Pyoderma gangrenosum-like necrotizing panniculitis associated with Imatinib: A case report

Jorge Hernández,1,2 Alicia Sanz,3 Beatriz Isla-Tejera,1,2 Juan Ruano1,4
1Department of Pharmacy, Reina Sofia University Hospital; 2Instituto Maimonides de Investigacion Biomedica de Cordoba - IMIBIC, Reina Sofia University Hospital, University of Cordoba; 3Department of Pathology, Reina Sofia University Hospital; 4Department of Dermatology, Reina Sofia University Hospital, Córdoba, Spain

Abstract

Imatinib mesylate is a small tyrosine kinase inhibitor that targets BCR-ABL, c-kit and platelet-derived growth factor receptor. It is prescribed by hematologists for chronic myeloid leukemia and acute lymphoblastic leukemia and by oncologists for Gastrointestinal Stromal Tumors (GIST). Cutaneous reactions to Imatinib are common but their incidence and severity widely varies between patients. A self-limited skin rash is the most common adverse effect but there have been reported cases of patients with maculopapular rash, pigmented changes, superficial edema and rarer and clinically distinctive features such as lichenoid reactions or psoriasis. We here describe for the first time a case of pyoderma gangrenosum-like necrotizing panniculitis, a rare dermatological condition, after initiating therapy with Imatinib.

Case Report

A 53-year-old man with stage IIIa gastrointestinal tumor of the stomach (pT3cN0cM0) positive for KIT (CD117) and high risk of relapse was started with Imatinib 400mg daily for 36 months in an adjuvant setting after laparoscopic removal of the tumor. The patient exhibited durable response and acceptable tolerance, however, after a year and two months he presented one black crusted plaque on the anterior surface of the right lower limb that caused redness and swelling of the surrounding skin (Figure 1a). No history of trauma was reported and no signs of systemic infection were present. Blood tests showed no abnormalities.

Under the clinical suspicion of tick bite or spider bite he was started on 1 month-course of doxycycline with ibuprofen, but failed to improve and after two weeks new lesions appeared in the form of ulcers with erythematous-violaceous raised edges and a fibrinous layer, all localized in the same extremity close to the first lesion (Figure 1b). After a risk-benefit analysis, Imatinib was discontinued under suspicion of a late onset adverse effect. Punch biopsy of the ulcer edge showed acute and non-specific chronic inflammation of the dermis (Figure 2a) with extensive necrosis of the subcutaneous tissue (Figure 2b) Full-body computed tomography found no evidence of disease progression while anti-cardiolipin antibodies, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies and anticentromere antibodies tests resulted negative. Laboratory and biopsy results led to the definitive diagnosis of pyoderma gangrenosum-like necrotizing panniculitis.

In addition to Imatinib withdrawal, the patient received 1mg of intraleisonal trimciclinol acetone and was started on prednisone 0.5 mg/kg/d for 45 days and cyclosporine 4mg/kg/d and for 30 days. He rapidly improved and on 3 weeks the size of the injuries had reduced to 40% with no new lesions and no signs of infection, to finally resolve completely (Figure 1c). After 6 months, no relapse was observed and he still remains asymptomatic.

Discussion

It is often difficult to categorize a panniculitis given their heterogeneous nature. Regrettably, commonly used punch biopsies yield insufficient amounts of subcutaneous adipose tissue for a full histopathologic assessment. When possible, panniculitides are categorized by the pattern of the inflammatory cell infiltrate into lobular panniculitides, such as erythema induratum (also known as “nodular vasculitis”) or septic panniculitides like erythema nodosum, but histopathological findings depend on the stage of evolution and may vary among samples. In our case the biopsy showed perivascular inflammation with septal vascular alterations and lymphohistiocytic infiltration that had intensively extended into the lobule, but necrosis was so prevalent it was not possible to establish the predominance with certainty. Interestingly, erythema induratum is typically characterized for presenting ulcerating nodular lesions. Its predominant relation to tuberculosis is well-known, but it has also been associated with hepatitis C, inflammatory bowel disease or drugs.

In our patient, Imatinib withdrawal and steroid-cyclosporine therapy led to an almost complete resolution of the lesions. Anti-phospholipid syndrome and Wegener’s granulomatosis were discarded after antibodies tests resulted negative, and a full body computed tomography discarded pancreatitis or disease progression. Patients with pancreatitis or α-1-antitrypsin deficiency have been reported to develop panniculitis with zones of fat necrosis as a complication, in our case lab tests results did not show this deficiency. Based on our findings, a cause-effect relationship for Imatinib was deemed highly likely in the Naranjo and WHO-UMC probability scales for drug adverse reactions, and so it was reported to our local Pharmacovigilance Center. Imatinib mesylate has often been reported for its cutaneous manifestations (rash, hypopigmentation, superficial edema, psoriasis, and lichenoid reactions) but it has seldom been associated with panniculitis with necrotic ulceration. Ugurel et al. and Breccia et al. both described a case of panniculitis in patients with chronic myelogenous leukemia using Imatinib. Also, Imatinib has several times been linked to neutrophilic dermatoses, such as acute generalized exanthematous pustulosis, Sweet syndrome and neutrophilic ecrine hidradenitis, but the mechanism behind these adverse effects has yet to be fully understood. A case of pyoderma gangrenosum, a rare ulcerative neutrophilic dermatosis has also been documented in a patient treated with Imatinib. Myeloproliferation has been documented in mice at 10-fold higher concentration than seen in human treatment which is consistent with the clinical response in our patient.
lower doses than the usual, mimicking a physiological increment in number of circulating monocytes and neutrophils to a bone marrow infection. Clinicians should be aware of potential necrotizing panniculitis pyoderma gangrenosum-like in patients treated with Imatinib and consider stopping treatment until resolution of symptoms. Further studies ought to be performed to determine the exact mechanism linking Imatinib and other c-Kit inhibitors with their cutaneous side effects.

Conclusions

Clinicians should be aware of potential necrotizing panniculitis pyoderma gangrenosum-like in patients treated with Imatinib and consider stopping treatment until resolution of symptoms. Further studies ought to be performed to determine the exact mechanism linking Imatinib and other c-Kit inhibitors with their cutaneous side effects.

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