CLINICAL IMAGE

Ibrutinib-induced pyoderma gangrenosum

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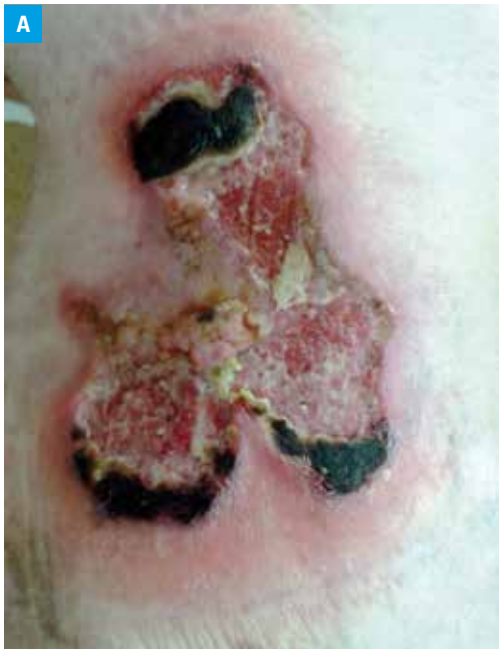
A 64-year-old man with a history of B-cell chronic lymphocytic leukemia (B-CLL) diagnosed 8 years earlier, with concomitant diabetes, permanent atrial fibrillation, and benign prostate hyperplasia presented with multiple, painful, ulcerative skin lesions that had occurred 2 months before. The first lesion developed on the left lower limb as a pustule rapidly evolving to an enlarging, painful skin ulcer. The following lesions occurred on the right lower limb, abdominal wall, left forearm, right buttock area, and, periungually, on the fourth finger of the right hand (FIGURE 1A and 1B). Despite receiving topical and systemic (prednisone, 30 mg/d) treatment, the progression of the disease was observed. Otherwise, the patient was in good general condition, with no serological and clinical signs of infection. Owing to the presence of comorbidities, he was treated with gliclazide (30 mg/d), sotalol (40 mg/d), dabigatran (2×150 mg/d), and tamsulosin (0.4 mg/d). Additionally, 6 months before hospital admission, he had started an oral ibrutinib therapy (3×140 mg/d), due to B-CLL. An ulcer biopsy revealed lymphocyte and neutrophil infiltration. No histopathologic signs of carcinoma or vasculitis were observed. After consultation with a hematologist, a tentative diagnosis of ibrutinib-induced pyoderma gangrenosum (PG) was established. In addition to ibrutinib discontinuation, daily prednisone dose was increased to 60 mg (7.3 mg/kg/d), and cyclosporin A therapy was started (150 mg twice daily; 3.3 mg/kg/d). After 10 days, a clinical improvement was observed, with pain and exudate reduction. In addition, the borders of the ulcers became flattened. The doses of corticosteroids and cyclosporin A were slowly tapered. After 6 weeks, the healing process was almost complete.

PG is a noninfectious neutrophilic skin disease, with a reported incidence of 3 to 10 cases/mln/y, affecting mostly people between 20 and 50 years old. The disease usually starts as a pustule or nodule, rapidly evolving to a painful ulcer with



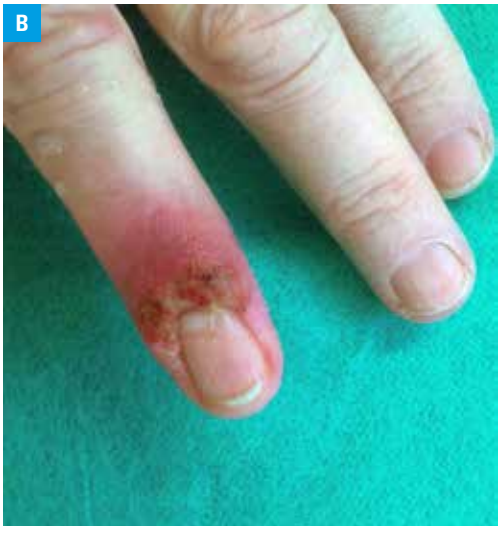


FIGURE 1 A – painful ulcers with raised, indurated borders and fibropurulent base located on the lower limbs; B – periungual ulcers

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undermined violaceous borders and fibropurulent base. The lesions may be single or multiple, and the most prevalent locations are lower limbs, followed by the trunk. More than 50% of patients with PG have an associated systemic disease, predominantly inflammatory bowel disease, arthritis, or a hematologic disorder.[1] Several drugs were previously related to PG, including tyrosine kinase inhibitors: gefitinib, sunitinib, and imatinib.[2,3]

To the best of our knowledge, ibrutinib-induced PG has not been previously reported. Ibrutinib is currently approved for the treatment of mantle cell lymphoma and chronic lymphocytic leukemia, and is considered to have a good safety profile. The most common adverse reactions are diarrhea, fatigue, bruising, and upper respiratory tract infections. The medication inhibits Bruton's tyrosine kinase, which is present predominantly in B cells and is crucial for lymphocyte survival and proliferation.[4] In addition, it is known that ibrutinib may inhibit other kinases, including the epidermal growth factor receptor. As the expression of the receptor in the basal layer of epidermis is very high, its blocking may negatively affect cell regeneration.[5] Thus, it could be a possible mechanism initiating the development of PG, especially in the skin areas exposed to frequent trauma. Further studies are needed to confirm this relationship, as well as to explain the underlying pathogenesis and optimal patient management.

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