Ibrutinib-Associated Multifocal Paronychia with Periungual Pyogenic Granulomas Involving Concomitant Finger and Toe Nails

Dear Editor,

Ibrutinib is an oral covalent inhibitor of Bruton's tyrosine kinase (BTK) pathway and is approved for the treatment of hematological malignancies such as mantle cell lymphoma and chronic lymphocytic leukemia (CLL). The safety profile of ibrutinib appears to be well-tolerated with major hematological and minor dermatological side effects. Herein, we report ibrutinib-induced multifocal paronychia with periungual pyogenic granulomas (PPPG) involving bilateral fingernails and toenails. On meticulous exploration of worldwide literature, less than 10 cases of ibrutinib-induced paronychia and periungual granulation tissue are reported, but none from the Indian literature.[1-4]

A 51-year-old male patient presented with painful swellings of proximal and lateral nail-folds (PNF, LNF) of multiple fingernails and toenails for 4 months, which initially involved left great toenail and gradually progressed to involve multiple fingernails and toenails with subsequent appearance of erythematous fragile outgrowths with a tendency to bleed on trivial trauma and/or friction. He was diagnosed with CLL (deletion of the *17p13* gene) and was taking oral ibrutinib 420 mg/day, allopurinol 300 mg/day, and folic acid 5 mg/day for the last 10 months; thus, the onset was after 6 months of drug initiation. There was no history suggestive of local trauma or ill-fitting foot-wear. Clinically, he had severe paronychia with erythematous, tender, and fragile granulation tissue arising from underneath the PNF and LNF of multiple fingernails and toenails [Figure 1].

The patient did not respond to oral antibiotics, analgesics and boric acid soaks. Considering the pain and difficulty in walking, left great toenail avulsion with chemical matricectomy and complete excision and histopathology of the granulation tissue was attempted, which was consistent with the diagnosis of pyogenic granuloma [Figure 2a]. Nevertheless, within 2 months of toenail avulsion, the lesion recurred and subsequently progressed to involve previously unaffected nails as well. Dermoscopy of the affected nail units revealed homogenous red areas with linear irregular vessels and whitish streaks or white rail lines throughout the lesion [Figure 2b].

After the oncology opinion, ibrutinib was temporarily withheld, whereas other drugs were continued as CLL was well-controlled. On subsequent follow-ups, there was significant improvement in the previous lesions, and reduced pain over nail folds. Eventually, ibrutinib was reintroduced; however, at a lower dose of 280 mg/day, following which the patient had a mild recurrence in only a single toenail [Figure 3]. The Naranjo adverse drug reaction probability scale[5] for ibrutinib was 9, indicating a definite causal relationship, whereas for other drugs it was 2.

Other differential diagnoses such as amelanotic melanomas and other causes implicated in multiple PGs of the nail other than drugs such as trauma, systemic diseases such as psoriasis, eczema, and cutaneous sarcoidosis were ruled out by history, complete physical examination, and lesional biopsy.[6]

Ibrutinib is often well-tolerated, with major side effects such as infections and hematological complications.

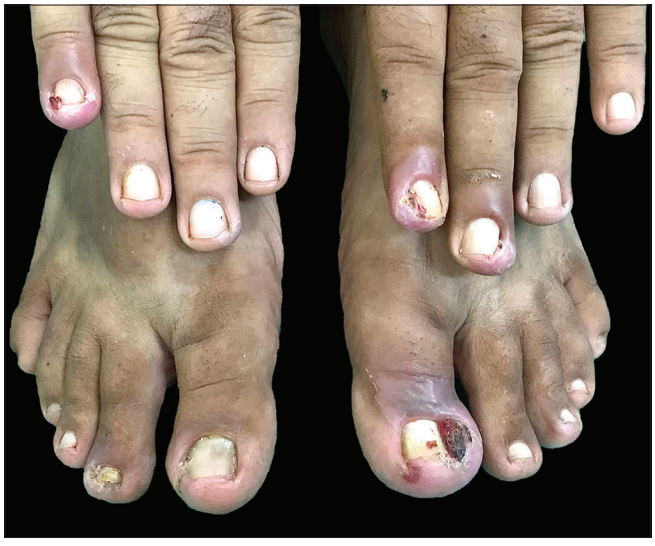

Figure 1: Initial presentation with swollen, erythematous nail folds with periungual granulation tissue involving multiple fingernails and toenails

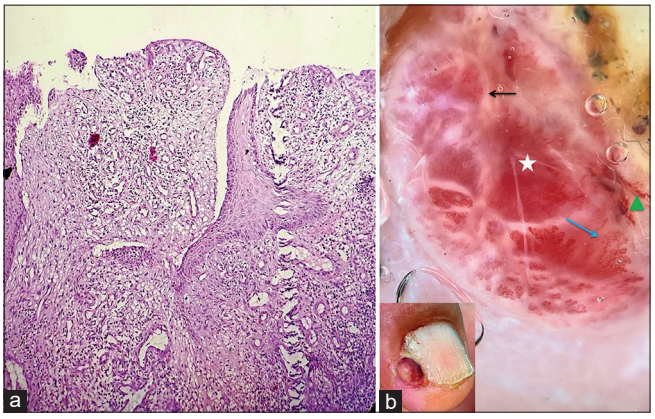

Figure 2: (a) Ulcerated epidermis with foci of suppuration; subepidermal tissue shows chronic inflammatory infiltrate and excessive granulation tissue (H and E, 100×); (b) Dermoscopy using DermLite DL4 (10×, polarized view and ultrasound gel as interface-medium) depicting red homogenous areas (white star), white rail lines (black arrow), irregular linear vessels (blue arrow), and focal hemorrhages (green triangle) consistent with periungual pyogenic granuloma; clinical image in the inset

Dermatological adverse effects include maculopapular rash, petechiae, pruritus, photosensitivity, skin infections, eczematous skin reactions, angular cheilitis, acute glossitis, textural hair changes, and brittle nails.[4]

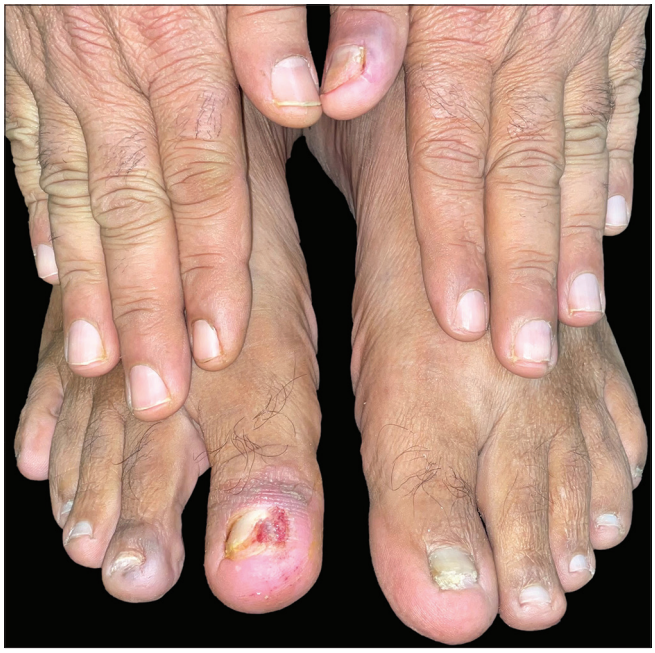

Figure 3: Near complete resolution with relapse in right great toenail at low-dose ibrutinib

Ibrutinib-associated PPPG has recently been reported in only nine cases worldwide [Table 1]; however, none are of Indian descent.[1-4] Of these, merely two had concomitant fingernail and toenail involvement.[4] In our patient, there was bilateral and multifocal involvement of both toenails and fingernails.

Moreover, none of the earlier reports have described dermoscopic features in ibrutinib-associated PPPG.

Ibrutinib covalently binds to the cysteine moieties of the Bruton's tyrosine kinase enzyme, ultimately disrupting the disulfide bonds of cysteine residues in the nail.[7] This may result in increased nail fragility and thus, formation and embedment of nail spicules in the nail fold, thereby precipitating foreign body reaction and inflammatory response causing PPPG formation. Ibrutinib might also have off-target activity against epidermal growth factor receptors. The cascade of events after BTK inhibition, such as the inhibition of survival signaling pathways, might also be responsible.[4]

The time of onset of PPPG possibly suggests the median time for ibrutinib to accumulate in acral sites. Pileri *et al.* observed a median time of onset of +120 days (range: +60

Table 1: Reported cases of Ibrutinib-associated paronychia with periungual pyogenic granuloma

Study (year)	Study type	Patient details	Indication	Dose	Onset time of PPPG after ibrutinib introduction	No. of nails affected	Nails affected	Rechallenge test	Recurrence on rechallenge
Mohandas, Davis (2016)[1]	Case report	79 y; F	MCL	NS	1 year	NS	Multiple toenails	-	-
Yorulmaz, Yalcin (2019)[2]	Case report	40 y; F	CLL	NS	18 months	2	Bilateral 1st toenails	-	-
Shah, Bowen, Hansen (2020)[3]	Case report	64 y; M	TCL, GVHD	420 mg	3 months	2	Bilateral 3rd fingernails	-	-
Pileri *et al.* (2020)[4]	Original article	58 y; F	MCL	560 mg	+400 days	2	Bilateral 1st toenails	-	-
		75 y; M	MCL	560 mg	+90 days	2	Bilateral 1st fingernails	-	-
		62 y; F	CLL	420 mg	+60 days	NS	Nails of both hands and feet	-	-
		78 y; M	CLL	560 mg	+120 days	4	Left 1st toenail, right 2nd and 3rd toenail; and right 4th finger nail	-	-
		63 y; F	WM	420 mg	+180 days	2	Bilateral 1st toenails	-	-
		62 y; F	MCL	560 mg	+120 days	2	Bilateral 1st toenails	-	-
Current case (2022)	Case report	51 y; M	CLL	420 mg	+180 days	9	Right 3rd and 5th fingernails; left 1st, 2nd and 3rd fingernails; left 1st toenail, right 1st, 2nd and 3rd toenails	Yes	Recurrence +, but mild at a lower dose of 280 mg/day

F=Female, M=Male, NS=Not specified, MCL=Mantle cell lymphoma, CLL=Chronic lymphocytic leukemia, TCL=T-cell lymphoma, GVHD=Graft versus host disease, WM=Waldenstrom macroglobulinemia, PPPG=Paronychia with periungual pyogenic granuloma

to +400 days) for nail involvement.[4] In the current case, the time of onset was 6 months after the introduction of ibrutinib. In addition, there was bilateral, multifocal affliction of toenails and fingernails and the temporal association was evident as PPPG improved dramatically on discontinuing ibrutinib and recurred on re-challenge. Besides that, the initial dose of ibrutinib was 420 mg/day; however, on re-introduction at a lower dose (280 mg/day), the recurrence was conspicuously very mild. This may direct towards the possibility of dose-dependent severity of ibrutinib-induced PPPG formation. In contrast, studies that proclaim that nail toxicity by ibrutinib is not a drug-limiting toxicity have studied ibrutinib-associated nail plate abnormalities only such as brittle nails and longitudinal ridging.[7,8]

Dermoscopy of pyogenic granuloma occurs as variable patterns of combinations of "white rail lines," "red homogenous areas," "white collarette," and "vascular structures".[9] Other than pyogenic granulomas, similar vascular structures have also been observed in amelanotic melanomas.[9] Dermoscopy, although a good screening tool, cannot substitute the gold-standard "histopathology," especially when "vascular structures" are evident in dermoscopy of PG. Dermoscopy in PG cannot differentiate the underlying cause.

Apart from its significance in creating awareness among clinicians regarding ibrutinib-associated PPPG, this case differs from earlier reports as it was proven by the ibrutinib re-challenge test. Our case also warrants the need for larger studies to investigate the dose-dependent relationship of severity of ibrutinib-associated PPPG which has not been highlighted earlier.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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