Case Report

Peculiar Acral and Oral Pigmentation after Docetaxel Therapy: An Unresolved Dilemma

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Abstract

Taxanes, which are widely used chemotherapeutic agents for treating breast carcinoma, are known to cause various cutaneous side effects with incidence as high as 65%. These cutaneous manifestations range from minor nonspecific dermatological manifestations to perplexing atypical manifestations of classic entities such as hand-foot syndrome. We report a case of 51-year-old previously healthy postmenopausal woman diagnosed with T1N1M0 adenocarcinoma breast, on docetaxel adjuvant chemotherapy, who developed peculiar oral and acral violaceous hyperpigmentation. Recognition of this type of presentation as part of HFS or a separate entity is still a debatable conundrum.

Keywords: Hand-foot syndrome, hyperpigmentation, taxanes

Introduction

Docetaxel, a chemotherapeutic agent of Taxane group, has been utilized in the management of breast cancer in adjuvant, neoadjuvant, and metastatic setting.[1] Although well tolerated by majority of patients, various cutaneous adverse events have been reported in literature, including acral erythematous reactions, hand-foot syndrome (HFS), plaque-like erythrodysthesia, erythema multiforme, scleroderma, radiation recall dermatitis, and flagellate erythema.[2] HFS, also known as palmar–plantar erythrodysthesia, is a more severe reaction to docetaxel as well as other cytotoxic chemotherapy agents.[3] We report a case of 51-year-old previously healthy postmenopausal woman diagnosed with T1N1M0 adenocarcinoma breast who on docetaxel adjuvant chemotherapy developed peculiar oral pigmentation which cannot be attributed to pigmentation secondary to extrinsic processes (dental amalgam), intrinsic processes (eg. Peutz jegher's syndrome), iatrogenic causes (smoker's melanosis) or any neoplastic causes. Whether this distinctive hyperpigmentation is a part of classical spectra of HFS observed with anthracycline/antimetabolite or docetaxel-induced HFS should be designated as a separate syndrome is still unclear.

Case Report

After taking consent from a patient who was a 65 year-old postmenopausal woman, operated for estrogen-receptor-positive, progesterone-receptor positive and Her2/neu negative, T1N1M0 adenocarcinoma of the right breast, on neoadjuvant chemotherapy for 3 months, presented to dermatology outpatient department with complaints of asymptomatic hyperpigmentation of the palms and soles accompanied by pigmentation and painful ulceration of oral mucosa. There was no history of any redness, swelling, or pain over these areas. These complaints started 10 days after the first cycle of chemotherapy comprising of docetaxel 80 mg/m² i/v in 5% dextrose along with cyclophosphamide. There was accentuation of hyperpigmentation with each subsequent cycle. Dermatologic examination was done which revealed violaceous to dark-brown hyperpigmentation which could not be explained by any common known patterns like lichenoid drug eruption, exogenous ochronosis or flagellate hyperpigmentation after chemotherapeutics involving both dorsal and ventral aspects (over metacarpophalangeal and proximal interphalangeal joints) of hands [Figure 1] and feet [Figure 2]. Examination of oral cavity showed violaceous hyperpigmentation involving buccal mucosa, palate, tongue, and floor of the mouth [Figure 3]. Longitudinal melanonychia...
investigations, including complete blood count, liver function test, renal function tests, thyroid profile, serum vitB12, and cortisol levels. On dermoscopy, homogeneous yellowish-brown pigmentation without melanocytic or vascular structure was present. Patient was managed conservatively with emollients. Oral ulceration was managed with anesthetic oral gel along with maintenance of oral hygiene. On follow up, pigmentation faded gradually over 6 months after the completion of chemotherapy.

**DISCUSSION**

Taxanes are a group of chemotherapeutic agents that act as mitotic inhibitors. Like many other antineoplastic drugs, they have various toxicities that include myelosuppression, neuropathies and mucocutaneous manifestations like palmpoplantar erythrodysaesthesia erythema multiforme, scleroderma, radiation recall dermatitis, nail changes, palmpoplantar desquamation, and HFS. The incidence of docetaxel-induced cutaneous adverse effects varies significantly across published studies (6%–67%) depending on the dose intensity, dosing frequency, premedication regimen, and cumulative dose.

Currently, the mechanism of docetaxel-induced skin toxicity is still debatable. Few suggest a direct toxic effect of either docetaxel or polysorbate −80, the vehicle for docetaxel on keratinocytes due to their rapid turnover rate. Other theories on etiopathogenesis state that HFS-related chemotherapeutic agents are excreted through the sweat glands which are in high density over palms and soles. It was observed that lack of premedication with dexamethasone, concomitant use of H2-receptor blockers and other chemotherapeutic drugs which alter CYP 3A4 enzyme levels may result in higher incidence of HFS.

Our patient has also received cyclophosphamide which can also result in hyperpigmentation. There are numerous reports of pigmentation in taxane-cyclophosphamide regimen. However, Kumar et reported cyclophosphamide induced pigmentation after 6 cycles of cyclophosphamide-containing chemotherapy suggesting that it may occur after many days of cyclophosphamide therapy. Our patient developed acral and perioral pigmentation after 10 days of first cycle of docetaxel therapy which can be attributed more to docetaxel than cyclophosphamide. Similarly, HFS is more commonly seen with drugs such as 5-FU, capecitabine, pegylated liposomal doxorubicin, and cytarabine. Cyclophosphamide alone causing typical or atypical HFS is not known to the best of our knowledge. Classical clinical presentations of HFS in the form of dysesthesia, tingling sensation, erythema over the palms and soles eventually leading to painful vesiculation, edema, and desquamation has been reported with various cytotoxic chemotherapy agents (5-Fluorouracil and its oral prodrug, capecitabine, cytarabine, doxorubicin, epirubicin, docetaxel, hydroxyurea, and mercaptopurine).

Variations in the spectrum of clinical presentation of HFS observed so far include keratoderma-like thickening,
longitudinal melanonychia, sclerodermoid skin changes, and painful fissured eczematous eruption.[10] In the present case, 10 days after docetaxel therapy, patient developed asymptomatic, and hyperpigmentation over acral areas with oral and nail involvement. The pigmentation resolved within 6 months of cessation of docetaxel, thereby corroborating the causative agent as docetaxel. This pattern of asymptomatic hyperpigmentation has not been mentioned so far in any grade of HFS. Thus it is still not clear whether to name this type of adverse effect to docetaxel therapy as HFS or it deserves to be renamed as separate entity. The pathophysiology of chemotherapy-induced HFS remains unknown. Few case reports in literature have documented atypical presentations of HFS. Saif and Sandoval reported asymptomatic hyperpigmentation of palms alone in an African patient treated with capecitabine.[11] Cases of corneal hyperpigmentation and scrotal involvement along with acral palmar-plantar erythrodysesthesia have been reported.[12] Atypical case of HFS with oral and acral hyperpigmentation has been reported after capecitabine therapy. It is still an enigma whether docetaxel-induced hyperpigmentation versus antimitabolite-induced HFS should be regarded as same entity or separate nomenclature should be reserved for this type of presentation.

Thus, we report a case of atypical HFS possibly due to docetaxel therapy with peculiar feature of perioral pigmentation.

**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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