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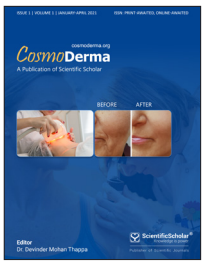

Letter to the Editor

Paclitaxel-induced nail changes with palmoplantar erythrodysesthesia

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Dear Sir,

Nail changes are frequent in patients undergoing cancer chemotherapy, which may result in pain and functional limitations. However, these changes remain underreported. This discrepancy can be attributed, at least in part, to the grading system employed by oncologists, which only recognizes five specific alterations, viz., paronychia, nail loss, nail ridging, nail discoloration, and nail infection. However, this classification falls short of capturing the full spectrum of nail alterations resulting from anticancer therapies and their impact on a patient's quality of life.[1-4] For instance, taxane-induced painful nail bed hemorrhages can significantly impair a patient's daily activities, yet these symptoms cannot be adequately reported using the existing grading system. Here, we report a case of taxane-induced onycholysis with palmoplantar erythrodysesthesia (PPE). Although paclitaxel-induced nail changes are described in the literature, the co-occurrence of nail changes with PPE is uncommon and rarely reported.

A 33-year-old female diagnosed with stage IIB (T3N0M0) breast cancer, undergoing chemotherapy, presented with nail changes along with redness and swelling over palms and soles. She had completed four cycles of doxorubicin (100 mg/m^2) and cyclophosphamide (1000 mg/m^2), which were administered every two weeks followed by 12 weekly cycles of paclitaxel (150 mg/m^2). The patient experienced chemotherapy-induced alopecia at two months following initiation of chemotherapy. During the fourth cycle of paclitaxel, she developed redness and tingling in her palms and soles. On examination, there was nail plate thinning, distal xanthonychia, onycholysis, paronychia, and bluish-gray chromonychia affecting the lunula and the proximal half of all the finger and toenails [Figure 1] along with erythema, edema, and tenderness over the palms and soles [Figure 2]. Her routine hematological and biochemical investigations were within normal limits. Based on history and examination, a diagnosis of paclitaxel-induced nail changes with PPE was made. The patient was treated symptomatically with oral analgesics (ibuprofen 400 mg three times/day) and topical application of betamethasone dipropionate 0.05% cream twice daily. She was also advised to use either ice packs or frozen gloves and socks during subsequent chemotherapy infusions and apply urea and lactic acid-based (10%/5%) moisturizer. The patient improved significantly after two weeks of treatment and was able to continue her chemotherapy cycles without any dose alteration or change in regimen. Further cycles were administered without recurrence.

Taxanes are the most common chemotherapeutic agents causing nail changes, primarily due to their direct toxicity. The overall incidence of taxane-induced nail changes was found to be 43.7% with paclitaxel and 34.9% with docetaxel. Compared to controls, docetaxel had a significantly

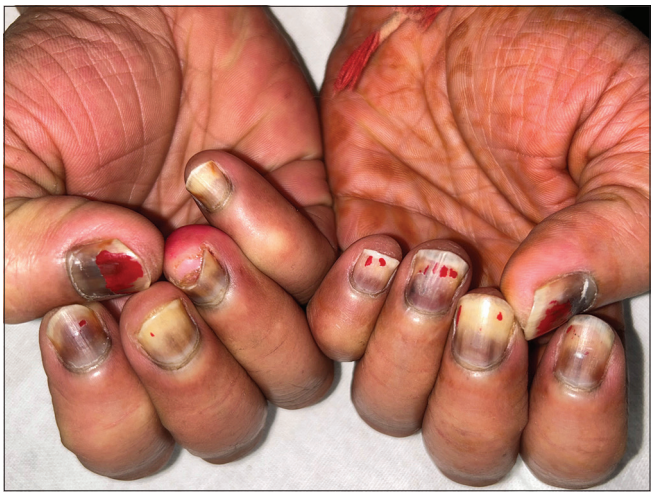

Figure 1: Nail plate thinning, along with distal xanthonychia, distal onycholysis, and bluish-gray chromonychia affecting the lunula and the proximal half of all the fingernails in addition to erythema and edema of proximal nail folds.

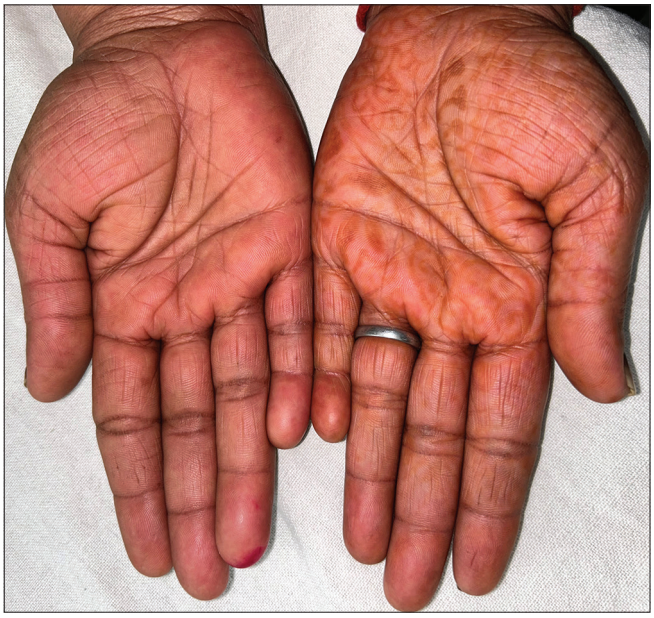

Figure 2: Erythema and edema of bilateral palms.

higher relative risk of 77.74 (95% ci: 41.88–144.32; $P < 0.001$), and some studies report rates as high as 89% after three treatment cycles.[5-7] In the majority of the patients (46.8%), both fingers and toenails are involved. However, isolated fingernail involvement is seen in 11.4% of patients while exclusive toenail involvement is seen in 41.8% of the patients.[6]

The most common taxane-induced nail changes are Beau's lines, which are characterized by transverse linear depressions.[7] Docetaxel is associated with a higher frequency of hemorrhagic onycholysis compared to paclitaxel. In some cases, complete loosening of the nail bed epithelium can result in hemorrhagic blisters beneath the nail plate causing increased pressure and painful detachment of the nail plate. Rarely, erythema over the dorsal hands, perimalleolar, and Achilles regions may accompany this condition, referred to as periarticular thenar erythema with onycholysis syndrome.[3,4]

Taxanes can result in various nail discolorations. Orange chromonychia occurs due to hemorrhagic suffusion from the nail bed while secondary infections can cause chloro or xanthonychia. Taxane-induced onycholysis often accompanies painful paronychia. Nail matrix involvement can lead to melanonychia, true leukonychia, Beau's lines, onychomadesis, and brittle nails with ridging and thinning. In contrast, nail bed involvement leads to onycholysis and apparent leukonychia, splinter hemorrhage, onycholysis (with or without hemorrhage), subungual hematoma (with or without pain), and subungual pyogenic granuloma. Periungual involvement manifests as mild-to-severe paronychia and periungual pyogenic granuloma.[1-6] The different nail changes associated with various antineoplastic agents are summarized in Table 1.[8-10]

The precise mechanism of taxane-induced onycholysis is not completely understood. Two potential hypotheses involve neuropeptides and prostaglandins, which may contribute to inflammation.[11] Nail lesions become noticeable after several weeks of treatment due to the slow growth rate of the nail plate and tend to increase with the number of treatment cycles. However, these changes typically resolve and regress after treatment discontinuation.

PPE, also known as hand-foot syndrome or acral erythema, is a condition characterized by localized erythema and edema that primarily affects the palms of the hands and the soles of the feet. It is often preceded by dysesthesia and paresthesia and can progress to painful swelling, skin peeling, and even blistering. The onset of symptoms can occur within a day to several months after starting treatment. In severe cases, the condition can extend to other areas of the body such as the neck, chest, trunk, and pressure points. If the causative drug is not discontinued, it may result in epidermal necrosis.[12,13]

The exact mechanisms underlying the development of acral erythema are not fully understood. However, several factors including the specific drug, dosage, treatment schedule, and infusion duration can influence its occurrence. One hypothesis proposes that the palms and soles have a higher concentration of capillaries leading to increased drug accumulation and toxicity. It is suggested that local inflammation may be triggered by drug extravasation from microcapillaries and penetration into the outermost layer of the skin (stratum corneum) following local trauma, potentially mediated by the enzyme cyclooxygenase (COX)-2. Alternatively, direct cytotoxicity of the drug has also been proposed as a cause of local inflammation. Some

Table 1: Different nail changes associated with various antineoplastic agents.

Drug class	Drugs	Nail changes
Alkylating agents	Cyclophosphamide	Diffuse or longitudinal melanonychia Onychodystrophy Onycholysis Beau's lines Muehrcke's lines
	Platinum-based agents (e.g., cisplatin)	Lindsay's nails Melanonychia Onycholysis Onychomadesis Beau's lines Mees' lines Muehrcke's line Paronychia Subungual hyperkeratosis
Topoisomerase inhibitors	Etoposide	Nail bed pigmentation Beau's lines Onycholysis Paronychia
Mitotic inhibitors	Docetaxel Paclitaxel Vincristine	Orange discoloration Diffuse melanonychia Onychomadesis Onycholysis (exudative/ hemorrhagic) Onychorrhexis Brittle nails Beau's lines Paronychia Pyogenic granuloma Subungual hyperkeratosis Splinter hemorrhage Mees' line Muehrcke's line Koilonychia
Antitumor antibodies	Anthracyclines	Longitudinal melanonychia Transverse melanonychia Transverse leukonychia (Mees' line)
	Bleomycin	Diffuse melanonychia Beau's line Muehrcke's line Raynaud's phenomenon
Antimetabolite analogues	5-Fluorouracil	Onycholysis Onychodystrophy Onychomadesis Diffuse and transverse melanonychia Paronychia
	Capecitabine	Periungual inflammation Paronychia Pyogenic granuloma
EGFR inhibitors	Erlotinib Gefitinib Panitumumab Cetuximab	Paronychia Pyogenic granuloma Brittle nails Onycholysis
MEK inhibitors	Trametinib Cobimetinib Selumetinib	Paronychia Pyogenic granuloma Brittle nails Onycholysis
HER inhibitors	Trastuzumab Lapatinib Afatinib	Paronychia pyogenic granuloma Brittle nails Onycholysis
mTOR inhibitor	Everolimus Sirolimus	Paronychia Pyogenic granuloma Mild onycholysis Brittle nails Xanthonychia Twenty nail dystrophy
c-kit inhibitor	Imatinib Dasatinib	Diffuse, transverse, or longitudinal melanonychia
Bruton kinase inhibitor	Ibrutinib	Brittle nails Onychorrhexis Onychoschizia Onycholysis
VEGFR inhibitors	Sunitinib Sorafenib	Splinter hemorrhages Xanthonychia Brittle nails

EGFR: Epidermal growth factor receptor, MEK: Mitogen-activated extracellular signal-regulated kinase, HER: Human epidermal growth factor receptor, mTOR: Mammalian target of rapamycin, VEGFR: Vascular endothelial growth factor receptor

researchers speculate that the basal cells of the palms have higher expression of a cell proliferation marker called Ki67 compared to other areas of the skin making them more susceptible to the effects of cytotoxic drugs. In addition, the high density of eccrine glands present on the palms and soles have been suggested to contribute to the accumulation of cytotoxic drugs in these areas.[12,13]

Treatment options for acral erythema are currently limited, and there are no established guidelines for treatment. Definitive treatment includes reducing the dose or temporarily stopping the drug until symptoms improve. General measures include emollients, cold compresses, wound care, and limb

elevation. Prophylactic pharmacological interventions include pyridoxine, vitamin E, dexamethasone and COX-2 inhibitors, and topical application of urea/lactic acid cream.[12,13]

Although PPE is not life threatening, recognizing cutaneous side effects of cytotoxic agents, pre-informing patients, and adequate management is crucial for preventing the interruption of chemotherapy.

In conclusion, we report a case of paclitaxel-induced nail changes with PPE, emphasizing the imperative for improved identification and handling of these symptoms.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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