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CASE REPORT

Ichthyosiform Pityriasis Rubra Pilaris-Like Eruption Secondary to Ponatinib Therapy: Case Report and Literature Review

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Abstract Tyrosine kinase inhibitors have revolutionized the chemotherapy arena as targeted therapies for a multitude of malignancies. They are more selective than conventional chemotherapy, and often elicit fewer systemic adverse events, however toxicities still exist. Cutaneous toxicities are common and their management presents a novel challenge to physicians and patients. Ponatinib is a third-generation tyrosine kinase inhibitor increasingly reported to cause cutaneous eruption. A 50-year-old woman with a history of chronic myelogenous leukemia presented with a 4-month history of worsening atrophic and ichthyosiform pink plaques involving the axillae, thighs and abdomen; red patches were also observed on the cheeks and forehead. She was started on the third-generation, ponatinib, 5 months earlier because of disease refractory to previous therapies including interferon, imatinib, dasatinib and bosutinib. A skin biopsy revealed perifollicular fibrosis, alternating orthokeratosis and parakeratosis, and a sparse perivascular lymphocytic infiltrate consistent with a pityriasis rubra pilaris-like reaction. Topical tretinoin 0.025% cream was initiated, resulting in resolution within 3 weeks without discontinuation of ponatinib. A review of previous reports identified significant similarities among the ponatinib-induced drug reactions. Here, we highlight not only that cutaneous eruptions occur on ponatinib therapy, but that the dermatologic manifestations are characteristic and unique, and benefit from retinoid therapy, without requiring interruption of vital chemotherapy.

Key Points

Tyrosine kinase inhibitors are potent anti-cancer therapies, but may result in cutaneous adverse events

Ponatinib is a new third-generation tyrosine kinase inhibitor that may induce an ichthyosiform pityriasis rubra pilaris-like eruption

Treatment with topical tretinoin results in resolution of skin disease without requiring termination of chemotherapy

Introduction

Tyrosine kinase inhibitors (TKIs) have revolutionized the field of chemotherapy as targeted therapies against aberrant cellular pathways. While more selective than conventional chemotherapy, and often with fewer systemic adverse events, toxicities still exist and frequently include cutaneous manifestations. Appropriate management of cutaneous toxicities presents a challenge to physicians and patients. We report a case of an ichthyosiform pityriasis rubra pilaris (PRP)-like eruption resulting after initiation of a third-generation TKI, ponatinib, and demonstrate its effective treatment with topical retinoids.

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Case Report

A 50-year-old woman presented with a 4-month history of a worsening rash on her face, trunk, and extremities. Her main complaint was dryness of the involved areas. She was previously diagnosed with xerosis; however, no improvement was demonstrated with emollients or topical corticosteroids. Past medical history included a 20-year history of chronic myelogenous leukemia. She had been started on the third-generation TKI, ponatinib, 5 months earlier after having a disease refractory to numerous previous therapies including interferon, imatinib, dasatinib, and bosutinib. Our patient was not taking any other medications or modifiers of the cytochrome P450 3A enzyme. After initiation of ponatinib 45 mg once daily, the patient obtained her lowest levels of the associated Bcr-Abl gene as demonstrated by polymerase chain reaction. Physical examination demonstrated xerotic, atrophic, and ichthyosiform pink plaques involving the bilateral axillae, proximal thighs and abdomen; red patches were additionally observed on the malar cheeks and forehead (Fig. 1a–d). Our patient did not demonstrate keratoderma. A skin biopsy of the axilla demonstrated perifollicular fibrosis, alternating orthokeratosis and parakeratosis, and a sparse perivascular lymphocytic infiltrate consistent with a PRP-like reaction (Fig. 2a–d). Specifically, this resembled an eczematous type II PRP-like reaction with the exception of palmoplantar involvement. Treatment with tretinoin 0.025% cream was initiated and significant improvement resulted within 3 weeks of therapy (Fig. 1e–h). Outpatient follow-up confirmed sustained resolution. Written informed consent was obtained from the patient for the publication of this case report and the accompanying images. A copy of the written consent may be requested for review from the corresponding author.

Discussion

Since the advent of TKIs in the late 1980s, and the US Food and Drug Administration approval of imatinib in 2001, a vast array of cutaneous manifestations have been described [1]. The initial clinical trials of the first and second generation Bcr-Abl TKIs (imatinib, dasatinib, and nolitinib) reported high rates of cutaneous adverse events [1–5]; The most common include a keratosis pilaris-like rash, superficial edema, maculopapular rash, dyschromia, lichenoid reaction, psoriasiform eruption, and a hand-foot skin reaction [2, 3]. Recently, a newer broad-spectrum Bcr-Abl TKI has joined the battle against refractory disease.

Ponatinib is a third-generation TKI developed for drug-resistant chronic myelogenous leukemia and acute lymphoblastic leukemia. In addition to blocking the constitutively active Bcr-Abl tyrosine kinase implicated in the pathogenesis of chronic myelogenous leukemia, it also inhibits the activity of other kinases including fibroblast growth factor, FMS like tyrosine kinase-3, KIT, platelet-derived growth factor, vascular endothelial growth factor,

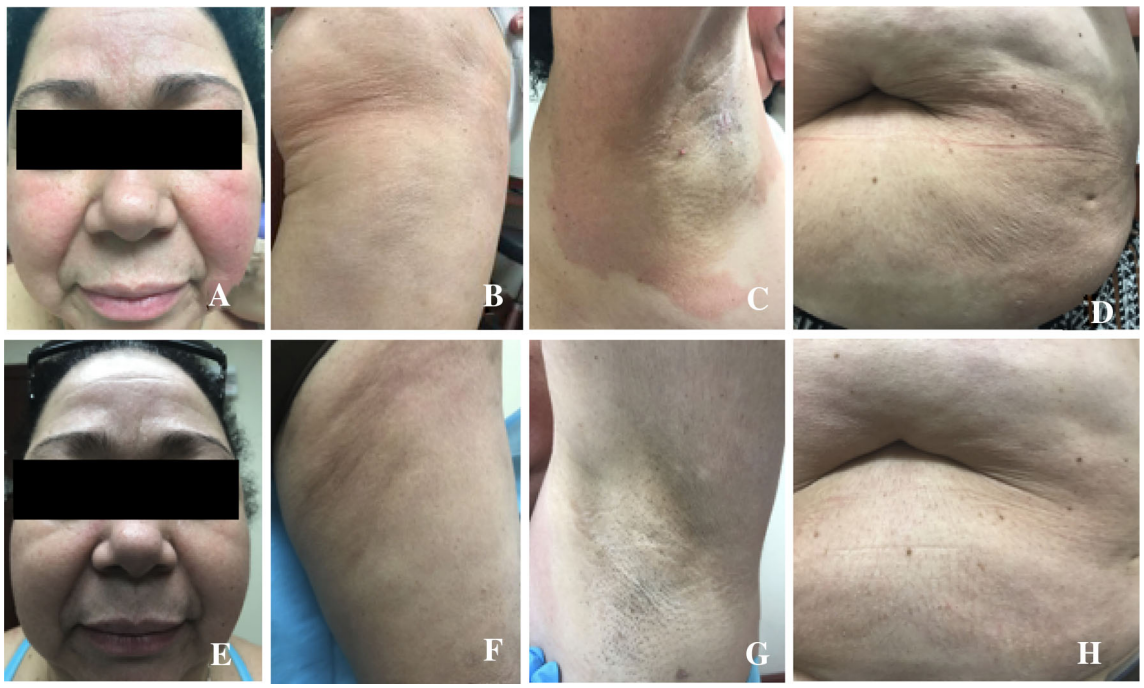

Fig. 1 Clinical photographs of the patient before (**a–d**) and after (**e–h**) treatment with tretinoin

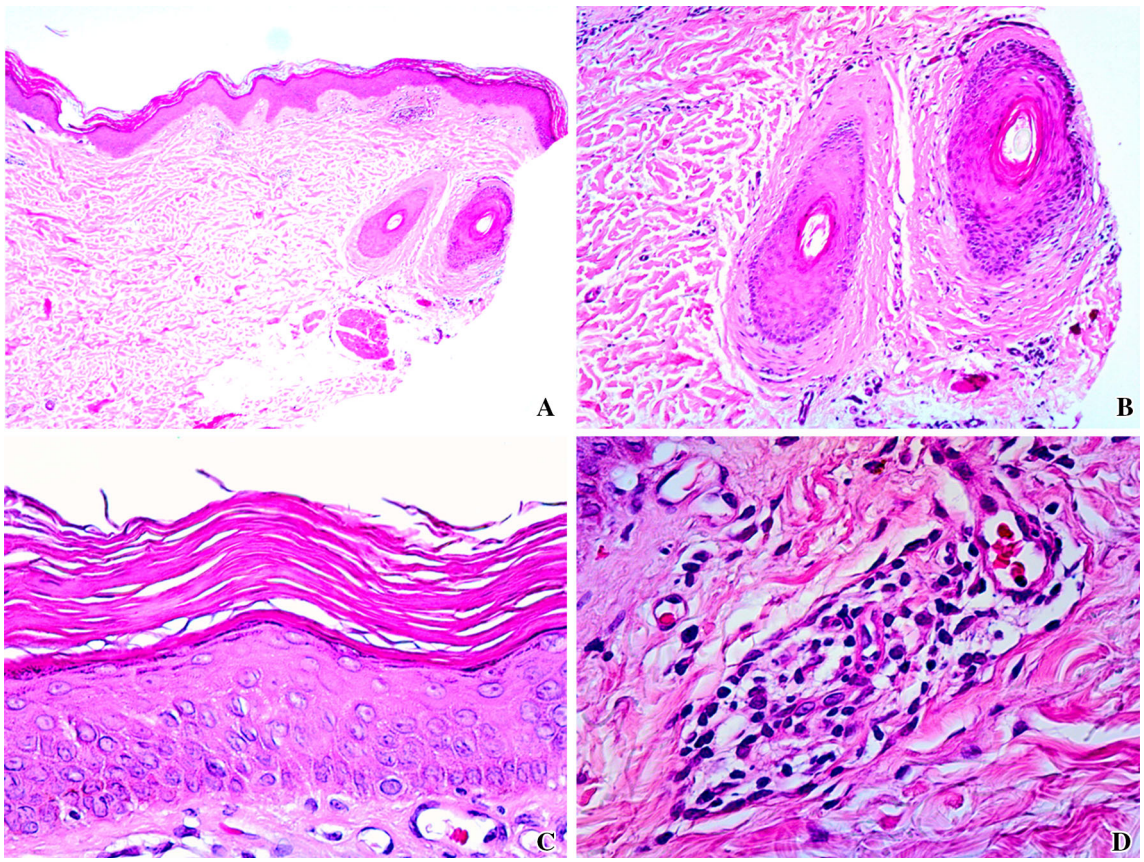

Fig. 2 Representative images of histopathologic features. **a** Low power shows two hair follicles with perifollicular fibrosis and a slightly thickened stratum corneum and a sparse perivascular lymphocytic infiltrate in the upper dermis (magnification 4). **b** Perifollicular fibrosis is evident around two hair follicles (magnification 10). **c** Compact orthokeratosis and focal parakeratosis are present (magnification 20). **d** The perivascular inflammatory infiltrate is composed mainly of lymphocytes (magnification 20)

and the SRC families [6]. This broadened activity, while paramount for treatment-resistant cancers, may contribute to off-target effects in the skin. Dermatologic adverse events in both phase I and II clinical trials were similar in profile to those seen in first- and second- generation TKIs [7, 8]. Since ponatinib became commercially available in 2014, several reports of cutaneous adverse events have been described, all with relevant clinical and histological similarities. Notably, of those reports revealing clinical photos, a follicular rash coalescing into pink-orange plaques demonstrating islands of sparing was almost always seen. Furthermore, several cases described significant xerosis and pruritus. Histologically, the majority of skin biopsies revealed perifollicular fibrosis, hyperkeratosis with varying orthokeratosis and parakeratosis, and scant perivascular lymphocytic infiltrate [9–12].

Given the similarities in cutaneous eruptions, numerous authors have responded with congruous therapies. Clearance of lesions was achieved without interruption of TKI therapy in ten out of ten cases. Of these, only one patient required a dose reduction [13]. Treatments included topical corticosteroids, keratolytics, retinoids, and antifungals. Systemic corticosteroids (20 mg prednisone, interval not specified) and retinoids (10 mg acitretin, four times daily) were each used in one patient, respectively. Our patient improved significantly on topical retinoids only within 3 weeks of therapy. While the pathogenesis behind retinoids as an effective therapy has not been completely elucidated, a few theories are proposed. First, topical retinoids have been shown to upregulate levels of heparin-binding epidermal growth factor-like growth factor in keratinocytes [14]. Heparin-binding epidermal growth factor-like growth factor is associated with chemotherapeutic resistance [1]. Thus, retinoids may cause local chemotherapeutic resistance in keratinocytes, reducing cutaneous effects. Additionally, all-trans retinoic acid derivatives help terminally differentiate epidermal cells [15]. This may cause diminished uptake of drug therapy within keratinocytes, thereby protecting them from the effects of chemotherapy. Finally, given the similarity to PRP, known treatments such as retinoids, should be effective while continuing critical TKI therapy.

Conclusion

In summary, TKIs are emerging as novel directed cancer therapies while minimizing adverse effects compared with traditional chemotherapy. However, cutaneous eruptions are common. Our case and literature review reveal that a characteristic rash occurs within the same time frame on similar doses of ponatinib, manifesting as a PRP-like eruption with ichthyosis and xerosis. This observation provides insight into the possibility of a unique pathogenic mechanism. Here, we highlight not only that cutaneous eruptions occur on ponatinib therapy, but that the dermatologic manifestations are characteristic and unique and benefit from retinoid therapy without requiring interruption of life-saving anticancer therapies.

Compliance with Ethical Standards

Ariel Eber, Alyx Rosen, Kate Oberlin, Alessio Giubellino, and Paolo Romanelli have no conflicts of interest directly relevant to the content of this article.

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