Helicobacter-induced pyoderma gangrenosum–like skin ulcers in a case of Bruton's agammaglobulinemia

Dear Editor,

A 20-year-old underweight and stunted boy, a known case of Bruton's agammaglobulinemia, presented with painful ulcers over both lower legs and left foot for 2 years. The lesions started as painful reddish swellings which ulcerated within a few weeks to leave behind small ulcers. The ulcers gradually increased to the present size of around 6 × 5 cm and 4 × 3 cm over the medial malleolus and lower third of the right leg, respectively, and 20 × 10 cm over the left leg and foot [Figure 1]. The ulcers showed necrotic slough over the granulation tissue, hyperpigmented thick margin and were tender to touch.

There was no history suggestive of the pathergy phenomenon. The patient gave a history of recurrent fever, lower respiratory tract and gastrointestinal tract infections since early childhood, the frequency of which had decreased over time.

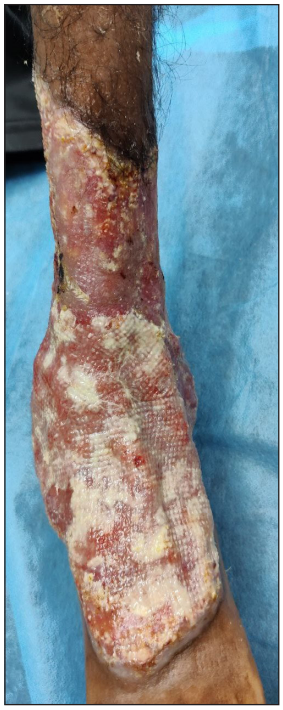

Figure 1: Ulcer involving the lower third of the left leg and dorsum of the left foot.

He has been on replacement monthly intravenous immunoglobulin therapy for Bruton's agammaglobulinemia since 10 years of age. In the past, a dermatologist at his native place had administered multiple short courses of antibiotics and apremilast with no improvement in ulcers. There was no history of agammaglobulinemia in the family. There was no evidence of varicose veins over the lower limbs or significant lymphadenopathy. Based on the history and examination, we kept the clinical differentials of pyoderma gangrenosum, cutaneous tuberculosis, atypical mycobacterial infection and deep fungal infection.

A biopsy from the ulcer edge showed irregular epidermal acanthosis [Figure 2a]. The dermis showed proliferating capillaries and a diffuse infiltrate of neutrophils, lymphocytes and histiocytes with focal extravasation of red blood cells [Figure 2b]. X-rays of bilateral legs showed diffuse osteopenia. Pus culture was sterile.

With the clinical possibility of pyoderma gangrenosum, we started the patient on oral dapsone, thalidomide and topical potent corticosteroid (clobetasol propionate 0.05%). Given the background of primary immunodeficiency disease, we avoided oral corticosteroids and cyclosporine. Physiotherapy, regular dressing of ulcers, non-steroidal anti-inflammatory drugs (ibuprofen and paracetamol combination) and amoxicillin-clavulanic acid combination were also given. After 2 months, the ulcer size worsened.

Given no response to therapy and the possibility of chronic infection in an immunocompromised individual, we did a literature search and found reports of Helicobacter-induced ulcers in Bruton's agammaglobulinemia cases. Based on the suspicion of Helicobacter in our patient, we ordered a Warthin starry stain on the biopsy section which revealed elongated, brownish-black, curvilinear rods [Figure 3]. The tissue and blood culture did not reveal Helicobacter while polymerase chain reaction–based tests were not available in our institute.

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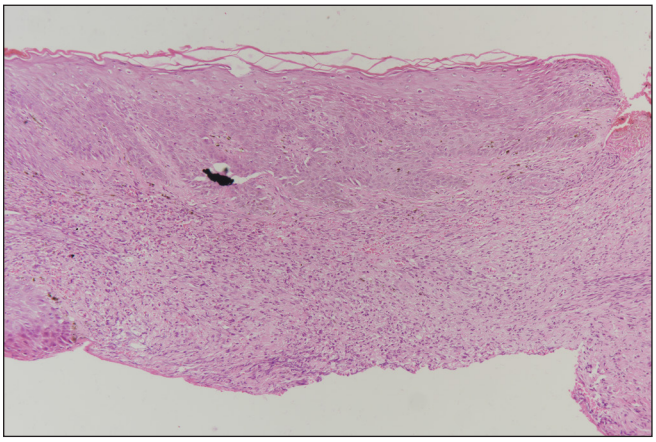

Figure 2a: Ulcer edge biopsy shows irregular epidermal acanthosis and diffuse dermal infiltrate of neutrophils, lymphocytes and histiocytes. (H&E-100×)

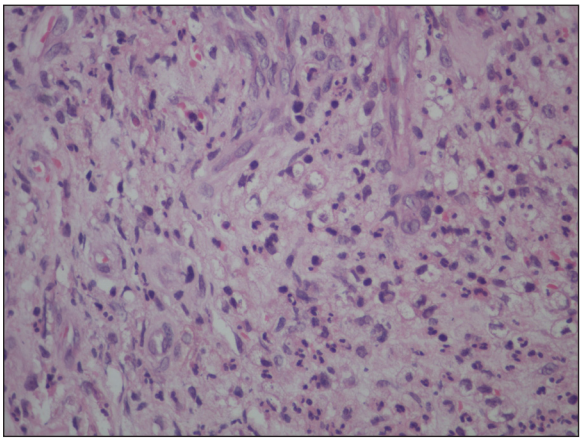

Figure 2b: The dermis shows proliferating capillaries and a diffuse infiltrate of neutrophils, lymphocytes and histiocytes with focal extravasation of red blood cells. (H&E-400×)

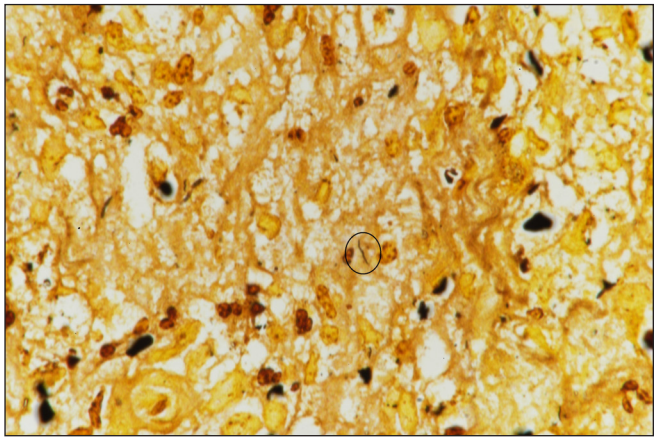

Figure 3: Elongated, brownish-black, curvilinear rods (encircled with a black circle). (Warthin starry stain-1000×)

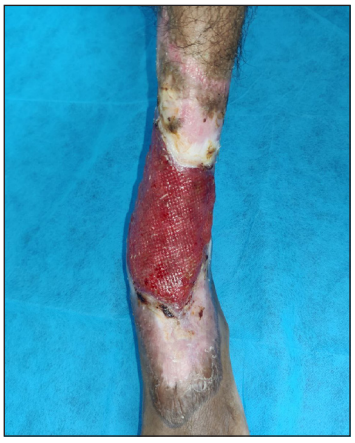

Figure 4: Left leg ulcer showed significant re-epithelisation.

We made the final diagnosis of Helicobacter-induced pyoderma gangrenosum–like skin ulcers in a case of Bruton's agammaglobulinemia and started ertapenem injection (1 g/day) and doxycycline tablet (100 mg/day). Ertapenem was changed to clarithromycin tablet (500 mg/day) after 4 weeks. After 4.5 months of therapy, there was complete resolution of right leg ulcers while the left leg ulcer showed significant re-epithelisation [Figure 4]. The patient is being continued on the same regime (doxycycline plus clarithromycin) with further healing of ulcers without any side-effects till now. There was no history of gastrointestinal symptoms, urticaria or prurigo in the patient.

The genus *Helicobacter* includes two species, namely, gastric and enterohepatic. Enterohepatic Non-*Helicobacter Pylori Helicobacter* can cause disease, especially in immunocompromised individuals like those with Bruton's agammaglobulinemia, acquired immunodeficiency syndrome, asplenia and liver cirrhosis. The infection source is unknown, but the migration of these organisms from the gastrointestinal tract and zoonosis are the accepted hypotheses. Clinically, most relevant species like *Helicobacter cinaedi* and *Helicobacter bilis* colonise the biliary tract, intestine and liver of animals and humans. The natural hosts of *Helicobacter cinaedi* are dogs, hamsters and rhesus macaques and of *Helicobacter bilis* are cats and mice. These species have been found to be associated with bacteremia and systemic illness in humans supporting the hypothesis of zoonosis. The clinical manifestations include cellulitis, abscess formation, cutaneous ulcers, pleurisy, synovitis, suppurative cholangitis and sepsis.[1] The lower extremity followed by the upper extremity is the commonest site of cutaneous involvement. There are no specific management guidelines for such cases but combination antibiotics have been used in the past with variable responses.

There are a few reports in the literature of cutaneous ulcers induced by Helicobacter in Bruton's agammaglobulinemia [Table 1].

Ours is a rare case of Helicobacter-induced leg ulcers responding to long-term antibiotics. This diagnosis must be considered in an immunocompromised individual presenting with pyoderma gangrenosum–like ulcers.

Table 1: Reports of cutaneous ulcers induced by Helicobacter in Bruton's agammaglobulinemia

Author	Age (years)/ Gender	Helicobacter species (sample analysed)	Clinical manifestation	Treatment	Response
Cuccherini *et al.*, 2000[2]	21/Male	Helicobacter-like organisms (blood)	Leg ulcer, synovitis, fever, osteomyelitis	Imipenem and gentamicin followed by imipenem and meropenem (9 months)	Substantial improvement
Murray *et al.*, 2010[3]	17/Male	*Helicobacter bilis* (skin)	Leg ulcer	Tobramycin and meropenem (2.5 months)	Almost complete healing
Dua *et al.*, 2011[4]	26/Male	*Helicobacter cinaedi* (skin)	Leg ulcer, synovitis	Amikacin and meropenem (1 month) followed by doxycycline and ertapenem (2 months)	Ulcer reduced in size; joint pain resolved
Sharp, 2011[5]	25/Male	*Helicobacter fennelliae* (skin)	Lower limb ulcers	-	-
Gonzalez *et al.*, 2022[1]	18/Male	*Helicobacter bilis* (skin)	Leg ulcer, osteomyelitis	Multiple (2 years)	No response

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

Bhavya Swarnkar, Gouri RP Anand, Sujay Khandpur, Arun Kumar Panda[1], Mehar Sharma[1]

Departments of Dermatology and Venereology, [1]Pathology, AIIMS, New Delhi, India.

Corresponding author:
Dr. Sujay Khandpur,
Department of Dermatology and Venereology, All India Institute of Medical Sciences, New Delhi, India.
sujay_khandpur@yahoo.com

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