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A case report of bosutinib-induced interstitial granulomatous drug reaction in a patient with chronic myelogenous leukemia: a case report

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Abstract

Bosutinib is a BCR-ABL tyrosine kinase inhibitor approved for the treatment of Philadelphia chromosome–positive chronic myelogenous leukemia. We report a case of bosutinib-induced interstitial granulomatous drug reaction in a 50-year-old Caucasian female with chronic myelogenous leukemia. Histologic analysis of a punch biopsy showed diffuse interstitial granulomatous infiltrates consisting of histiocytes amid thickened collagen accompanied by eosinophils. Her lesions improved with clobetasol 0.05% cream. No cases describing BCR-ABL tyrosine kinase inhibitor–associated interstitial granulomatous drug reaction were found in a search of the literature. It is important for physicians to be aware of the risk of interstitial granulomatous drug reaction associated with bosutinib treatment.

Keywords

Interstitial granulomatous drug reaction, bosutinib, chronic myelogenous leukemia

Introduction

Bosutinib was approved by the US Food and Drug Administration for the treatment of Philadelphia chromosome–positive (Ph+) chronic myelogenous leukemia (CML) in patients who were resistant to or unable to tolerate other treatments.[1] A translocation between the breakpoint cluster region (BCR) on chromosome 22 and the Abelson (ABL) gene on chromosome 9 results in a BCR-ABL tyrosine kinase which is constitutively active, leading to unchecked myeloid proliferation in CML.[2] Bosutinib inhibits this BCR-ABL tyrosine kinase, decreasing growth and proliferation of malignant CML cells. We report a case of bosutinib-induced interstitial granulomatous drug reaction (IGDR) in a patient with CML.

Case report

The patient is a 50-year-old Caucasian female with a history of Ph+ CML. She was initially treated with hydroxyurea and was switched a week later to dasatinib (a BCR-ABL tyrosine kinase inhibitor (TKI)). She remained on dasatinib therapy on and off for 4 years. Breaks in treatment were required due to thrombocytopenia and pleural effusions. Due to a persistent pleural effusion, she was eventually switched to bosutinib by mouth. Early side effects from bosutinib treatment included diarrhea and "a pruritic", diffuse rash on the trunk and extremities that appeared a week after beginning treatment. The rash resolved within a week after a methylprednisolone taper and oral diphenhydramine.

After 2 months of starting bosutinib treatment, the patient developed tender papules on her forearms and the medial aspect of her feet. Her oncologist referred her to the dermatology clinic. On physical exam, the patient had erythematous, infiltrated papules and plaques on the forearms and tender, erythematous dusky papules and plaques along the medial aspect of the feet (Figure 1). The lesions were not pruritic. A punch biopsy of the right forearm was performed. Diffuse interstitial granulomatous infiltrates consisting of histiocytes amid thickened collagen accompanied by eosinophils were

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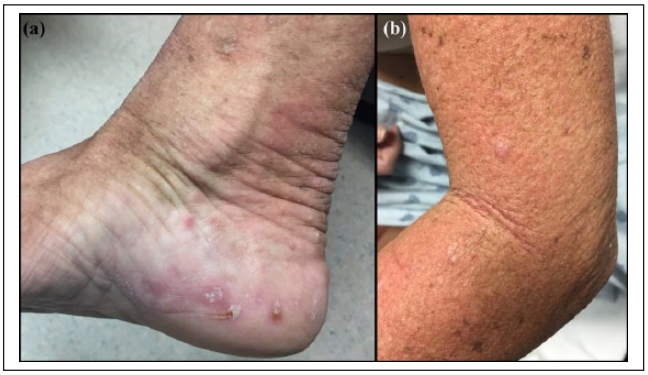

Figure 1. Interstitial granulomatous drug reaction. Papules on the (a) medial feet and (b) bilateral forearms.

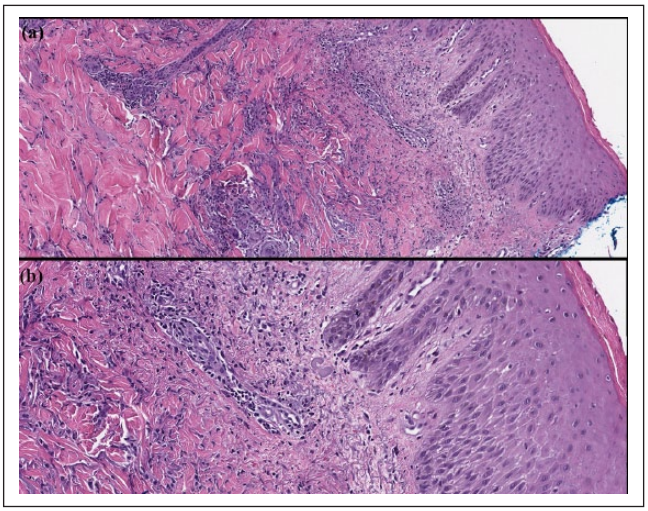

Figure 2. Interstitial granulomatous drug reaction. Pathology demonstrates diffuse interstitial granulomatous infiltrates consisting of histiocytes amid thickened collagen accompanied by eosinophils (H&E, (a) ×5 original magnification and (b) ×10 original magnification).

present on histopathology. Interface dermatitis was present focally. Special stains (Fite acid fast, gram, and Grocott's methenamine silver stain) were negative for fungi and bacteria, including mycobacteria. Features were consistent with IGDR (Figure 2). She was given clobetasol 0.05% cream to be applied to her lesions twice daily and reported mild improvement on follow-up. She subsequently developed new lesions on her thighs (Figure 3), but denied any joint pain.

Discussion

The most common adverse events associated with bosutinib use include rash and gastrointestinal upset including diarrhea, nausea, and vomiting.[2] Kantarjian et al.[2] reported a 33% incidence of rash in the phase I and II trials of bosutinib. While the specific clinical characteristics of rashes caused by bosutinib have yet to be studied in detail, data exist for rashes

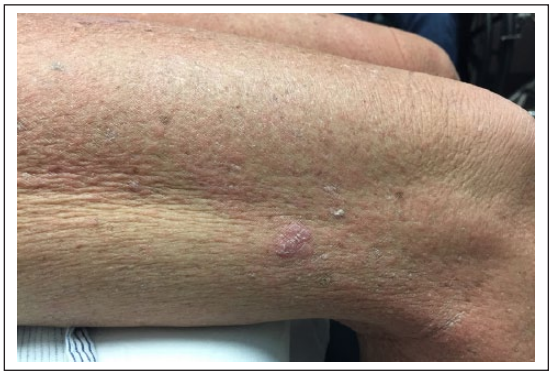

Figure 3. Interstitial granulomatous drug reaction. Papules and plaques on bilateral thighs.

caused by other BCR-ABL TKIs. Drucker et al.[3] conducted a meta-analysis on the clinical appearance of the rash caused by dasatinib and nilotinib and found that it was frequently described as 1- to 2-mm perifollicular, pruritic hyperkeratotic papules with no predilection for a specific area of the body. Options for treating BCR-ABL TKI-induced skin lesions include topical glucocorticoids, immunomodulatory agents, systemic antibiotics, and oral glucocorticoids.[1]

There is considerable overlap in the literature regarding classification of granulomatous dermatitis due to drugs. Some distinction between IGDR as opposed to drug-induced interstitial dermatitis (IGD) has been described by Rosenbach and English.[4] Classically, IGD has been most commonly associated with connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, and seronegative spondyloarthropathies.[5] Drug-induced IGD has been reported to be caused by tumor necrosis factor (TNF) alpha inhibitors, angiotensin-converting enzyme inhibitors, and furosemide.[4,6,7] IGDR differs from drug-induced IGD due to its very rare association with connective tissue diseases and its complete resolution after discontinuation of an offending agent.[5] In IGDR, the distribution favors the skin folds such as the axillae or popliteal fossae but can also involve the proximal extremities, palms, and soles as in our patient. Distinctive histological characteristics of IGDR when compared to drug-induced IGD include basal cell vacuolization with degeneration, dyskeratotic keratinocytes, and lichenoid changes with prominent eosinophilia.[4,5,8] Interface dermatitis was observed in our patient. Numerous drugs have been reported as responsible for IGDR, the most common of which include beta-blockers, calcium channel blockers, gemfibrozil, statins, and angiotensin-converting enzyme inhibitors (also reported to be associated with drug-induced IGD).[4] We believe that our patient had IGDR as opposed to drug-induced interstitial granulomatous dermatitis (IGD), but clinicians have proposed to group these entities together as drug-induced reactive granulomatous dermatitis.[4]

Martinez-Moran et al.[9] reported a case of IGDR caused by sorafenib, a multi-targeted kinase inhibitor, in a patient with hepatocellular carcinoma. We performed a review of

the literature and could find no cases describing BCR-ABL TKI-associated granulomatous drug reaction.

It is worth noting the possibility that our patient could have had malignancy-associated IGD. Although there have been no cases of CML-associated IGD, Federmann et al.[10] reported three patients with IGD and chronic myelomonocytic leukemia, a malignant white blood cell disorder that is Philadelphia chromosome negative. In addition, IGD associated with chronic lymphocytic leukemia and IGD associated with acute promyelocytic leukemia have also been reported.[11,12] After 4 years of CML with treatment, our patient developed her cutaneous lesions shortly after she started bosutinib therapy. This temporal relationship coupled with the IGDR-specific histologic findings present in our patient's biopsy greatly decreases the likelihood that CML is the casual factor in this case. It is important for physicians to be aware of the risk of IGDR associated with bosutinib treatment. In addition, treatment options are available for this adverse reaction and other bosutinib-associated cutaneous lesions, allowing physicians to avoid discontinuation of necessary CML therapy.

Declaration of conflicting interests

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Informed consent

Consent to publish was obtained from our patient in writing.

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