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Drug induced periarticular thenar erythema with onycholysis related to nano-albumin bound paclitaxel therapy

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ABSTRACT

Introduction: A rather rare hypersensitivity reaction, periarticular thenar erythema with onycholysis (PATEO) syndrome, has been associated with the taxane class. To date, only docetaxel and paclitaxel have been associated with PATEO. This current case is highly suggestive of an association of nab-paclitaxel with PATEO.

Presentation of case: A 48 year-old female receiving first-line systemic therapy using nanoparticle albumin-bound paclitaxel (nab-Paclitaxel) for metastatic breast cancer developed a dark erythema on the dorsal surface of both hands and excoriation of the skin of the palmar surfaces of both hands which worsened despite continuing daily topical triamcinolone 0.1% ointment. Skin tightness, along with significant pain, resulted in difficulty ambulating. The rash was diagnosed as PATEO by the Dermatology consult service. Hydrocortisone 2.5% cream applied twice daily and mupirocin 2% cream applied three times daily was prescribed and subsequently nab-paclitaxel was discontinued.

Discussion: PATEO is clinically distinct from traditional palmar-plantar erythrodysesthesia (hand foot syndrome) associated with anthracyclines, antimetabolites, or multikinase inhibitors with unique clinical manifestations. The erythema in PATEO appears on the dorsum of the hand as opposed to the palmar surface and around the metacarpal joints. In addition, the thenar eminence and periarticular area of the Achilles tendon are often involved with erythema and violaceous plaques which may blister. Nail changes including discoloration, paronychia, onycholysis and exudation are observed in more severe cases.

Conclusion: This case study suggests PATEO may also be induced by the taxane molecule in the protein bound formulation and may be a risk for all patients receiving taxane therapies.

1. Introduction

A previously healthy 48 year-old female presented to the emergency room with sudden onset aphasia and seizure. Work-up included head computed tomography (CT) imaging, which revealed a 2 cm left frontoparietal mass. Subsequent brain magnetic resonance imaging (MRI) showed at least 4 enhancing foci, the largest of which was in the left lateral parietal lobe measuring 2.1 cm × 2.2 cm × 1.9 cm with marked vasogenic edema.

The patient also had a right breast mass, and right breast ultrasound was performed, revealing a 2 cm × 2.4 cm × 2.1 cm mass and a suspicious right axillary lymph node. Ultrasound-guided biopsy of the mass was performed producing a diagnosis of invasive ductal carcinoma with focal lobular features, grade 2, estrogen receptor and progesterone receptor negative, human epidermal growth factor receptor 2 negative by fluorescence *in situ* hybridization. A CT/PET scan was ordered which showed foci of increased uptake in the brain parenchyma, liver, and skeleton. The patient's final diagnosis was T2N1M1 stage IV breast cancer with brain, skeletal, and hepatic involvement.

Three weeks after stealth guided left parietal craniotomy and excision of the parietal brain mass, the patient initiated first-line systemic therapy using nanoparticle albumin-bound paclitaxel (nab-paclitaxel) at a dose of 150 mg/m^2 intravenously weekly on days 1, 8, and 15 of a 28 day cycle. The patient tolerated three doses of chemotherapy fairly well, with toxicities limited to significant fatigue.

After the first three doses of nab-paclitaxel, the patient noted dark erythema on the dorsal surface of both hands and excoriation

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of the skin of the palmar surfaces of both hands. She was prescribed topical triamcinolone 0.1% ointment with directions to apply daily to help treat these symptoms. Subsequently, the fourth dose of nab-paclitaxel was held. She resumed treatment a week later and received three more weekly doses of nab-paclitaxel. Her last dose of nab-paclitaxel was dose reduced by 20% due to the rash. During this time, the rash continued to worsen, spreading to her upper extremities and posterior thighs, despite continuing daily topical triamcinolone 0.1% ointment. In total, she received six doses of nab-paclitaxel. Her chemotherapy was then held while receiving whole-brain radiation therapy and radiation to a left hip metastasis.

Two weeks later, the patient presented with a significant worsening of her rash. The patient described the rash as her skin feeling tight, along with significant pain, resulting in difficulty ambulating. Erythema was present on the dorsal aspects of her hands, especially prominent over the joints as well as the thenar eminence (Fig. 1). There was similar erythema with exfoliative scale on the extensor and flexural crease of the elbows, anterior neck, dorsal feet, buttocks, and popliteal areas (Figs. 2 and 3). A number of areas within the rash had blistered and were open. Her fingernails were all affected by distal onycholysis. The patient reported profound weakness and fatigue.

Dermatology consultation was obtained, and the rash was diagnosed as periarticular thenar erythema with onycholysis (PATEO). The patient was prescribed hydrocortisone 2.5% cream to be used on all involved skin areas twice daily and mupirocin 2% cream to be applied three times daily to all open sores which was continued until resolution of the rash. Nab-paclitaxel was discontinued.

2. Discussion

Microtubules are involved in the assembly of the protein tubulin which is a crucial component in cellular mitosis. By inhibiting the action of microtubules, mitosis is halted and apoptosis is rapidly induced. Antimicrotubule agents are a broad pharmacologic class of cytotoxic therapies which include the taxanes: docetaxel, paclitaxel, nab-paclitaxel, and cabazitaxel. The primary mechanism of action of taxanes is to cause disruption of microtubule function. This disruption is accomplished by promoting the assembly of microtubules from the tubulin dimers and then stabilizing guanosine diphosphate-bound tubulin in the microtubule, preventing depolymerization. The resulting stability will cause an inhibition of reorganization of the microtubule network, causing the loss of mitotic cellular functions [1,2].

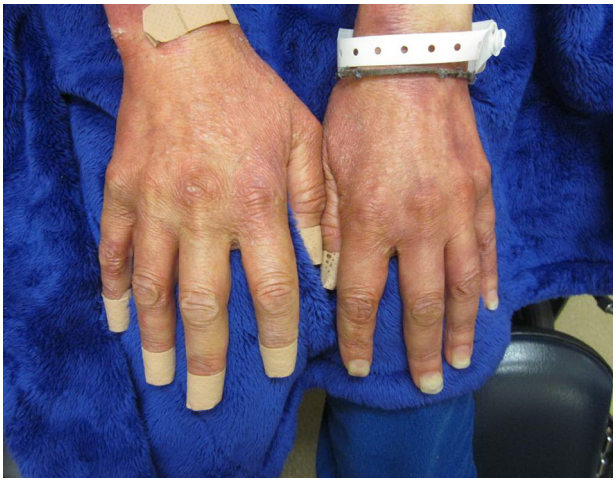

Fig. 1. Erythema on dorsal hands/joints and distal onycholysis.

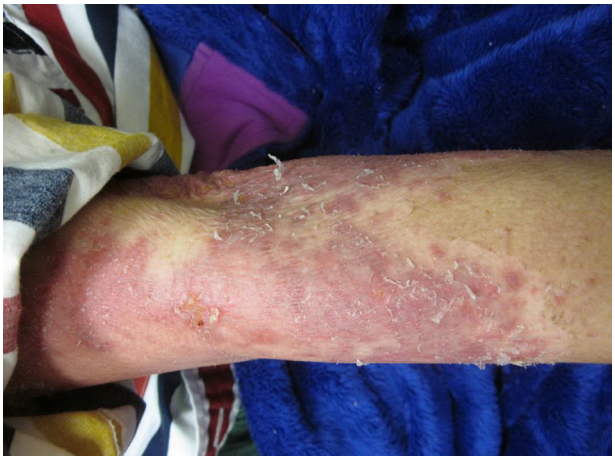

Fig. 2. Erythema with exfoliative scale on extensor and flexural crease of left arm and elbow.

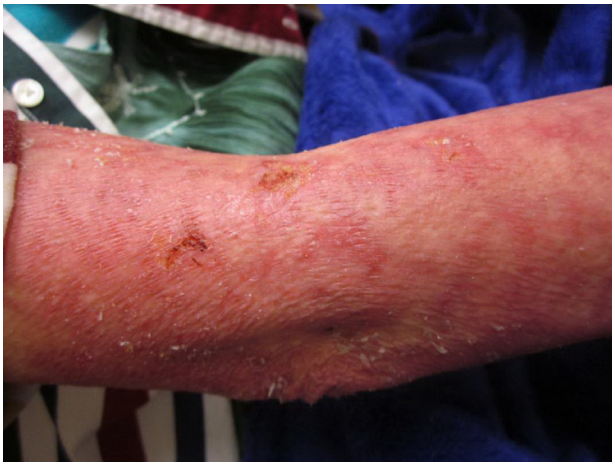

Fig. 3. Erythema with exfoliative scale on extensor and flexural crease of right arm and elbow.

Paclitaxel is associated with numerous skin toxicities including radiation recall dermatitis, erythema multiforme, painful nail changes, and reversible alopecia [3]. Similar to paclitaxel, dermatologic toxicities are also common with docetaxel; for example, localized erythema of the extremities, coupled with edema has been observed [4].

Nail changes are another side effect associated with the taxane class. Chemotherapy-induced nail toxicity is not only a significant cosmetic concern, it is also associated with pain, infection, and can impact a patient's quality of life. Onycholysis is commonly seen with docetaxel and paclitaxel [5]. The overall incidence of onycholysis with the taxanes ranges from 0% to 44% and is more commonly seen with docetaxel [5].

In contrast to the other taxanes, nab-Paclitaxel is a solvent-free formulation that does not require the use of Cremphor EL® for intravenous administration. Nab-paclitaxel is associated with dermatologic reactions such as generalized skin irritation coupled with spotty areas of skin eruption on the trunk, limbs, and face in up to 30% of patients. There have been case reports of patients reporting a grade 3 macular and papular rash 1–7 days following chemotherapy [6,7,8]. Additionally, mild pigmentation or discoloration of the nail bed is a frequent side effect reported in patients who receive nab-paclitaxel.

A rather unique hypersensitivity reaction termed PATEO syndrome has been associated with the taxane class. PATEO is