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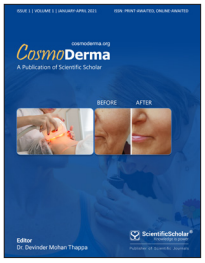

Letter to the Editor

Nilotinib-induced confluent and reticulated papillomatosis in a patient with chronic myeloid leukemia

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Dear Sir,

Tyrosine kinase inhibitors (TKIs) are anticancer drugs which are being used for the targeted treatment of various malignancies. Nilotinib is a second-generation TKI used in the treatment of chronic myeloid leukemia (CML). Although systemic adverse effects with nilotinib are rare, various cutaneous adverse effects have been reported. The development of confluent and reticulate papillomatosis (CARP) following treatment with nilotinib has never been reported as per our knowledge. This report is, therefore, the first to describe the development of CARP in a patient on nilotinib therapy.

A 29-year-old male visited the dermatology department with a non-pruritic rash on the trunk and axilla which persisted for about 5 months. He had a medical history of CML with a Bcr-Abl kinase mutation diagnosed 2 years ago. He was first started on imatinib 2 months after the diagnosis, with a change to nilotinib 2 years later due to imatinib resistance. The patient had received nilotinib 400 mg twice a day for 30 days before the onset of the rash. He did not have any similar episode in the past and none of the family members had a similar disease. The patient was not on any other medication except nilotinib before the onset of the rash. On examination, the patient had multiple hyperpigmented and scaly macules and papules present on the chest, abdomen, back, and axilla. The lesions coalesced centrally to form confluent patches and plaques and showed reticulation peripherally [Figure 1]. The differential diagnosis consisted of Darier's disease, pityriasis versicolor, biphasic amyloidosis, Dowling-Degos disease, and dermatopathia pigmentosa reticularis. The patient had applied topical ketoconazole for 4 weeks, but the lesions did not regress. The microscopy and culture were negative for fungal elements, thus excluding pityriasis versicolor. Dermoscopic examination showed whitish fine scaling, dark brown areas separated by whitish striae, creating a cobblestone pattern [Figure 2]. Histopathological examination revealed hyperkeratosis, papillomatosis, increased melanin pigmentation, and mild superficial perivascular lymphocytic infiltration which were suggestive of CARP [Figure 3]. Davis *et al.* proposed a set of criteria for the diagnosis of CARP as follows: (1) clinical findings include scaly brown macules and patches, some of which appear reticulated and papillomatous, (2) involvement of the upper trunk and neck, (3) negative fungal staining of scales, (4) no response to antifungal treatment, and (5) an excellent response to minocycline.[1] Apart from the histopathological and dermoscopic correlation, we found a good concordance between the clinical criteria set and the findings in our patient. Conglomerating our findings, a diagnosis of CARP was made. Nilotinib was discontinued

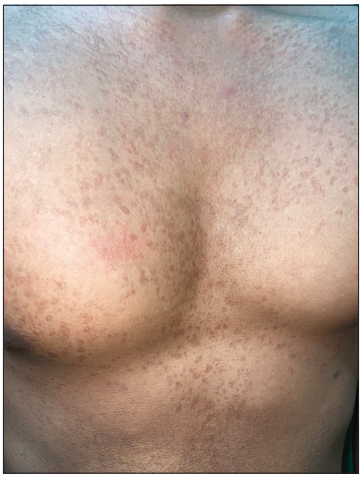

Figure 1: Multiple hyperpigmented macules and papules on the chest and abdomen, which are confluent in the centre and reticulate at the periphery.

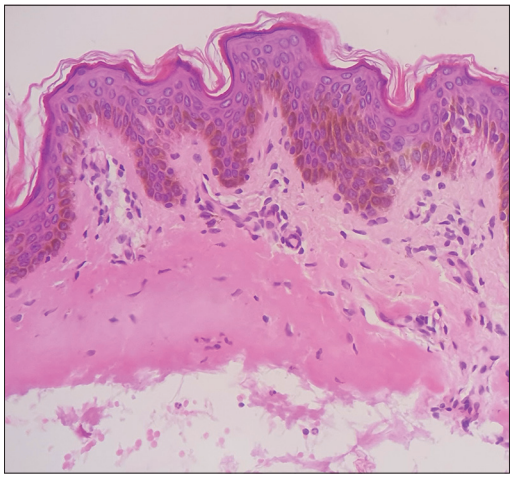

Figure 3: On histopathology, mild hyperkeratosis, papillomatosis, increased melanin pigmentation, and perivascular dermal lymphocytic infiltrates were seen (hematoxylin-eosin, original magnification ×40).

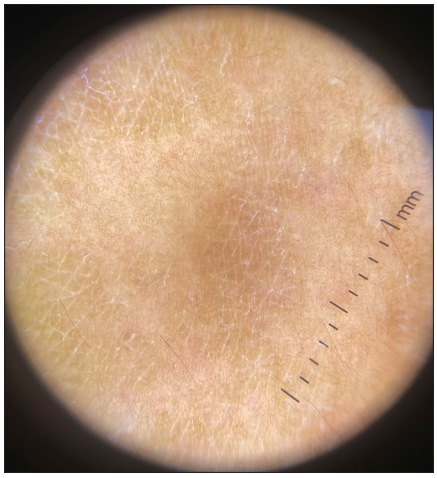

Figure 2: Dermoscopic examination showed whitish fine scaling, dark brown areas separated by whitish striae, creating a cobblestone pattern.

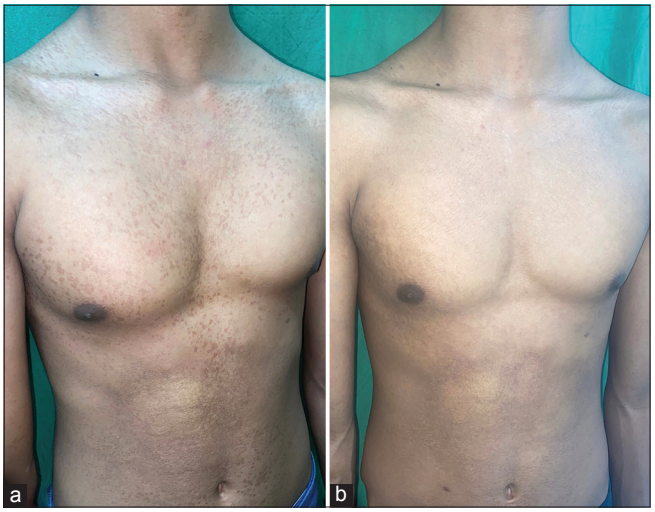

Figure 4: (a) Confluent and reticulated hyperpigmented patches and plaques present on the chest and abdomen while on nilotinib therapy. (b) Improvement of the lesions after temporary withdrawal of nilotinib and treatment with oral minocycline.

for 2 weeks on consultation with the oncologist. The patient was prescribed oral minocycline 100 mg once daily along with topical tazarotene (0.05%) gel. The lesions showed considerable improvement by the end of 20 days [Figure 4a and b]. Although the cause for CARP remains unclear, prevailing postulates include a bacterial trigger by *Dietzia papillomatosis*, an increased cutaneous response to *Malassezia furfur*, amyloid deposition, ultraviolet light, insulin resistance, and a loss-of-function mutation in keratin 16. Based on the absence of the above causes of CARP, timely correlation of onset of the rash with intake of nilotinib, and improvement of the rash on its withdrawal, we confirmed the temporal association of CARP with the intake of nilotinib. However, as nilotinib had a crucial role in the control of CML in the patient, it was restarted and topical retinoids were prescribed to relieve the cutaneous symptoms.

Nilotinib is a second-generation Bcr-Abl TKI which is approved for the treatment of imatinib-resistant chronic myeloid leukemia expressing the Bcr-Abl mutation. Although these medications are generally well tolerated, cutaneous adverse drug reactions occur in nearly 34.3% of patients receiving nilotinib, with 2.6% of them exhibiting a high-grade rash.[2] The most common dermatologic complications of nilotinib includes rash, pruritus, dry skin, and alopecia.

Table 1: The various adverse cutaneous reactions reported due to intake of nilotinib.

Author	Age/Sex	Disease	Dose of drug	Cutaneous adverse effect
Leitão *et al*., 2016	55 yr/F	CML	Nilotinib (400 mg/day)	Lichen planopilaris-like eruption after 6 weeks of intake
Sayin *et al*., 2016	40 yr/F	CML	Nilotinib (400 mg) twice daily	Xanthelasma palpebrarum after 15 months of intake
Tawil *et al*., 2017	45 yr/M	CML	Nilotinib (300 mg) twice daily	Keratosis pilaris after 4 months, Alopecia areata after 2 months, Eyebrow thinning after 3 months of intake
Sadatmadani *et al*., 2022	35 yr/F	CML	Nilotinib (800 mg/day)	Elephantine psoriasis after 7 months of intake
Our case	29 yr/M	CML	Nilotinib (400 mg) twice daily	Confluent and reticulated papillomatosis after 4 weeks of intake

*CML: Chronic myeloid leukemia

A thorough search of literature reveals various reportings of cutaneous adverse effects associated with the intake of nilotinib, summarised in Table 1.[3-6] The mechanism of the cutaneous reaction in our case is possibly attributed to c-kit (one of the targets of TKIs) as it is also expressed in the basal skin cells and melanocytes, apart from the cancer cells.

These adverse reactions may influence the compliance to nilotinib therapy, thereby affecting the oncologic cure. A greater emphasis is required in the recognition of such associations. Timely identification and administration of treatment for these cutaneous reactions might help in better adherence to the oncological treatment with better outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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