

Pyoderma gangrenosum in association with microscopic colitis, idiopathic hypereosinophilic syndrome, selective IgE deficiency and diabetes mellitus

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Summary

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis of unknown aetiology. We report a 27-year-old male patient with diabetes, who presented with a nonhealing ulcer on the left leg, pruritic hyperpigmented papules distributed over the trunk and limbs, and chronic diarrhoea. He had eosinophilia, low haemoglobin and serum IgE levels, and raised erythrocyte sedimentation rate. Histopathology of the leg ulcer was consistent with the diagnosis of PG, while the histology of the hyperpigmented papule revealed tissue eosinophilia. Subsequent evaluation was conclusive of the diagnosis of PG, idiopathic hypereosinophilic syndrome (IHES) and selective IgE deficiency. Dexamethasone pulse therapy achieved resolution of the ulcer and reduction in the eosinophilia. Further evaluation for the persistent diarrhoea led to a diagnosis of lymphocytic colitis (LC), which responded to budesonide. To our knowledge, the association of PG with IHES, selective IgE deficiency or LC has not been previously reported.

Pyoderma gangrenosum (PG) is frequently associated with systemic diseases. We report a patient with PG who also had type 1 diabetes mellitus, idiopathic hypereosinophilic syndrome (IHES), selective IgE deficiency and lymphocytic colitis (LC).

Report

A 27-year-old man presented with a 2-month history of a nonhealing ulcer (160 × 100 mm) on the lower part of his left leg (Fig. 1a). The initial lesion was a pustule that broke down to form a rapidly spreading painful ulcer, with a score of 6 for pain on visual analogue scale. The patient also had hyperpigmented, pruritic papules scattered over his trunk and limbs

(Fig. 2a), which had been present for 1 month. The patient's medical history included Type 1 diabetes mellitus (T1DM) treated with insulin for the past 4 years, chronic watery diarrhoea with fecal urgency and incontinence for the past 1 year, and eosinophilia varying between 2 and $3.5 \times 10^9/\text{L}$ (normal range $0.04\text{--}0.4 \times 10^9/\text{L}$) for the past 8 months.

Laboratory investigations revealed low haemoglobin (9 g/dL; normal range 13.0–18.0 g/dL), raised erythrocyte sedimentation rate (85 mm/h; 0–15 mm/h) and absolute eosinophil count ($2.3 \times 10^9/\text{L}$), and positive pathergy test. Peripheral smear showed eosinophilia without blast forms or parasites. Stool fat estimation, stool microscopy, renal, liver and pancreatic function tests, and random blood sugar level were within normal limits. Tests were negative for antinuclear antibody and antineutrophil cytoplasmic antibodies. Serology test for syphilis and infections due to human T-cell leukaemia viruses 1 and 2, human immune deficiency viruses 1 and 2, and hepatitis B and C viruses were negative. Serum electrophoresis, CD4 count, chest radiography, echocardiogram, Doppler study of the vessels in the legs,

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barium meal follow-through, colonoscopy, ultrasonography examination of the abdomen and pelvis, and contrast-enhanced computed tomography (CECT) of abdomen were within normal limits. Detailed pulmonary evaluation by a specialist excluded underlying lung pathology. Serum immunoglobulin assay revealed low IgE levels (lower than the normal level of < 2 kIU/L) with normal IgG, IgA and IgM levels.

Histological findings of a skin biopsy from the ulcer were suggestive of neutrophilic vasculopathy (Fig. 3). Biopsy from the pruritic papule showed eosinophilic infiltration of the dermis, indicating tissue eosinophilia (Fig. 2b).

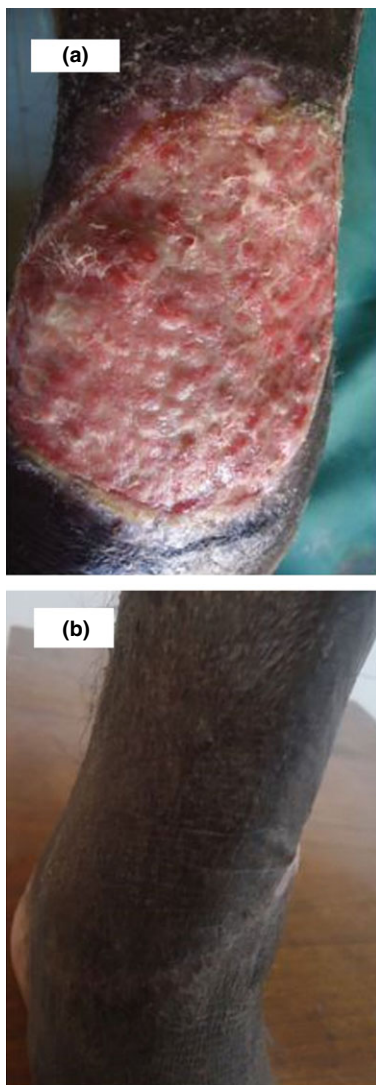


Figure 1 (a) Leg ulcer due to pyoderma gangrenosum; (b) complete resolution of the ulcer following dexamethasone pulse therapy.

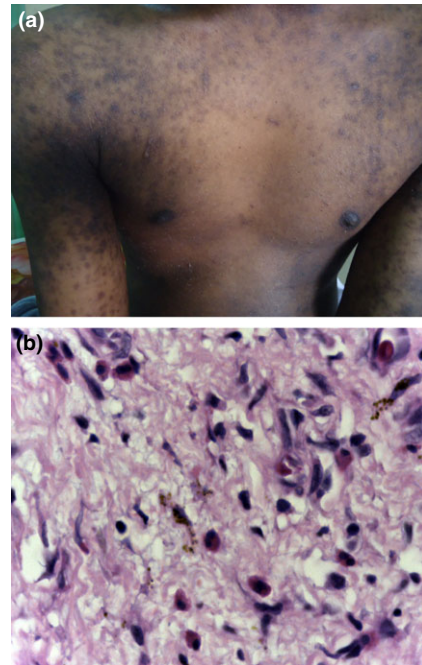


Figure 2 (a) Hyperpigmented pruritic papules of idiopathic hypereosinophilic syndrome; (b) dermal infiltration of inflammatory cells, mainly eosinophils indicating tissue eosinophilia (haematoxylin and eosin, original magnification $\times 1000$).

We made a diagnosis of PG with T1DM and probable selective IgE deficiency (as other immunoglobulins were within normal limits),¹ and considered the possibility of IHES in view of the pruritic skin lesions, with histological evidence of tissue eosinophilia and unexplained peripheral blood eosinophilia of $> 1.5 \times 10^9/L$ persisting for > 6 months.²

Myeloproliferative and lymphoproliferative variants of hypereosinophilic syndrome were excluded by normal serum vitamin B12 and leucocyte alkaline phosphatase levels, absence of FIP1-like-1–platelet-derived growth factor receptor- α (FIP1L1-PDGFR α) fusion mutated clones on bone marrow aspirate analysis, normal flow cytometry of blood sample, and absence of abnormal cells in peripheral smear and bone marrow examination.³ Serum troponin level and computed tomography of the thorax were also within normal parameters.

The patient's anaemia and eosinophilia failed to respond to iron and vitamin supplements and to diethyl carbamazepine and albendazole, respectively. The ulcer also progressed, in spite of topical treatment with halobetasol propionate 0.05% and tacrolimus 0.1%. Subsequent dexamethasone pulse therapy (100 mg in 500 mL dextrose 5% daily for 3 days every 28 days)

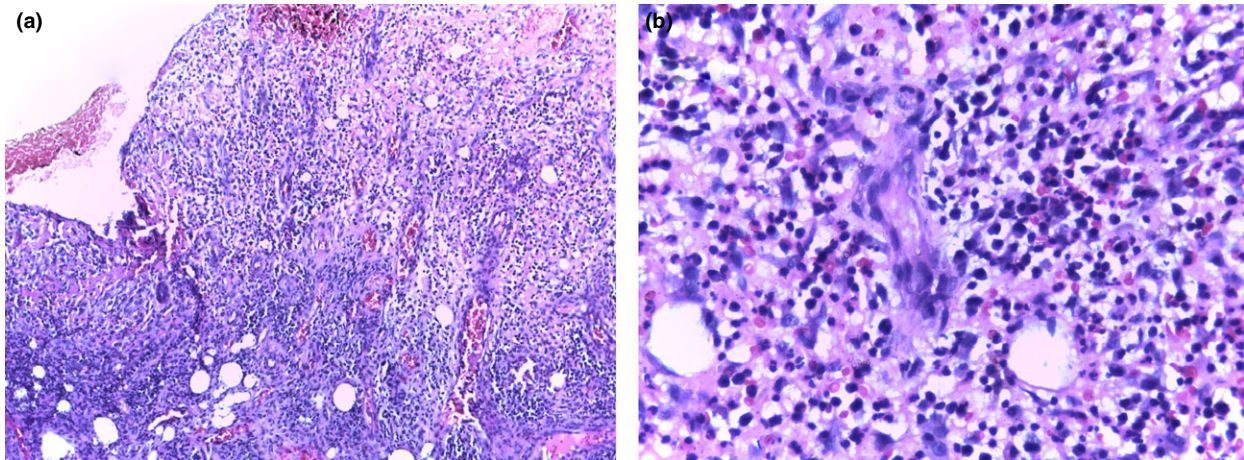


Figure 3 (a) Biopsy of the leg ulcer showing ulcerated epidermis and inflammatory infiltrate in the dermis; (b) high-power view of the dermal inflammatory infiltrate, showing neutrophils surrounding vessel walls. Haematoxylin and eosin, original magnification (a) $\times 100$; (b) $\times 400$.

resulted in improvement after the second pulse, and was stopped after the 10th pulse, as complete resolution of the ulcer was obtained (Fig. 1b) with marked improvement in the pruritic skin lesions and eosinophils ($0.8 \times 10^9/L$). However, the anaemia (8.2 g/dL), low serum IgE and diarrhoea persisted.

Colonic biopsy performed for the persistent diarrhoea showed lymphoplasmacytic infiltration of colonic epithelium and lamina propria, with > 20 lymphocytes per 100 enterocytes without any architectural distortion (Fig. 4) which was diagnostic of LC.⁴ Subsequent jejunal biopsy and jejunal aspirate analysis showed no evidence of coeliac disease or

parasitic infestation, respectively.⁵ The diarrhoea improved with budesonide 9 mg. The selective IgE deficiency was left untreated, as it is an asymptomatic condition in isolated form.¹

The patient is being followed up for detection of any systemic complications and for gradual tapering of budesonide.

The rapidly progressing painful ulcer, lack of response to antibiotics, positive pathergy test, histological evidence of neutrophilic infiltrate around cutaneous blood vessels, and response to treatment with systemic steroids were the features indicating PG in our patient.⁶

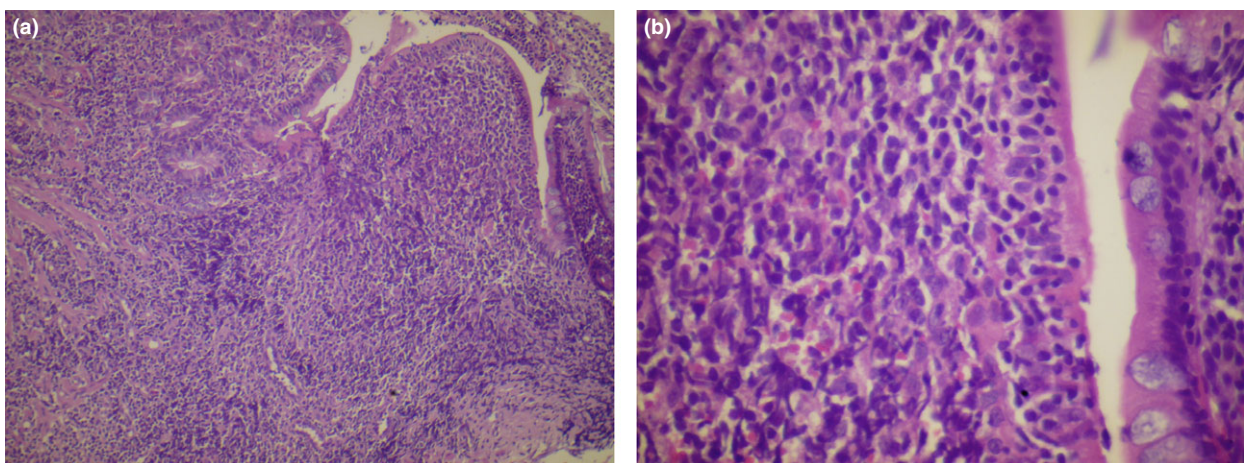


Figure 4 (a) Colonic biopsy showing lymphoplasmacytic infiltration of the epithelium and lamina propria; (b) high-power view, showing > 20 lymphocytes per 100 enterocytes, without any architectural distortion. Haematoxylin and eosin, original magnification (a) $\times 100$; (b) $\times 400$.

The diagnosis of IHES was based on the criteria of Chusid *et al.*² The persistence of anaemia despite resolution of long-standing ulcer and the eosinophilic infiltration of dermis revealed by histopathology examination of pruritic skin lesions could be attributable to the IHES. IHES was unlikely to be the cause of the leg ulceration, as the ulcer histology indicated a neutrophilic vasculopathy.

We thought it worthwhile to rule out the possibility of myeloproliferative and lymphoproliferative clonal eosinophilias, as our patient had PG, a disease known to be associated with haematological malignancies.

The association of IHES with PG has not been reported previously. Bundino and Zina reported PG with selective hereditary IgA deficiency in a 4-year-old child but there are no reports of PG occurring with selective IgE deficiency.⁷

LC, diagnosed in our patient, is a variant of microscopic colitis. Despite normal colonoscopy findings, affected individuals show typical histology, and this is the basis for diagnosis of lymphocytic or collagenous colitis.⁴ LC is occasionally associated with autoimmune disorders, and its co-existence with IHES was documented in one Korean study.⁸ Association of PG (a disease well known to be associated with inflammatory bowel disease) with collagenous colitis has been documented previously.⁹ Its co-existence with LC in our patient emphasizes the need for a detailed evaluation of the probable link between microscopic colitis and inflammatory bowel disease.¹⁰ Systemic steroids are known to produce flare in microscopic colitis, if not slowly tapered, which might have been the reason for the lack of response to dexamethasone pulse therapy in our patient.^{5,8}

In conclusion, we report a case of PG associated with selective IgE deficiency, IHES and LC, which highlights three new associations for PG. Multinational case series studies of PG may enable us to understand the varying manifestations and the disease associations of this rare entity in different population groups.

Learning points

We report three new associations for pyoderma gangrenosum: selective IgE deficiency, idiopathic hypereosinophilic syndrome and lymphocytic colitis.

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