Case Report

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A patient with maculopapular rash and lichenoid skin damage caused by ponatinib

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Abstract

Tyrosine kinase inhibitors (TKIs) are invaluable for the treatment of patients with chronic myelogenous leukemia. Although TKIs are generally better tolerated than traditional chemotherapy, dermatologic side effects are common and present a significant cause of concern for both patients and physicians. Ponatinib is a third-generation TKI and the only kinase inhibitor effective in patients with certain *BCR-ABL1* mutations, including the T315I mutation. However, ponatinib is associated with an increased risk of serious side effects, and severe cutaneous reactions have increasingly been reported. We present a patient who developed a cutaneous lichenoid eruption following the initiation of ponatinib, which resolved after treatment with a topical retinoid. This case demonstrates that cutaneous side effects caused by ponatinib can be managed relatively easily, allowing patients to continue treatment with ponatinib. This is important considerting the limited alternative treatment approaches available for *BCR-ABL1* T315I chronic myelogenous leukemia.

Keywords

Chronic myelogenous leukemia, tyrosine kinase inhibitor, ponatinib, skin reaction, retinoid, *BCR-ABL1*

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Introduction

Ponatinib is a third-generation tyrosine kinase inhibitor (TKI) approved for the treatment of Philadelphia chromosome-positive leukemia, including patients with *BCR-ABL1* kinase mutations such as T315I, which confers pan-resistance to first- and second-generation TKIs.[1–3] Ponatinib treatment is associated with risks of severe side effects, including hypertension, arterial and venous thrombosis, cardiac failure, congestive heart failure, pleural effusion, and severe bone marrow depression. Dermatological adverse reactions, typically including non-specific cutaneous eruptions, are also common and rashes with varying histopathological patterns have recently been reported in association with ponatinib treatment. We present a patient who developed a lichenoid cutaneous eruption following the initiation of ponatinib, but who recovered after treatment with a topical retinoid.

Case report

A 45-year-old male patient diagnosed with Philadelphia chromosome-positive chronic myelogenous leukemia (CML) started treatment with the first-generation TKI imatinib, which was well tolerated. However, after an initial optimal response, his *BCR-ABL1*/*ABL1* transcript ratio started to increase after 15 months. Failure of imatinib treatment was suspected, and *BCR-ABL1* mutation analysis confirmed the *BCR-ABL1* T315I mutation. The T315I mutation is associated with resistance to conventional TKIs, with ponatinib the only TKI with a documented effect against this *BCR-ABL1* mutation.[1,3] Treatment with ponatinib was therefore initiated. The patient achieved cytogenetic remission after 4 months of treatment, and his initial dose of 30 mg was reduced to 15 mg/day. He also received acetylsalicylic acid 75 mg/day for thrombosis prophylaxis.

The patient started to complain of pruritus and skin irritation after treatment with ponatinib for 6 months, although no clear rash was seen during clinical examination. However, 3 months later, after 9 months of ponatinib therapy, the patient developed a non-specific maculopapular rash with some comedones, most prominent on his front torso (Figure 1). Skin biopsy demonstrated a mild lichenoid reaction with scattered epidermal basal cell vacuolization and some civatte bodies (Figure 2). There were no eosinophilic granulocytes. Mild chronic perivascular inflammation was seen in the upper dermis, not associated with the follicles. Based on these findings, a drug-related reaction could not be ruled out. Based on the available literature[4] and in cooperation with a local dermatologist, treatment with the third-generation topical retinoid adapalene, and the bactericidal oxidizing compound benzoyl peroxide was initiated. The patient responded to the treatment with recovery of the skin lesions and reduced pruritus.

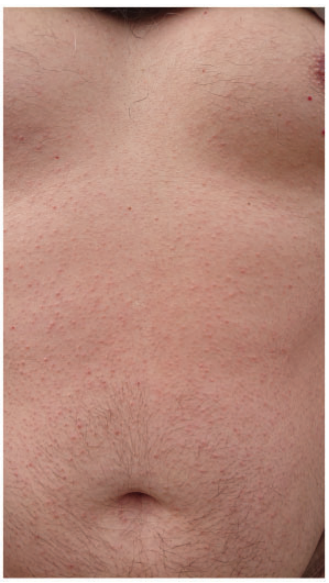

Figure 1. Patient's front torso demonstrating general maculopapular rash with some comedones.

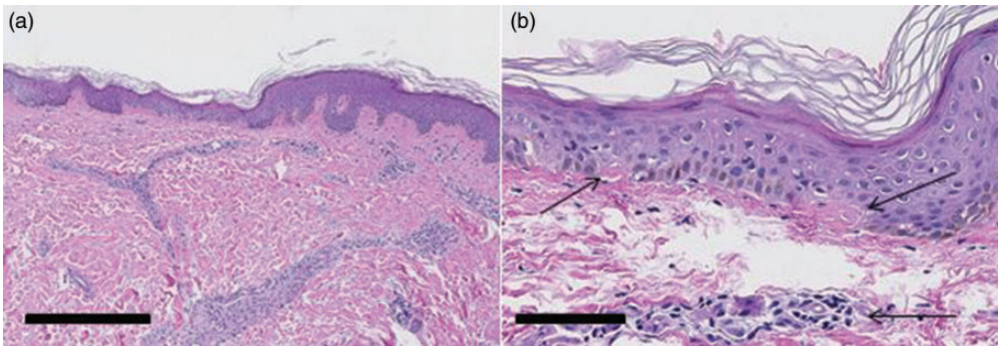

Figure 2. Skin biopsy at low magnification (a) and high magnification (b) demonstrating thin epidermis and signs of mild lichenoid damage with sparse vacuolization, and a few civatte bodies; mild chronic perivascular inflammatory infiltrate predominantly in the upper dermis; no eosinophilic granulocytes. Scale bars about 400 μm (a) and about 70 μm (b).

Written consent was obtained from the patient for publication of this case report.

Discussion

Cutaneous eruptions are common side effects of all TKIs used in the treatment of leukemia.[4] In phase II clinical trials, 39% of patients with CML treated with ponatinib developed a rash. Most of these emerged within 3 months of treatment, but some reactions did not develop until 24 months after therapy initiation.[5] Published case reports have described lamellar ichthyosis-like, keratosis pilaris-like, lichen planopilaris-like, and pityriasis rubra pilaris-like eruptions, as well as folliculocentric and seborrheic changes after the initiation of ponatinib.[6–11] Suggested treatment options for these skin reactions include topical steroids, retinoids, keratolytics, and antifungals, as well as systemic retinoids in more severe cases.[4] Unlike the current patient, most previously reported cases described an ichthyosiform appearance, as well as follicular involvement on histopathological examination. It is possible that the early identification and treatment of the condition in the present case prevented its further development into a more severe dermatological reaction. This and previous cases demonstrate that topical retinoids may be efficient for treating a wide range of cutaneous reactions associated with ponatinib, including lichenoid eruptions. However, the mechanisms responsible for the dermatologic side effects of ponatinib, and the potential therapeutic effects of retinoids have yet to be established. Some researchers have suggested that retinoids may strengthen the local chemotherapeutic resistance of keratinocytes by upregulating heparin-binding epidermal growth factor.[7]

Dermatological adverse reactions are common after treatment with TKIs. The impacts of these side effects on the patient's appearance and quality of life may ultimately lead to interruption of their anticancer therapy. The current case demonstrates that lichenoid cutaneous eruptions caused by ponatinib may be treated with topical retinoids, supporting the hypothesis that retinoids possibly increase the local chemotherapeutic resistance of keratinocytes. We therefore conclude that some of the cutaneous effects of ponatinib may be alleviated by topical retinoids, possibly allowing life-saving anticancer therapy to be continued in more patients.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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