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Authors

Xu, Haoming
Busam, Klaus J
Mauro, Michael J
et al.

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Ponatinib-induced ichthyosiform drug eruption: insights into acquired ichthyosis

Haoming Xu¹ BS; Klaus J Busam² MD; Michael J Mauro³ MD, Alina Markova¹ MD

Affiliations: ¹Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, ²Dermatopathology Service, Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York, ³Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York

Corresponding Author: Alina Markova MD, Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 16 E. 60th Street, New York, NY 10022, USA, Email: markovaa@mskcc.org

Abstract

Cutaneous adverse events are commonly experienced with use of tyrosine kinase inhibitors in the treatment of leukemia and typically include nonspecific cutaneous eruptions and xerosis. We report the case of a man who experienced an ichthyosiform drug eruption while taking ponatinib, a third-generation tyrosine kinase inhibitor. Disruption of epidermal growth pathways through inhibition of various receptor tyrosine kinases by ponatinib may offer insights into the pathophysiologic mechanisms behind acquired ichthyosis.

Keywords: cancer therapy, drug reactions, ponatinib, acquired ichthyosis

Introduction

Ponatinib is a third-generation tyrosine kinase inhibitor (TKI) used in treatment of refractory chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). Cutaneous adverse events associated with its use include nonspecific skin eruptions and dry skin [1]. We report the case of a patient treated with ponatinib who developed a prominent ichthyosiform drug eruption.

Case Synopsis

A 76-year-old man with refractory Ph+ ALL presented with a mildly pruritic, scaly, thickened rash. His leukemia was previously treated with CD19 chimeric antigen receptor (CAR) T-cell therapy, followed by ponatinib 15mg daily combined with mercaptopurine,

vincristine, methotrexate, and prednisone (POMP) maintenance; subsequently, ponatinib 30mg daily was administered as a single agent. The patient reported he previously had a similar rash with prior ponatinib exposure, which resolved with “shedding” of the thickened skin without other sequelae upon ponatinib holiday.

Skin examination revealed thickened ichthyosiform plate-like shiny patches with scale distributed diffusely on the forehead, trunk, and extremities bilaterally. The patient also had poorly demarcated erythematous patches with areas of sparing on the abdomen (**Figure 1**). A biopsy of the rash from the forearm revealed histologic features resembling lamellar ichthyosis: compact predominantly ortho-hyperkeratosis with focal parakeratosis, normal granular cell layer and sparse perivascular lymphocytic infiltrate (**Figure 2**). The patient did not tolerate topical urea or topical retinoids owing to secondary xerosis and cracking. Topical corticosteroids caused associated burning and he declined systemic retinoids. He had moderate improvement with petrolatum/lanolin ointment and was able to continue this TKI.

Case Discussion

Cutaneous eruptions are common side effects of TKIs used in the treatment of leukemia. The most commonly described dermatologic adverse events for TKIs include maculopapular rash, pruritus, and xerosis [2]. These toxicities can be challenging to manage owing to their symptoms, visibility, and frequency and can result in dose reduction or discontinuation of anti-cancer therapy.



Figure 1. Clinical findings of ichthyosiform eruption associated with ponatinib. Ichthyosiform plate-like shiny scaly patches distributed diffusely on the trunk and extremities.

As a rationally designed TKI with specificity for both wild-type and mutated Bcr-Abl as well as other targets, ponatinib has demonstrated efficacy in the treatment of imatinib-resistant leukemias and other malignancies such as gastrointestinal stromal tumors (GIST). Low grade skin eruptions and dry skin were the most common non-hematologic adverse events experienced by patients in a phase II clinical trial of ponatinib, occurring in 34% and 32% of patients, respectively [1]. In a phase 3 trial of ponatinib versus imatinib for the treatment of newly diagnosed CML, the ponatinib treatment group experienced a higher incidence of rash (37% versus 16%), dry skin (18% versus 3%), and pruritus (18% versus 8%) compared to the imatinib treatment group [3]. This trial was terminated early after twelve months owing to non-



Figure 2. Biopsy of the left forearm demonstrating compact hyperkeratosis associated with an intact granular cell layer and very sparse inflammatory cell infiltrate in the superficial dermis, H&E, 100%.

cutaneous serious adverse events in the ponatinib treatment group.

To date, there have been two reported cases of ponatinib causing an ichthyosiform drug eruption [4, 5]. Other reports have documented ponatinib-induced keratosis pilaris-like, lichen plano-pilaris-like, and pityriasis rubra pilaris-like eruptions as well as folliculocentric and seborrheic changes [2, 4]. The mechanism behind this reaction is poorly understood, but we postulate that the inhibition of various receptor tyrosine kinases by ponatinib, including VEGFR, FGFR, and the Src family of kinases [6] may result in the disruption of epidermal growth pathways. Specifically, Fyn, a member of the Src family of kinases has been shown to play an active role in keratinocyte differentiation control [7] and may be a target of study for new insights into the pathophysiology of acquired ichthyosis.

Conclusion

In conclusion, we present the case of a patient who developed an ichthyosiform drug eruption while being treated with the TKI ponatinib. Improvement of this eruption upon drug interruption and recurrence with drug re-introduction supports the assumption that this eruption is ponatinib-induced. Further classification of the cutaneous toxicities associated with ponatinib may provide insight into various pathophysiologic mechanisms and kinase targets affecting normal skin function. Early recognition and

treatment of these cutaneous adverse events allows for conservative management and improvement of patient quality of life without discontinuation of anti-cancer therapy.

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