrophilic infiltrate in derma and subcutaneous tissue without vasculitis. Significant upper dermal edema and erythrocyte extravasation were evident within the epidermis and dermis (fig. 1).

Histological examination of the recurrent ulcers on the hands of case 2 showed necrosis in the epidemis, fibrinoid necrosis in the middle dermis and a moderate infiltrate in the deep dermis (fig. 2). The infiltrate consisted of neutrophils and lymphocytes (fig. 3).

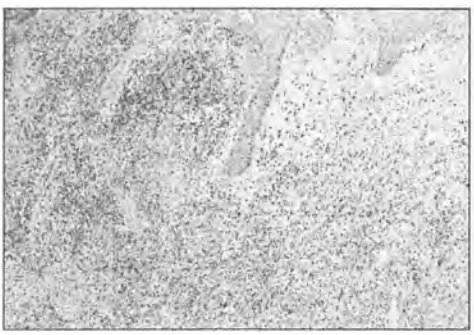

Fig. 1. Case 1 – dense neutrophilic infiltrate in derma and subcutaneous tissue, significant upper dermal edema and erythrocyte extravasation (HE, × 80)

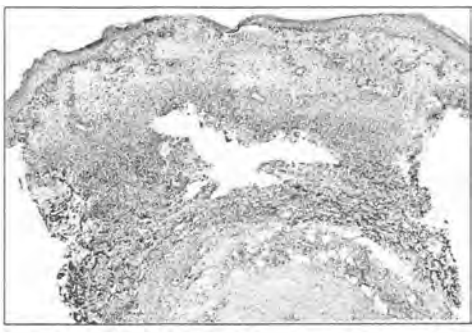

Fig. 2. Case 2 – fibrinoid necrosis in the epidermis, necrosis and moderate infiltrate in the dermis (HE, × 40)

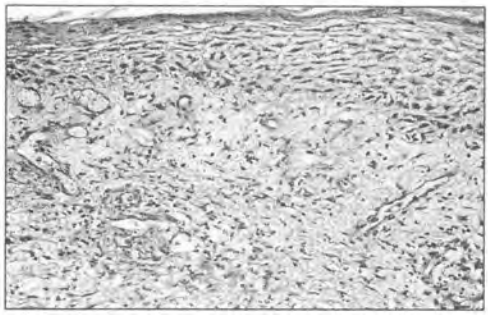

Fig. 3. Case 2 – moderate infiltrate of neurtophils and lymphocytes in the dermis (HE, × 80)

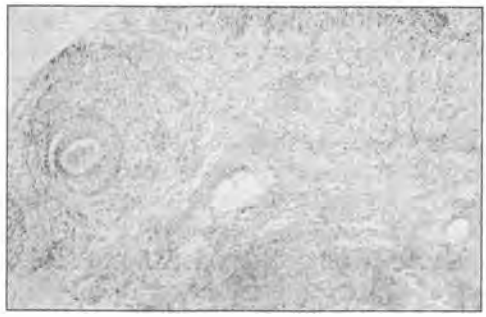

Fig. 4. Case 3 – dermal neutrophilic infiltrate and endothelial swelling without vasculitis (HE, × 80)

The ulcers of case 3 did not have underminded borders which is not typical for PG. The histological picture demonstrated dermal neutrophilic infiltrate and endothelial swelling without vasculitis (fig. 4). The patient had possitive IgGaCL and a previous spontaneous abortion. From this point of view we put also the diagnosis of Antiphospholipid syndrome (APS) and considered it as an association with PG. However, she had not any occlusion in the vessels on the histopathology.

Case 4 tended to be a pustular form of PG as the other three ones were ulcerative. Histopathological finding defined very well a subcorneal pustule with neutrophils, eosinophils and acantolitic cells. An inflammatory infiltrate of neutrophils, eosinophils and mononuclear cells were seen mainly around the vessels. Endothelial swelling was present in the dermis (fig. 5).

We reported four unique clinical cases presented within two main clinical forms– pustular and ulcerative. The histomorphological findings were quite different in the investigated biopsy's specimens. What is important is that the neutrophilic infiltrates was constant and dominated everywhere. The typical vasculitis was absent. It was difficult to demonstrate a vessel origin of the lesions and we would like to understand why PG is included in the vasculitis classification.

The histopathologic findings in lesions of PG are controversial and usually not diagnostic. Some authors studying early lesions report a primary neutrophilic infiltrate, whereas others describe a primarily lymphocytic infiltrate. Degrees of vessel involve-

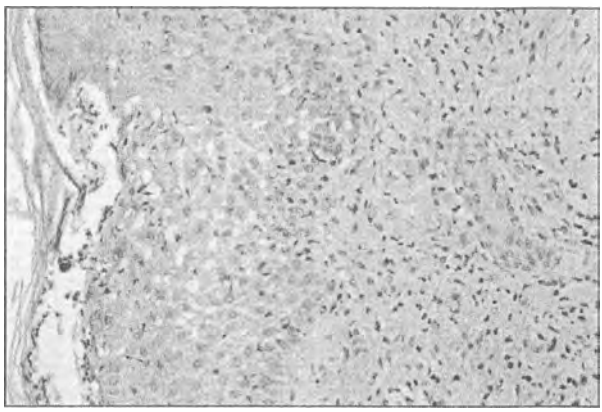

Fig. 5. Case 4 – subcorneal pustule with neutrophils, eosinophils and acantolitic cells, inflammatory infiltrate around the vessels and endothelial swelling in the dermis (HE, × 100)

ment reported vary from none to endothelial swelling to fibrinoid necrosis. Fully developed ulcers of typical PG show pronounced tissue necrosis surrounded by mild inflammatory cell infiltrate with occasional foreigh body giant cells deeper in the dermis. Subcorneal pustule and perifollicular neutrophilic infiltrate are seen in the pustular clinical variant of PG.

Regarding the major controversy concerning vascular involvement two main opinions exist [1]. Some investigators emphatically deny any involvement in the vasculature while others support it finding histologic evidence of cutaneous vasculitis, mainly necrotizing, consisting in angiocentrical segmental inflammation, endothelial cell swelling and fibrinoid necrosis of blood vessels.

Although an immune-mediated pathogenesis is suspected, a review of published reports leads to the conclusion that no consistent immunologic abnormality is found in PG patients. One of our cases is associated with chronic hepatitis and has circulated immune complexes (CIC) and another has an associated APS. An interesting possibility is that PG could be a cutaneous manifestation of APS as it has been suggested [5]. All our cases demonstrated neutrophilic infiltrate and were successfully treated with medications with an action towards neutrophils- colchicin, tetracycline, thalidomid.

The association of PG with diseases in which CIC are present (case 1), the finding of pathergy (case 1 and case 2), the overlap of PG with APS (case 3), our view of the histopathology of the lesions of all our patients and good therapeutic results have led us to two main conclusions:1. We consider neutrophils as a significant mediator of inflammation in the pathogenesis of these cutaneous lesions, and 2. We view PG as a neutrophil-mediated vascular inflammatory disorder.

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