

## CAPECITABINE INDUCED HAND-FOOT SYNDROME

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Sir,

The hand-foot syndrome, also known as palmar-plantar erythrodysesthesia is a relatively common adverse effect of some chemotherapeutic drugs. 5-Fluorouracil, capecitabine, doxorubicin, docetaxel, idarubicin, and cytarabine are the most frequently involved agents.<sup>1</sup> This syndrome is clinically characterized by the gradual onset of bilaterally symmetric erythema, tenderness, tingling, numbness and desquamation over the palms and soles. Here we report a case of HFS along with keratoderma on capecitabine therapy for colorectal cancer. As clinical dermatologists, we should be aware of the cutaneous adverse effects of common chemotherapeutic agents which would help in timely diagnosis and management.

A 52 year old male presented to our outpatient department with 6 months history of darkening and thickening of skin of palms and soles associated with swelling and pain [Fig 1,2]. On detailed history, patient revealed taking chemotherapy for stage II colorectal adenocarcinoma (T2N0M0), which was operated upon 6 months back.



Fig. 1



Fig. 2

**Figure 1,2:** darkening and thickening of skin of palms and soles After the surgery patient was started on oral capecitabine in

cycles of 14 days with 1 week gap in between cycles. The dose of capecitabine was slowly increased from 1500 mg to 2500 mg daily during this period. After 2 cycles of chemotherapy patient started to developed painful tingling sensation over palms and soles followed by desquamation, erythema, hyperpigmentation and stiffness of skin, affecting his daily routine activities.

On clinical examination, patient had erythema, keratoderma and desquamation of palms and soles, and dorsa of fingers, associated with dysaesthesia. Patient refused biopsy of the skin of hand or feet. He was clinically diagnosed as a case of grade 2 HFS induced by capecitabine. Patient was treated with topical steroids, emollients and reduction of dose of capecitabine, and showed significant improvement within 3 weeks.

Hand foot syndrome (HFS), also called palmar-plantar erythrodysesthesia, is a cutaneous toxic reaction to several chemotherapeutic drugs. It was first reported by Zuehlke in 1974.<sup>2</sup> Most common drugs implicated are 5-FU, Capecitabine, cytarabine, doxorubicin, epirubicin, high dose interleukin-2, fluorodeoxyuridine, hydroxyurea, mercaptopurine, cyclophosphamide and Docetaxel.<sup>1</sup> The orally administered prodrug capecitabine is converted to 5-fluorouracil by the body. It is FDA approved for adjuvant treatment of colon cancer, metastatic colorectal cancer, and metastatic breast cancer. The hand-foot syndrome is a well-defined adverse effect of capecitabine; others being diarrhoea, nausea, and suppression of the bone marrow.

Histopathological changes include vacuolar degeneration of basal keratinocytes, dermal perivascular lymphocytic infiltration, apoptotic keratinocytes and dermal edema.<sup>3</sup>

The pattern of presentation appears to be drug-dose dependent. Several theories have been suggested regarding pathogenesis of HFS. The chemotherapeutic drugs secreted through sweat ducts accumulate and cause local direct damage to the keratinocytes. This theory explains the localization of the cutaneous changes to the hands and feet.<sup>4</sup> Some hypothesize increased expression of metabolizing enzyme thymidine phosphorylase that converts capecitabine to 5 fluorouracil and increases toxic injury to the tissue.<sup>4</sup>

The manifestations of HFS are classified into 3 grades according to their severity by the National Cancer Institute Cancer Therapy Evaluation Program.<sup>5</sup> Grade 1 shows erythema of lateral aspects of fingers, progressing to thenar and hypothenar eminences, with swelling, numbness, dysesthesia/paresthesia, and tingling, especially over the pads of distal phalanges. A similar picture may also be seen on the feet. However, this does not interfere with the patient's normal daily activity. Grade 2 shows a progression of manifestations of grade 1, with the pain,

tenderness and discomfort affecting daily activities. In grade 3, along with severe pain, there is also development of blisters, moist desquamation and ulcer formation.<sup>6</sup>

Along with HFS our patient also presented with palmoplantar keratoderma which has not been mentioned in the grading. It has been suggested that keratoderma can develop during capecitabine chemotherapy as a sequential event of HFS.<sup>7</sup>

Treatment includes cold compresses, topical emollient, antibiotics to prevent secondary infection, topical steroid, oral pyridoxine<sup>8</sup> and topical retinoids<sup>9</sup> in mild to moderate cases. Severe cases may require reduction of dose or discontinuation of the drug. In such cases, capecitabine may be cautiously re-introduced in a lower dose, which may gradually be stepped up.

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