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Case Report

The road to diagnosis: presentation from erythema nodosum to vegetative pyoderma gangrenosum

診斷歷程：從結節性紅斑演化為增殖型壞疽性膿皮症

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We report the rare occurrence of erythema nodosum and pyoderma gangrenosum at different times during the clinical course in a 30-year-old gentleman. He initially presented with biopsy-proven erythema nodosum over both shins. He subsequently developed multiple violaceous and vegetative nodules over the upper and lower limbs. Three serial skin biopsies were performed thereafter. A diagnosis of vegetative pyoderma gangrenosum was made based on the clinical findings and histopathological features. He showed good treatment response to oral steroid.

我們報告了一名三十歲男仕的罕見臨床病況，他在不同時期出現了結節性紅斑及壞疽性膿皮症。他最初在雙腿脛部出現活檢證實的結節性紅斑，四肢繼而長出多個紫蘿蘭色的增殖性結節。其臨床表現結合其後三個切皮檢查的病理組織學特徵，被確診爲增殖型壞疽性膿皮症；施以口服類固醇治療後，病情得到明顯改善。

Keywords: Erythema nodosum, vegetative pyoderma gangrenosum

關鍵詞：結節性紅斑、增殖型壞疽性膿皮症

Introduction

Pyoderma gangrenosum is an uncommon, ulcerative skin disorder, which may associate with various comorbidities. It has no characteristic histological feature but skin biopsy helps to exclude other important diagnoses.

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Case report

A 30-year-old gentleman, who had good past health, presented with a two-month history of painful, erythematous subcutaneous nodules over bilateral shins (Figure 1a). He experienced no joint pain, constitutional symptom or gastrointestinal symptom. He had no oral or genital lesion. He was not on any regular medication. His family history was unremarkable. Investigations revealed mild anaemia (haemoglobin 11.0 g/dL), and elevated serum ESR (74 mm/1 hr) and CRP

(153 mg/L). Liver and renal function tests, anti-nuclear antibody, anti-extractable nuclear antigen antibody and anti-neutrophil cytoplasmic antibody were either normal or negative. The first incisional skin biopsy which was done over the right shin lesion showed septal panniculitis with granulomatous inflammation featuring epithelioid cells, multinucleated giant cells, neutrophils, eosinophils and lymphocytes (Figures 1b & 1c). There was a mild perivascular lymphocytic infiltrate in the dermis. Direct immunofluorescence study was negative. The clinical and histological features were compatible with erythema nodosum. The patient had poor treatment response to naproxen 250 mg twice daily. Screening by the chest clinic showed no evidence of tuberculosis infection.

One month later, he developed multiple hyperkeratotic and violaceous nodules over both forearms (Figure 2a) and had persistent fever. A second skin biopsy was done over the left forearm lesion and it showed multiple suppurative granulomas in the dermis (Figure 2b). Periodic acid-Schiff with diastase stain and Grocott's stain showed no fungus. Ziehl Neelsen and Wade-Fite stains revealed no acid-fast bacillus. The skin biopsy was negative for fungal and mycobacterial cultures.

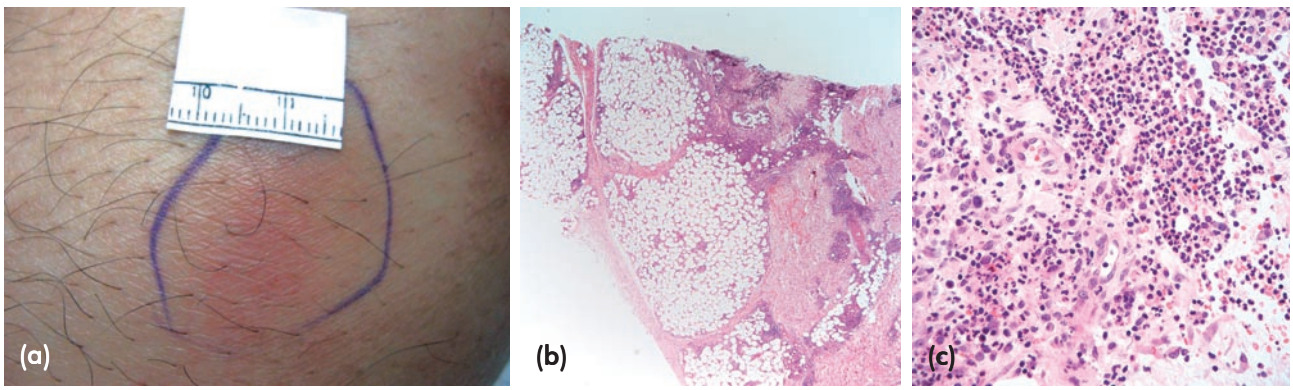

Figure 1. (a) Erythematous subcutaneous nodule over the right shin. (b) Low power view shows septal panniculitis (septal thickening and periseptal inflammation) (H&E, original magnification x 25). (c) Inflammatory infiltrate rich in neutrophils (H&E, original magnification x 400).

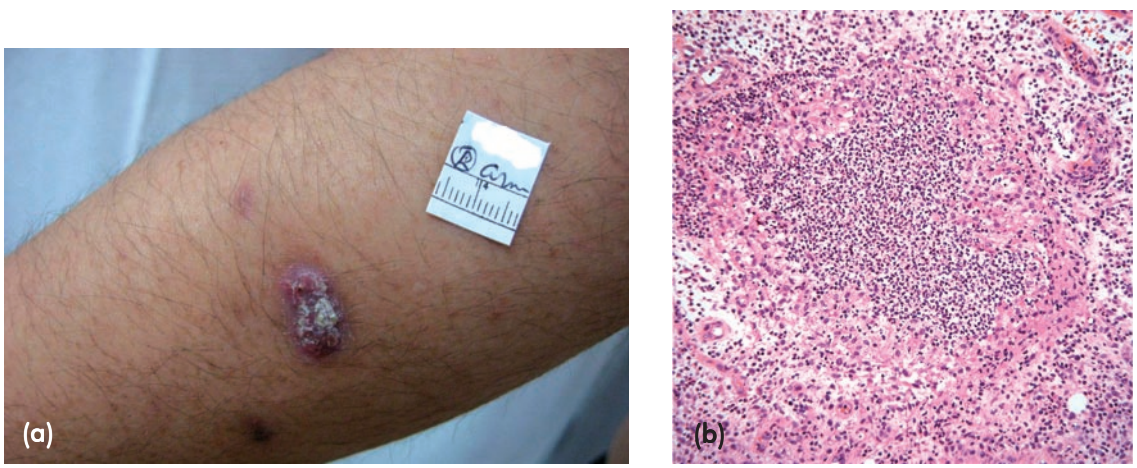

Figure 2. (a) Hyperkeratotic and violaceous nodule over the right forearm. (b) Suppurative granuloma with neutrophilic abscess rimmed by histiocytes (H&E, original magnification x 200).

The nodules then spread to the abdomen and bilateral lower legs. Lesions over both calves developed vegetative growth with ulcerations (Figure 3a). Differential diagnoses of these vegetative lesions included typical or atypical mycobacterial infection, deep fungal infection, viral wart, pyoderma vegetans, squamous cell carcinoma, malignant melanoma, cutaneous lymphoma and vasculitis. A third skin biopsy was undertaken over the left calf lesion which revealed pseudoepitheliomatous hyperplasia with multiple abscesses within the bulbous elongated rete ridges, dermis and subcutis. Abundant inflammatory granulation tissue infiltrated by neutrophils, mononuclear cells and a few multinucleated giant cells was present. The diagnosis of pyoderma gangrenosum was made.

The patient was treated with cyclosporin A 300 mg per day (3 mg/kg/day). However, he responded poorly to a 3-month course of cyclosporin A. A fourth skin biopsy was performed over the right calf lesion and it showed pseudoepitheliomatous hyperplasia, mixed inflammatory infiltrates (lymphocytes, histiocytes and polymorphs) in the dermis and some scarring in the lower dermis (Figures 3b & 3c). Clinico-pathological correlation of all the findings supported the diagnosis of vegetative pyoderma gangrenosum. He had no gastrointestinal symptom all along. Investigations revealed no evidence of rheumatological or haematological diseases. He was then given minocycline 100 mg twice daily for four weeks. In view of the poor response to minocycline, he was subsequently treated with oral prednisolone 60 mg daily. Rapid clinical improvement with healing of ulcers and thinning of vegetative lesions was observed after two weeks of prednisolone treatment. All lesions resolved with post-inflammatory hyperpigmentation and scars after administration of systemic steroid for two months (Figure 4). Prednisolone was gradually tailed off over five months.

Discussion

Pyoderma gangrenosum is an uncommon, inflammatory neutrophilic dermatosis. Classic pyoderma gangrenosum presents as painful ulcer(s) with violaceous and undermined border. Other clinical variants include vesiculobullous/bullous pyoderma gangrenosum, pustular pyoderma gangrenosum, peristomal pyoderma gangrenosum and vegetative pyoderma gangrenosum (superficial granulomatous pyoderma).

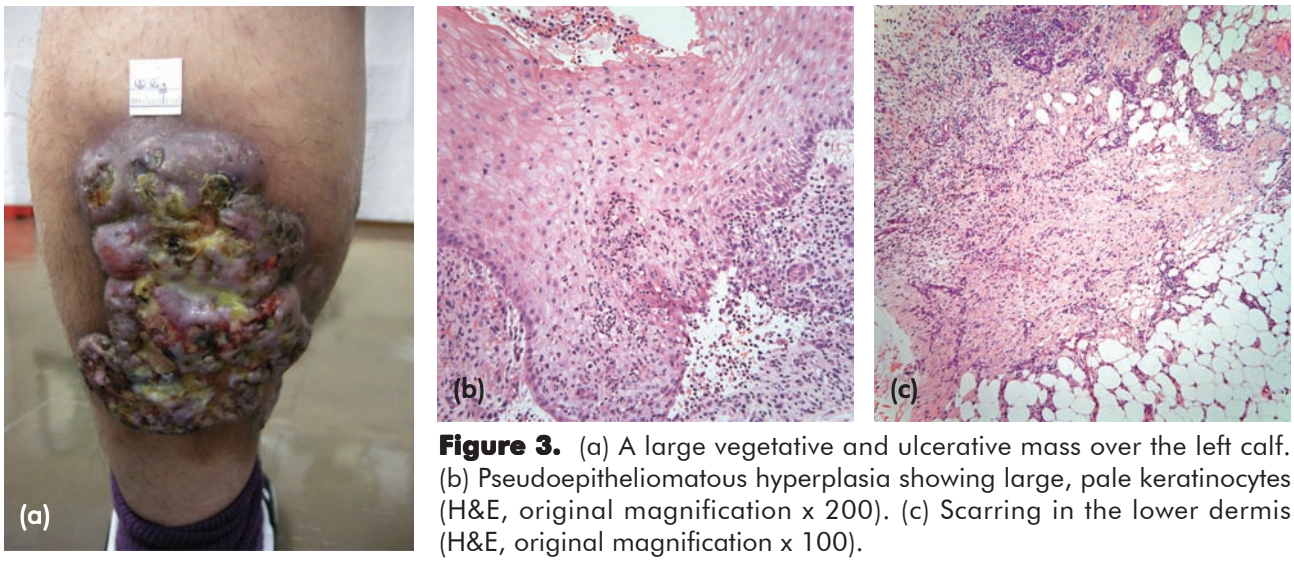

Figure 3. (a) A large vegetative and ulcerative mass over the left calf. (b) Pseudoepitheliomatous hyperplasia showing large, pale keratinocytes (H&E, original magnification x 200). (c) Scarring in the lower dermis (H&E, original magnification x 100).

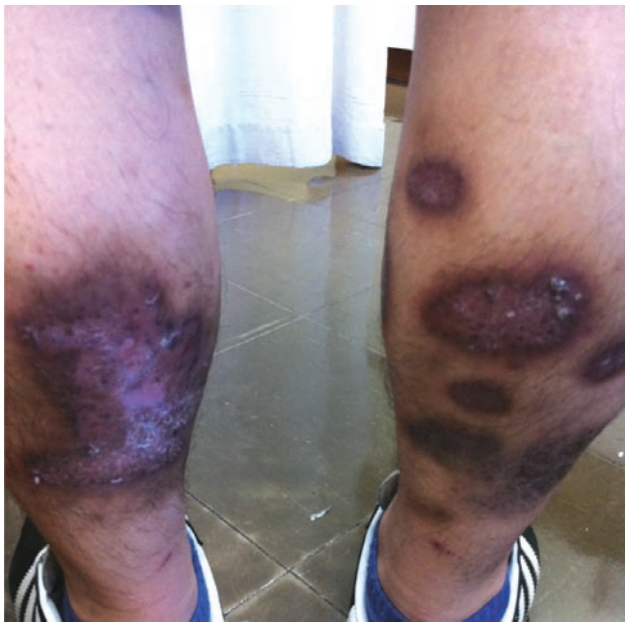

Figure 4. Lesions over the calves resolved with post-inflammatory hyperpigmentation and scars.

In a review of 46 cases of vegetative pyoderma gangrenosum, the mean age of the patients was 50.2 (8-82) years and the male-to-female ratio was 1.2:1. The most common site of involvement was the trunk (52%), followed by the limbs (31%), face (9%), groin (5%) and scalp (2%). Many cases had multiple sites of involvement. Treatments given to these cases included oral and intralesional steroids, minocycline, dapsone and cyclosporin A. Complete remission was achieved within 6 months of treatment in 35% of the patients. The duration of disease ranged from 3 weeks to 12 years. There was no specific pattern of disease association. Of these patients, 18% had underlying medical conditions including chronic renal failure, diabetes mellitus, chronic lymphocytic leukaemia, paraproteinaemia, polymyalgia, splenectomy, rheumatoid arthritis, sarcoidosis, vitiligo, lichen planus, uterine myomata, cystic acne, scleritis, uveitis, polycythaemia rubra vera and Raynaud's phenomenon.[1] The diagnosis of vegetative pyoderma gangrenosum is made by clinico-pathological correlation and excluding other causes of suppurative granulomatous diseases such as deep fungal or mycobacterial infections. There are no pathological features specific for vegetative pyoderma gangrenosum. Wilson-Jones et al reviewed 40 biopsies of patients with vegetative pyoderma gangrenosum and noted that focal neutrophilic abscesses of the papillary dermis with peripheral palisading histiocytes and foreign-body giant cells were common findings. Other features included pseudoepitheliomatous, vegetative hyperplasia and sinus tract formation.[2]

Both topical and systemic medications are used to treat pyoderma gangrenosum. Topical treatments include highly potent topical steroids with or without occlusion, intralesional steroid injection and topical tacrolimus.[3,4] Minocycline has been reported to be effective.[5] Cyclosporin A (3-5 mg/kg/day) is another treatment option.[3,4,6] However, most patients require high dose oral prednisolone (1-2 mg/kg/day) for induction of remission.[3,4,6] Infliximab has also been shown to be effective in the treatment of pyoderma gangrenosum in a randomised, double-blind, placebo-controlled trial.[7] Our patient did not respond well to either minocycline or cyclosporin A, yet he showed a rapid response to oral steroid with all lesions subsiding within two months.

The association of erythema nodosum and pyoderma gangrenosum in the same patient has been reported in patients with Crohn's disease.[8] In a review study of 1015 patients with Crohn's disease,[9] only two patients have both erythema nodosum and pyoderma gangrenosum at different times of presentation. For our patient, biopsy-proven erythema nodosum was found in the initial presentation with subsequent development of pyoderma gangrenosum. Although he had no gastrointestinal symptoms suggestive of Crohn's disease, we need to monitor him carefully for the development of any evidence of inflammatory bowel disease in the future.

This report demonstrated a rare case of vegetative pyoderma gangrenosum with preceding erythema

nodosum. Association between these two diseases has been described in a few case reports. Clinically he had good response to systemic steroid. Vegetative pyoderma gangrenosum is a disease with diagnostic challenge as histopathological features are non-specific. The diagnosis of this entity is made mainly by correlation of clinical and pathological findings, and exclusion of other important differential diagnoses.

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