

## Liposomal doxorubicin-induced palmoplantar erythrodyesthesia syndrome

Sir,

Palmer-plantar erythrodyesthesia (PPE) is a relatively rare dermatologic toxic reaction associated with certain chemotherapeutic agents.<sup>[1]</sup> It is also called hand-foot syndrome (HFS), palmar-plantar erythema, acral erythema, and Burgdorf's reaction.<sup>[2]</sup> In 1984, Lokich and Moore first described this syndrome at the New England Deaconess Hospital.<sup>[3]</sup>

A 53-year-old man recently operated for pleomorphic sarcoma of his right forearm presented to us with a complaint of intense redness and burning of both palms and soles since four months. His complaint started after receiving two cycles of intravenous liposomal doxorubicin 80 mg that was started two weeks post-surgery. He continued to receive the chemotherapy three weekly for a total of six cycles. Cutaneous examination revealed bright red erythema of both palms and soles along

with psoriasiform scaling [Figures 1 and 2]. He also reported a difficulty in walking and discomfort in holding objects. He was thus classified as grade 3 PPE as per National Cancer Institute (NCI) grading system. He was treated with a potent topical steroid (clobetasol propionate ointment 0.05%) and bland moisturizers along with cold compresses. He was also prescribed oral nicotinamide (375 mg) twice daily and pyridoxine 40 mg once a day. On follow-up after two weeks, the patient showed significant improvement in his condition [Figures 3 and 4].

Hand-foot syndrome is associated with several chemotherapeutic agents, including methotrexate, mercaptopurine, cytarabine, fluorouracil, epirubicin, docetaxel, and doxorubicin.<sup>[4-8]</sup> The occurrence of PPE depends on the total cumulative dose and peak drug levels.<sup>[9]</sup>

It has been postulated that pegylated liposomal doxorubicin (PLD) extravasates from the deeper microcapillaries of the hands and feet following the local trauma. The hydrophilic coating of the liposomes facilitates the accumulation of PLD in the eccrine glands that are present in higher numbers in the hands and feet, making them the preferred sites for this syndrome.<sup>[10]</sup> Elevated concentrations of PLD have been demonstrated in the eccrine glands of the



**Figure 1:** Erythema and desquamation over both hands



**Figure 2:** Erythema and desquamation over both soles



**Figure 3:** After 3 weeks of treatment with oral nicotinamide and pyridoxine



**Figure 4:** After 3 weeks of treatment with oral nicotinamide and pyridoxine

palms and soles. In addition, the high proliferation rate of the epidermal basal cells in the palms make them more sensitive to cytotoxic drugs. Also, other factors such as gravitational forces, regional temperature gradients, friction, and vascular anatomy may add to its typical localization to the palms and soles.<sup>[10,11]</sup>

It has also been postulated that doxorubicin penetrates the capillary walls and interacts with copper ions to produce reactive oxygen species that attack keratinocytes and release chemokines and inflammatory cytokines, leading to HFS.<sup>[12]</sup>

Symptoms usually start as a localized numbness, dysesthesia or paresthesia, tingling and erythema of the palms and soles accompanied by swelling and discomfort. In severe cases, it progresses to blistering, ulceration, desquamation, and incapacitating pain. Histopathological examination may show keratinocyte vacuolar degeneration,

keratinocyte damage and apoptosis, intracytoplasmic inclusion bodies, dermal perivascular lymphocytic infiltration, and dermal edema.<sup>[13]</sup>

The US National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) has given a score for grading the HFS toxicity. In NCI-CTCAE version 3.0, Grade 1 HFS is characterized by minimal skin changes or dermatitis without pain; grade 2 is characterized by skin changes or pain, but not interfering with function, and grade 3 is characterized by ulcerative dermatitis or skin changes with pain interfering with function.<sup>[11]</sup>

Topical emollients and corticosteroid creams are the mainstay of treatment of HFS. The chemotherapeutic agent is interrupted in severe cases and can be restarted later at a low dose when symptoms subside. HFS usually resolves rapidly without any recurrence. However, if symptoms recur particularly with a higher grade of involvement, the drug

should be discontinued permanently. Supportive treatments such as topical wound care, elevation, and cold compresses may help to relieve the pain. Systemic corticosteroids, pyridoxine, blood flow reduction, and, recently, topical 99% dimethyl-sulfoxide have been used with variable outcomes. Lately it has been reported that celecoxib plays an important role in preventing chemotherapy-induced palmo-plantar erythrodyesthesia.<sup>[14]</sup>

**Nidhi Yadav, Bhushan Madke, Sumit Kar,  
Kameshwar Prasad**

Department of Dermatology, Venereology and Leprosy,  
Mahatma Gandhi Institute of Medical Sciences,  
Sevagram, Wardha, Maharashtra, India.

**Address for correspondence:**

Prof. Sumit Kar,

Department of Dermatology, Venereology and Leprosy,  
Mahatma Gandhi Institute of Medical Sciences,  
Sevagram - 442 102, Maharashtra, India.  
E-mail: karmgims@gmail.com

## REFERENCES

- Nagore E, Insa A, Sanmartín O. Antineoplastic therapy-induced palmar plantar erythrodyesthesia (“hand-foot”) syndrome: Incidence, recognition and management. *Am J Clin Dermatol* 2000;1:225-34.
- Gressett SM, Stanford BL, Hardwicke F. Management of hand-foot syndrome induced by capecitabine. *J Oncol Pharm Pract* 2006;12:131-41.
- Lokich JJ, Moore C. Chemotherapy-associated palmar-plantar erythrodyesthesia syndrome. *Ann Intern Med* 1984;101:798-9.
- Doyle LA, Berg C, Bottino G, Chabner B. Erythema and desquamation after high-dose methotrexate. *Ann Intern Med* 1983;98:611-2.
- Cox GJ, Robertson DB. Toxic erythema of palms and soles associated with high-dose mercaptopurine chemotherapy. *Arch Dermatol* 1986;122:1413-4.
- Revenga Arranz F, Fernández-Durán DA, Grande C, Rodríguez Peralto JL, Vanaclocha Sebastián F. Acute and painful erythema of the hands and feet. *Arch Dermatol* 1997;133:499-500, 502-3.
- Lokich JJ, Moore C. Chemotherapy-associated palmar-plantar erythrodyesthesia syndrome. *Ann Intern Med* 1984;101:798-9.
- Coukell AJ, Spencer CM. Polyethylene glycol-liposomal doxorubicin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the management of AIDS-related Kaposi’s sarcoma. *Drugs* 1997;53:520-38.
- Baack BR, Burgdorf WH. Chemotherapy-induced acral erythema. *J Am Acad Dermatol* 1991;24:457-61.
- Pagliuca A, Kaczmarzski R, Mufti GJ. Palmar-plantar erythema associated with combination chemotherapy. *Postgrad Med J* 1990;66:242-3.
- Milano G, Etienne-Grimaldi MC, Mari M, Lassalle S, Formento JL, Francoual M, *et al.* Candidate mechanisms for capecitabine-related hand-foot syndrome. *Br J Clin Pharmacol* 2008;66:88-95.
- Yoshioka N, Nagasawa T, Coler-Reilly A, Suzuki H, Kubota Y, Yoshioka R, *et al.* Pathogenesis of Hand-Foot Syndrome induced by PEG-modified liposomal Doxorubicin. *Hum Cell* 2013;26:8-18.
- Yang CH, Lin WC, Chuang CK, Chang YC, Pang ST, Lin YC, *et al.* Hand-foot skin reaction in patients treated with sorafenib: A clinicopathological study of cutaneous manifestations due to multitargeted kinase inhibitor therapy. *Br J Dermatol* 2008;158:592-6.
- Macedo LT, Lima JP, dos Santos LV, Sasse AD. Prevention strategies for chemotherapy-induced hand-foot syndrome: A systematic review and meta-analysis of prospective randomised trials. *Support Care Cancer* 2014;22:1585-93.

### Access this article online

#### Quick Response Code:



Website: [www.idoj.in](http://www.idoj.in)

DOI:  
10.4103/2229-5178.164488