Intralesional methotrexate as an adjuvant treatment for pyoderma gangrenosum: A case report

Sir,

Pyoderma gangrenosum is a chronic and relapsing ulcerative neutrophilic dermatosis. In up to 70% of cases, it is associated with systemic diseases, mainly inflammatory bowel disease, seronegative arthritis and lymphoproliferative disorders.[1]

The disease presents as painful, rapidly growing ulcers with erythematous-violaceous undermined borders that leave behind cribriform scars. First-line therapies include wound care, occlusive dressings, topical antimicrobial agents, topical and intralesional corticosteroids and high doses of systemic corticosteroids.[1]

We present the case of an otherwise healthy man with pyoderma gangrenosum who showed an excellent response to intralesional methotrexate and oral corticosteroids.

A 35-year-old man presented with an eighteen-month history of painful ulcers on both calves. Three ulcers with erythematous-violaceous undermined borders were noticed on his right leg and one on the left leg [Figure 1]. A detailed laboratory evaluation was done including complete blood counts, erythrocyte sedimentation rate, antinuclear antibodies, chest radiograph, quantiferon gold assay for tuberculosis and human immunodeficiency virus (HIV) serology all of which were unremarkable. Bacterial, fungal and mycobacterial cultures from the ulcer were negative. A skin biopsy showed ulceration surrounded by granulation tissue with a scant, diffuse infiltrate of lymphocytes, neutrophils and plasmacytes and fibrosis but without any signs of vasculitis [Figure 2] and a negative periodic acid-Schiff stain, all suggestive of pyoderma gangrenosum. Associated systemic diseases were ruled out with normal blood and urine protein electrophoresis, sacroiliac radiography, rheumatoid factor and gastroenterology evaluation including colonoscopy.

Treatment was initiated with oral prednisolone, 60 mg/day and the ulcers were managed with regular wound care but there was hardly any response even after 40 days. Therefore, oral methotrexate 10 mg weekly was added for 2 months, again without much response. Then we decided to change the route of administration of methotrexate and intralesional methotrexate (injectable solution of methotrexate 50 mg/2 ml; given 25 mg/week) was given along the erythematous border of the ulcers, in addition to oral prednisone. The response

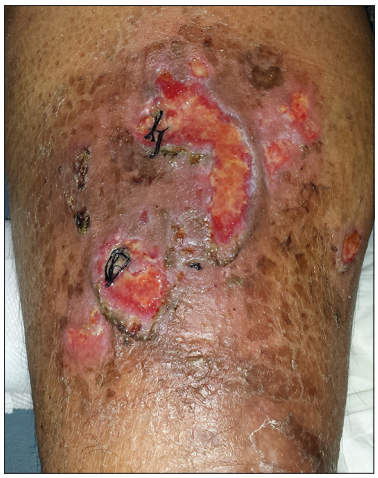

Figure 1: Painful ulcer with undermined borders, at first visit

was outstanding since the first dose and by the seventh injection, almost 90% of ulcers on his right leg were cicatrized [Figure 3]. Lesions on his left calf also showed a similar response. At 10 months of follow-up, the patient was completely free of disease and without new lesions.

Pyoderma gangrenosum is a painful ulcerating dermatosis that can be a cause of considerable disfigurement, impacting the quality of life and associated with high morbidity and even mortality.[1] There are no standardized guidelines for the management of pyoderma gangrenosum. For most workers, systemic corticosteroids and systemic cyclosporine are first-line therapies.[1,2] Second-line therapies include tumor necrosis factor-alpha inhibitors (infliximab, adalimumab and etanercept), dapsone and immunosuppressive agents.[2,3] Immunosuppressive agents such as mycophenolate mofetil, methotrexate and azathioprine are commonly used as adjunctive therapies.[2] For recalcitrant pyoderma gangrenosum, alkylating agents such as cyclophosphamide and chlorambucil as well as intravenous immunoglobulin have been tried with some success. However,

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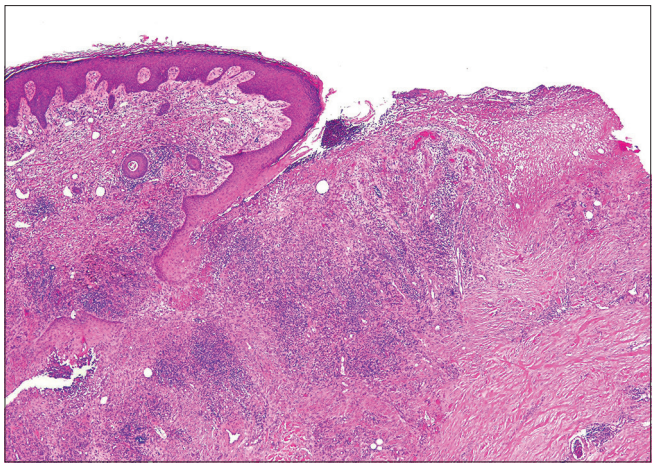

Figure 2: An ulcer surrounded by granulation tissue with fibrosis and scant diffuse infiltrate of lymphocytes, neutrophils and plasmacytes without signs of vasculitis (biopsy taken from the border of one ulcer) (H and E, ×100)

their high cost and potentially severe side effects prompt the use of other interventions.

Methotrexate is a potent anti-inflammatory agent when used in low concentrations.[4] Its mechanism in cutaneous disease is controversial but is thought to be mainly mediated by adenosine, a purine nucleoside with potent anti-inflammatory effects. Methotrexate inhibits 5-aminoimidazole-4-carboxamide ribonucleotide transformylase, promoting intracellular accumulation of 5-aminoimidazole-4-carboxamide ribonucleotide which increases local adenosine release.[4] There is inhibition of neutrophil and monocyte oxidative burst, inhibition of neutrophil chemotaxis and reduction in the secretion of inflammatory cytokines (tumor necrosis factor-alpha and interleukin-2).

In this case, the use of oral methotrexate elicited no clinical response even after 8 weeks, though response was expected in the first 4–8 weeks of treatment. However, after the first dose of intralesional methotrexate itself, there was a remarkable response. We believe that due to local inflammation, the bioavailability of oral methotrexate was lower in the wound site. Intralesional cyclosporine has been tried previously in patients with refractory pyoderma gangrenosum with complete resolution. However, in our country, the cost of cyclosporine is ten times higher than methotrexate. Besides, the fact that cyclosporine is not covered by public health insurance favored the use of methotrexate. On the basis of the case reports which cite successful response of keratoacanthomas, squamous cell carcinoma, primary cutaneous CD30+ T-cell lymphomas and other inflammatory conditions like nail psoriasis to intralesional methotrexate, we thought that intralesional methotrexate could have a better local bioavailability and faster action in comparison to oral methotrexate.[5]

We were unable to find any previous reports of pyoderma gangrenosum successfully treated with intralesional methotrexate in addition to systemic corticosteroids. Considering that pyoderma gangrenosum is a disease which requires long term treatment with immunosuppressive agents, intralesional methotrexate may be considered as a good adjuvant in the management of recalcitrant cases. Further studies are needed in order to confirm our findings.

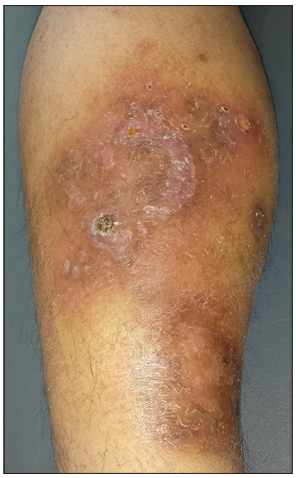

Figure 3: Almost complete response after the seventh injection of intralesional methotrexate

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Conflicts of interest
There are no conflicts of interest.

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