

# Concurrent pyoderma gangrenosum and tuberculosis: Diagnosis, treatment complexities and exploring cyclosporine's role – A literature review

Dear Editor,

Pyoderma gangrenosum (PG) is a chronic, progressive ulcerative disease often associated with systemic conditions (50–70%). Recently, the association of PG with tuberculosis (TB) has been increasingly reported.<sup>1–6</sup> Here, we report a diabetic male with PG and TB and explore the complex relationship between PG and TB.

A 48-year-old diabetic male presented with painful, expanding ulcers on his legs for 2 months. Four months earlier, the patient experienced low-grade fever, abdominal pain, and gradual weight loss. Triple-phase computed tomography revealed multiple, hypodense and variable-sized parenchymal lesions in the spleen and liver. Biopsy from the hepatic lesions revealed multiple ill-defined epithelioid cell granulomas with Langhans giant cells. The patient did not have a history of altered bowel habits, loose stools, or melena. In addition, stool tests for occult blood and fecal calprotectin were negative, whereas Mantoux and Interferon Gamma Release Assay (IGRA) were positive leading to the exclusion of inflammatory bowel disease (Crohn's). Two months into antitubercular therapy (ATT), ulcerative lesions developed on the legs. The patient presented with large, painful ulcers with perilesional erythema and tenderness [Figure 1].

The patient was evaluated, and the summary of significant findings are summarised in Table 1. There was no organism isolated in serial pus cultures. Histopathology from the ulcer edge [Figure 2] revealed pan-dermal perivascular mixed infiltrate with endothelial swelling and neutrophilic infiltrate of the wall but no fibrinoid necrosis. Based on these features, the patient was diagnosed as PG.

Managing the condition posed challenges as concurrent TB and poorly controlled diabetes limited the use of systemic



Figure 1: Giant ulcer at a presentation on right leg.

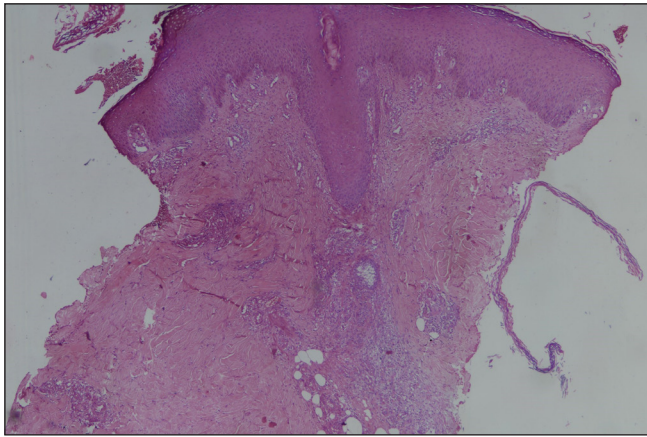
steroids and other immunosuppressants. Previously well-controlled diabetes became erratic upon admission (Blood sugar >200 mg/dL). Local wound care was complicated by active pathergy, managed with placental extract and non-adhesive dressings. Cyclosporine was initiated at 3 mg/kg, later increased to 5 mg/kg due to inadequate response, due to the CYP3A4 enzyme-inducing effects of Rifampicin. Cyclosporine levels 2 h after the first dose reached 260 µg/L which was deemed adequate. A combination of oral cyclosporine and careful local wound care yielded substantial results at 4 weeks [Figure 3]. The dose of cyclosporine was reduced after 6 weeks and completely stopped after 4 months. The patient is currently in remission and has completed 6 months of ATT.

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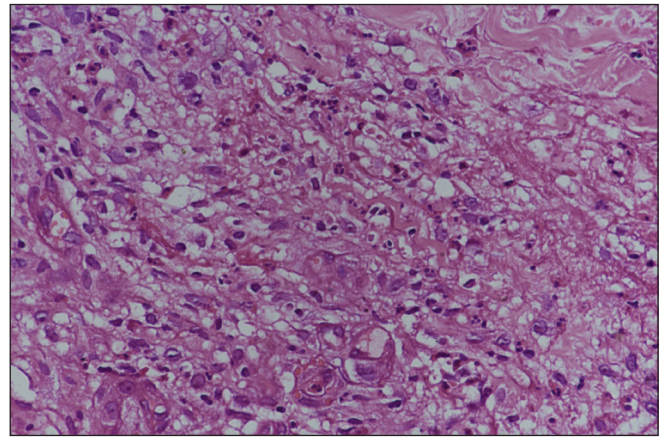
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**Figure 2a:** Histopathological examination from ulcer edge: Shows hyperkeratosis with irregular acanthosis. Dermis shows pan-dermal perivascular and peri-adnexal mixed inflammatory infiltrate. (Haematoxylin & Eosin, 40x)



**Figure 2b:** Mixed inflammatory infiltrate comprising lymphocytes, plasma cells, neutrophils, and eosinophils. Few vessels showed endothelial swelling with neutrophilic infiltrate of the wall but no fibrinoid necrosis. (Haematoxylin & Eosin, 400x)

**Table 1: Summary of investigations**

Investigations	Value
TLC † (10 <sup>9</sup> /L)	7,600
Platelet count (10 <sup>9</sup> /L)	150
Kidney and Liver function	Within normal limits
ANA*	+; Line immunoassay -ve
p-ANCA, c-ANCA §	Negative
CRP (mg/L) ¶	>0.6
RA Factor ††	+
Ultrasonography (Abdomen)	Hepatomegaly with grade I fatty liver. Hepatic hypoechoic lesions with central anechoic areas in segment VIII/VII with similar lesions in splenic parenchyma.
Pus culture	No growth in the three serial cultures
Pathergy	Negative
Stool for occult blood	Negative
Triple-phase computed tomography (Chest and abdomen)	Multiple hypodense splenic parenchymal lesions with no significant enhancement, larger one measuring ~27 × 20 mm towards the upper pole region. A few similar lesions are also seen in segments VIII and VII of hepatic parenchyma. Findings suggestive of granulomatous aetiology
Serum cyclosporine (2 h)	260 ug/L
AFP, CEA, CA 19-9 **	Negative

† TLC – Total leucocyte count, \*ANA – Antinuclear antibody, § p-ANCA, c-ANCA - Antineutrophilic cytoplasmic antibody, ¶ CRP – C-reactive protein, †† RA – Rheumatoid factor, \*\*AFP – Alpha Feto Protein, CEA – Carcinoembryonic Antigen, CA 19-9 – Carbohydrate antigen 19-9

Approximately, 50–70% of PG patients exhibit underlying systemic diseases, preceding or following PG, including inflammatory bowel disease, monoclonal gammopathy, and malignancy. Treatment of the associated systemic disease can lead to partial or complete resolution.

The association of PG and TB has been perplexing. On one hand, there are reports of latent as well as active TB

being associated with the onset of PG. On the other hand, immunosuppressive therapy for PG may lead to the activation of TB. There are reports of PG healing in the treatment of latent TB. Multiple case reports document the coexistence of TB and PG, with various presentations of TB, including active and latent forms, and a reported TB reactivation during PG treatment.<sup>1-6</sup> Table 2 presents a summary of all available case reports on the coexistence of PG and TB. In most instances of active TB cases with comorbid conditions, patients received ATT alongside immunosuppressive/biologic therapy, except for one case where the ulcer was re-epithelialized solely on ATT.<sup>4</sup>

Our patient developed lesions 2 months after starting ATT, worsening continuously, raising concerns about ATT as a triggering factor. Despite an extensive review, no previous reports linked ATT drugs to PG. The Naranjo adverse drug reaction probability scale score of 1, along with the patient’s improvement after restarting ATT (discontinued for 3 weeks), essentially ruled out drug-induced PG. TB is known to trigger system-wide inflammation which could potentially lead to PG, explaining the increasing number of reports of the coexistence of PG and TB.

Poorly controlled diabetes and TB prompted us to select cyclosporine over systemic corticosteroids, despite the lack of a completely ‘safe’ treatment option. Oral cyclosporine, an alternative first-line treatment for patients with contraindications to glucocorticoid therapy, has demonstrated comparable efficacy to prednisolone in randomised controlled trials (RCT).<sup>7</sup> However, due to the effects of rifampicin and pyrazinamide on serum levels, the dose of cyclosporine needed to be adjusted and monitored accordingly. The use of immunosuppressants in TB requires careful consideration with none deemed entirely safe. Decisions should be individualised due to potential complications, emphasising the importance of vigilance for drug interactions, particularly with anti-TB medications such as rifampicin.



**Figure 3a:** Ulcer at day 1 of cyclosporine treatment.

**Figure 3b:** Healing of ulcer on right leg on day 14 of starting cyclosporine.

**Figure 3c:** Healing of ulcer on right leg at day 90.

**Table 2: Summary of all reported cases with concomitant pyoderma gangrenosum and tuberculosis**

S.No.	Authors/Year	Type of tuberculosis	Comorbidities	Treatment and outcome of PG
1.	Saklecha <i>et al.</i> <sup>1</sup>	14 years with Latent TB	None	INH, 300 mg/day; new lesions of PG stopped after 3 months of Isoniazid Patient disease-free after 1 year of stopping INH (9-month course)
2.	Haghighi <i>et al.</i> <sup>2</sup>	49 years with Lymph Node Tuberculosis	None	Prednisone and cyclosporine
3.	Patvekar <i>et al.</i> <sup>3</sup>	49 years with bone TB	Ulcerative colitis	Dexamethasone – cyclophosphamide pulse and ATT
4.	Zaraa <i>et al.</i> <sup>4</sup>	60 years with LN TB	None	None; resolved with ATT
5.	Romańska-Gocka <i>et al.</i> <sup>5</sup>	49 years with pulmonary Kochs; ulcers started after Mantoux test	Monoclonal IgA gammopathy	Prednisone, dapsone, cyclosporine A
6.	Nanoudis <i>et al.</i> <sup>6</sup>	28 years with resistant TB	Chronic granulomatous disease, Aspergillus pneumonia	Dapsone, Intravenous immune globulin (IVIG), and intravenous pulse methylprednisolone 1g/day for 3 days f/b tab Methylprednisolone 16 mg; healed after 3 months

INH – Isoniazid, LN – Lymph Node

Managing PG becomes complex when combined with TB and diabetes. This case demonstrates significant improvement with oral cyclosporine and local wound care, emphasising the crucial need for careful management in the presence of concurrent systemic diseases.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent.

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**Conflicts of interest**

There are no conflicts of interest

**Use of artificial intelligence (AI)-assisted technology for manuscript preparation**

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the

writing or editing of the manuscript and no images were manipulated using AI.

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