

Observation Letters

Ponatinib-induced atypical pityriasis rubra pilaris-like rash

Sir,

The introduction of targeted chemotherapeutic agents like tyrosine kinase inhibitors elicit more selective anti-cancer effects and have lesser systemic toxicities when compared to traditional chemotherapeutic agents. Ponatinib, a third generation tyrosine kinase inhibitor, was approved by Food and Drug Administration (FDA) in 2012 for treatment refractory chronic myelogenous leukemia (CML) and Philadelphia chromosome positive (Ph+) acute lymphocytic leukemia.^{1,2} We present a patient with refractory CML who presented with an atypical skin rash after institution of ponatinib.

A 52-year-old woman presented to our out-patient department with complaints of an itchy skin eruption of one month duration. She had been diagnosed with BCR/ABL positive chronic myeloid leukemia 2 years back, but had failed to respond to the first line treatment. Oral Ponatinib 45mg once daily was thus initiated. Three weeks after starting the drug, she developed redness and itchy eruption initially over face and forearms which gradually extended to involve the trunk. Examination revealed multiple reddish folliculo centric papules distributed symmetrically over the trunk and upper arms resembling keratosis pilaris [Figure 1a and b]. Irregular ichthyosiform atrophic plaques were seen over the upper chest and neck with islands of sparing [Figure 1c]. Dorsum of hands, forearms and legs had a diffuse atrophic wrinkled appearance. However, palmoplantar keratoderma was conspicuously absent.

Dermoscopy highlighted the yellow orange areas with red dotted vessels and thin scales [Figure 2a]. Histopathology showed follicular plugging, alternative orthokeratosis and parakeratosis, lymphocytic exocytosis and focal interface activity [Figure 2b]. A diagnosis of atypical pityriasis rubra pilaris (PRP)-like rash was thus made and topical tazarotene 0.05% cream was advised to be applied once daily over the forearms. There was no photosensitivity following topical application of tazarotene. Due to progressive lesions, oral acitretin 25 mg once daily was added without discontinuing ponatinib. Tazarotene was stopped due to extensive involvement and emollients were prescribed instead. After 2 weeks of treatment with acitretin, there was significant response with near complete resolution of the folliculocentric and ichthyotic lesions [Figure 1d]. Acitretin was further continued along with ponatinib. Acitretin was continued for 10 weeks following which patient was lost to follow up. The dose was maintained at 25 mg once daily and was not hiked as there was satisfactory improvement with this.

The best evidence regarding frequency and management of skin toxicity due to ponatinib comes from few large randomized controlled trials such as the PACE trial in which dermatologic specific adverse effects were reported to be rash (47%) and dry skin (42%).³ The mechanism of these ichthyosiform eruptions has been poorly elucidated. Another common cutaneous eruption reported with tyrosine kinase inhibitors is keratosis pilaris-like lesions which are also



Figure 1a: Multiple folliculo centric papules coalescing to form large plaques with islands of sparing over the trunk



Figure 1b: Multiple erythematous folliculo centric keratotic papules over the arms resembling keratosis pilaris

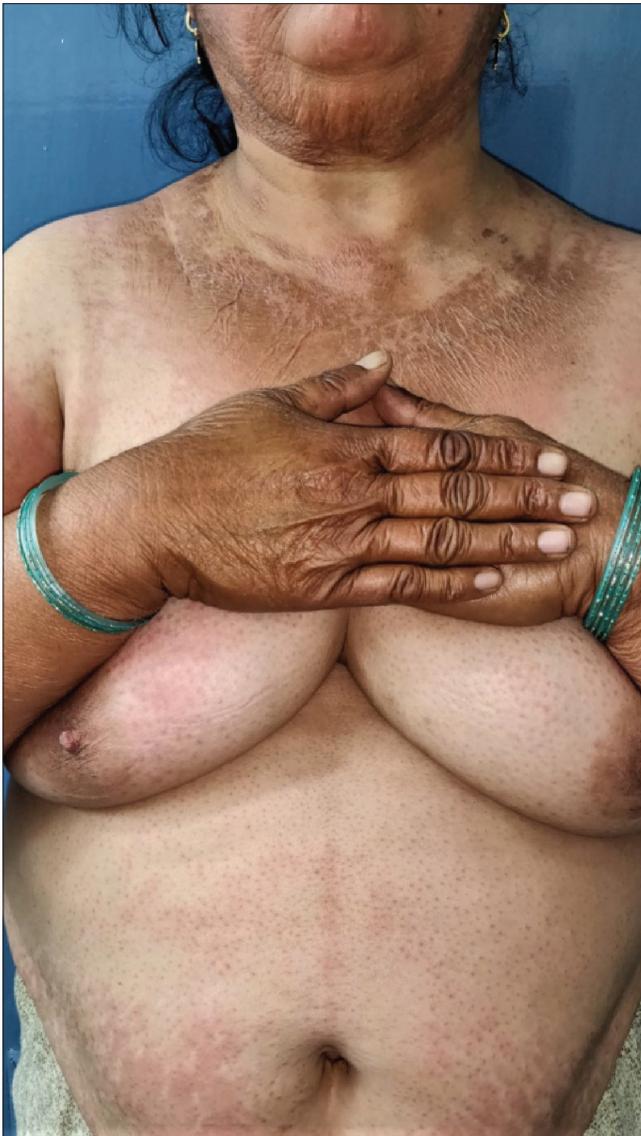


Figure 1c: Before treatment - Ichthyosiform atrophic plaques over the neck and trunk with islands of sparing

seen with Rapidly Accelerated Fibrosarcoma Gene (RAF) inhibitors. In addition to being a tyrosine kinase inhibitor, ponatinib also causes 'off target' inhibition of various other signaling pathways like fibroblast growth factor, platelet derived growth factor and sarcoma (SRC) family proteins amongst others. This might account for the similarity of cutaneous eruptions seen with other multikinase inhibitors.⁴

The index case had a type 2 PRP-like rash similar to the previously reported cases.^{4,5} Most of these cases had favorable response to treatment without discontinuing Ponatinib, although one needed Ponatinib dose reduction. Treatment options include topical steroids and retinoids. For more generalized cases oral corticosteroids, oral retinoids, phototherapy or combination of these have been successfully tried as in our patient.^{4,5}

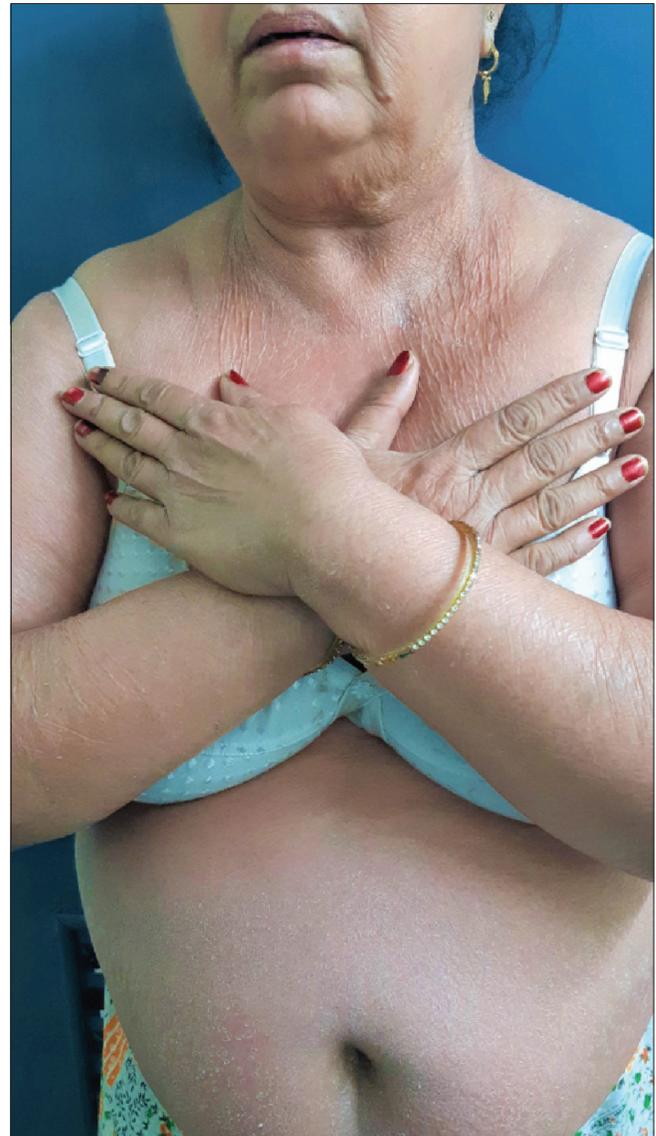


Figure 1d: After treatment - Resolution of the ichthyosiform plaques and folliculo centric papules after 2 weeks of therapy with oral acitretin

Systemic retinoids have also been used as a chemo-preventive agent in hematological malignancies, especially acute promyelocytic leukemia. All-trans retinoic acid induces differentiation of cancer stem cells and modulates the cell cycle. *In vitro* studies have also shown a suppressive effect of All trans retinoic acid on Ph⁺ cells in CML.⁶ In conclusion, dermatological side effects especially ichthyosiform eruptions are fairly common with ponatinib. Oral retinoids are effective for generalized PRP-like eruptions and most cases do not require discontinuation of ponatinib.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name

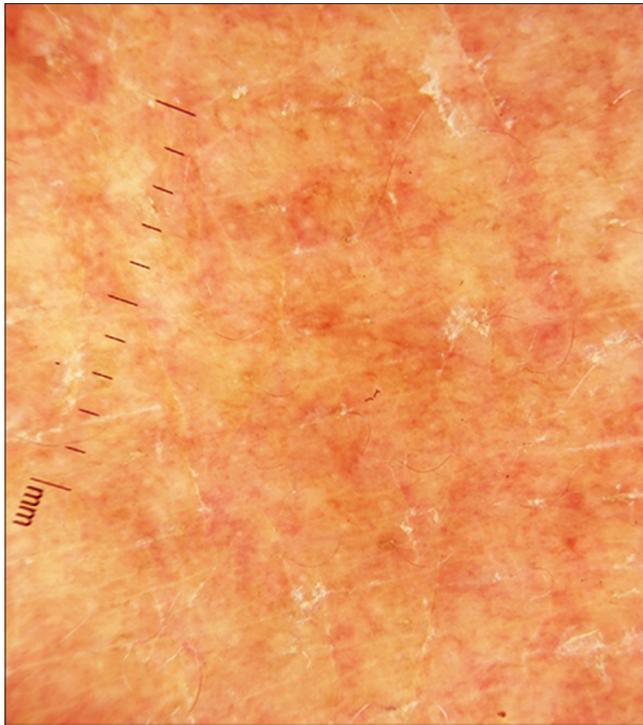


Figure 2a: Dermoscopy of the ichthyosiform plaques showing yellow orange areas with red dotted vessels and thin scales (DL3N, ×10, polarised)

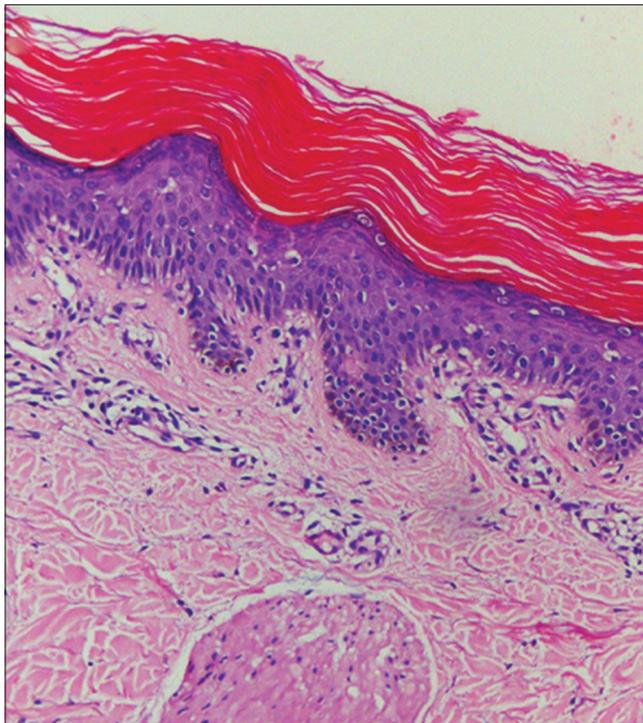


Figure 2b: Skin biopsy shows follicular plugging, alternative orthokeratosis and parakeratosis, lymphocytic exocytosis and focal interface activity (H and E, ×200)

and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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