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SHORT COMMUNICATION

Development of cutaneous squamous cell carcinoma after prolonged exposure to pegylated liposomal doxorubicin and hand–foot syndrome: a newly recognized toxicity

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Abstract

Pegylated liposomal doxorubicin (PLD) can be administered for prolonged periods with minimal toxicity. The risk of cutaneous squamous cell carcinoma (SCC) with this therapy has not been reported. We describe cutaneous SCC of the plantar foot in two patients exposed to high doses of PLD. A 50-year-old man with angiosarcoma received a total PLD dose of 1350 mg/m^2 and developed cutaneous SCC of bilateral plantar feet. A 45-year-old woman with cutaneous T-cell lymphoma was treated with a total PLD dose of 1142 mg/m^2 with subsequent diagnosis of cutaneous SCC of the right plantar foot. No risk factors for SCC of the plantar foot were identified in either patient. Cutaneous SCC is likely an unreported side effect of prolonged exposure to PLD. An extended duration of hand–foot syndrome from other anti-cancer drugs may also share this risk. Regular complete skin examination with early intervention for suspicious lesions is indicated in this patient population.

Keywords Pegylated liposomal doxorubicin · Doxorubicin · Sarcoma · Lymphoma · Drug-related side effect

Introduction

Hand–foot syndrome (HFS) is a common toxicity of several anti-cancer drugs, including capecitabine, pegylated liposomal doxorubicin (PLD), and several tyrosine kinase inhibitors (TKIs). The mechanism of HFS is likely due to the drug or its metabolites accumulating in the skin causing keratinocyte injury [1, 2]. HFS is associated with local inflammation. Since chronic inflammation may result in malignancy, this may also be relevant in some patients with prolonged HFS if survival allows. PLD has efficacy in a number of malignancies including ovarian cancer, breast cancer, and soft tissue sarcoma [3–5]. Though mechanistically similar to other anthracyclines that as a class have dose-limiting cardiotoxicity, the pegylated liposomal formulation reduces drug accumulation in cardiac tissue and allows for higher cumulative dosing [6, 7]. PLD is generally well tolerated with the usual dose-limiting toxicities being mucositis or HFS; myelosuppression is uncommon and anti-emetics are rarely needed. Here we describe two cases of cutaneous squamous cell carcinoma (SCC) of the plantar foot after extended PLD exposure, the first report of this associated toxicity.

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Case 1

A previously healthy 50-year-old man presented with chest discomfort and shortness of breath. Evaluation revealed a bloody pericardial effusion. Surgical resection of an atrial mass was required because of ongoing bleeding, and pathologic examination showed angiosarcoma.

After surgery, he received adjuvant paclitaxel for 6 months until disease progression. Therapy was changed to PLD 45 mg/m^2 every 4 weeks, and a good response was achieved. PLD was continued for a total of 30 cycles (total dose = 1350 mg/m^2), at which point treatment was stopped because of classic HFS that required occasional dose delays, especially in the feet. Examination showed hyperkeratotic papules and plaques with central ulceration on both heels. Three months after his last dose of PLD, a punch biopsy of the right heel showed in situ SCC. The lesion was treated with Mohs surgery, with pathology showing well-differentiated SCC (Fig. 1a).

Four months later, a punch biopsy of the left heel showed in situ SCC along with hypertrophic actinic keratosis of the left arch (Fig. 1b, c). Additional biopsies obtained of hyperkeratotic lesions on both palms were negative for malignancy, showing palmar keratosis (Fig. 1d). The patient

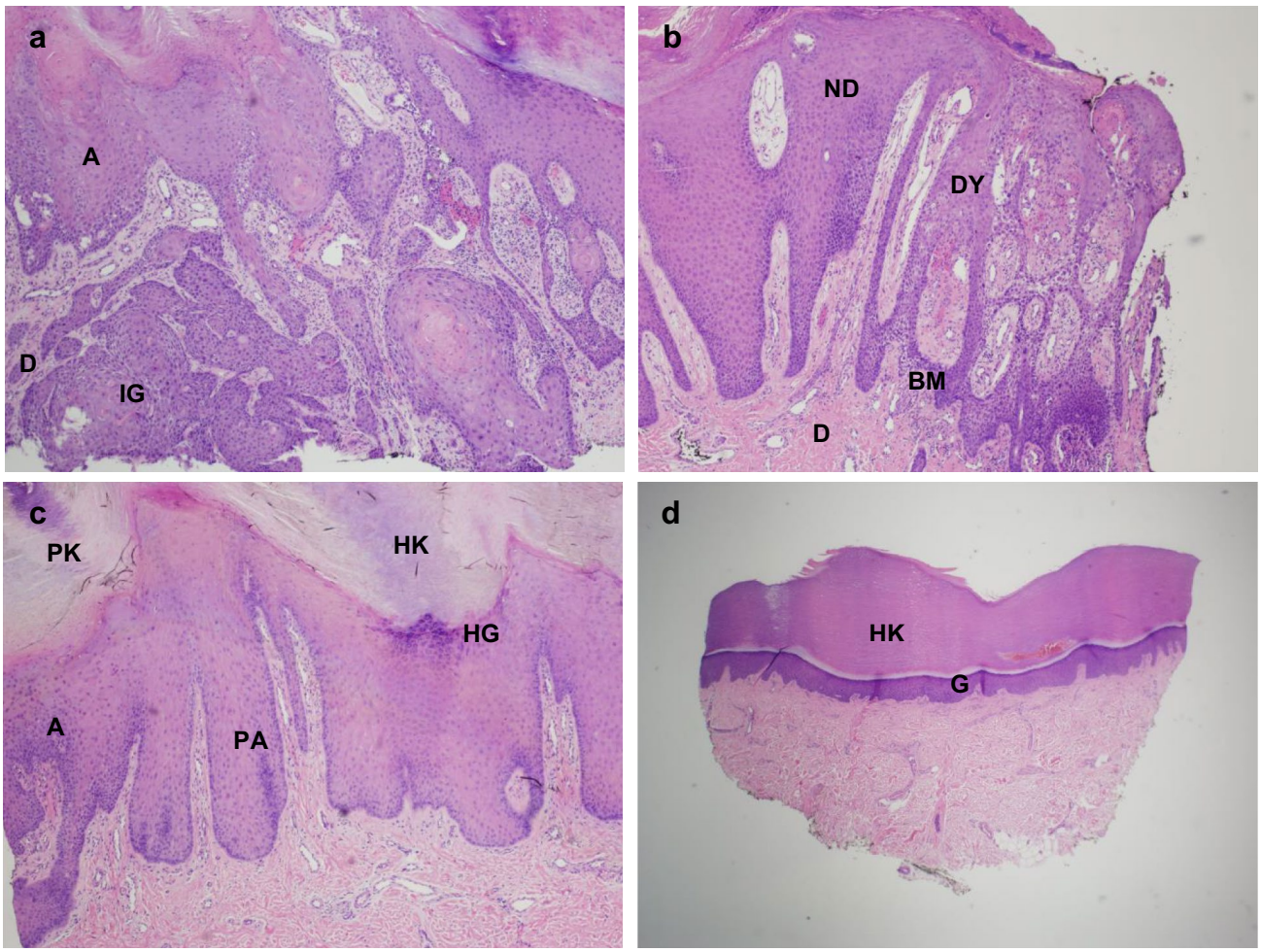

Fig. 1 Case 1, cutaneous squamous cell carcinoma (SCC) and premalignant lesions. **a** SCC, right heel. An irregular atypical proliferation of the epidermis is seen with acanthosis (A) and failure of keratinocyte maturation. The epidermis extends as irregular groups (IG) and nests of epithelium into the dermis (D). Cytologically, hyperchromasia, pleomorphism and mitoses are present. **b** SCC in situ, left heel. Abrupt transition from non-dysplastic epidermis on left (ND) to full thickness epidermal dysplasia on right (DY) characterized by hyperchromatic and pleomorphic nuclei. The dysplastic epidermis extends laterally to the edge of the biopsy but does not extend deep, leaving the basement membrane (BM) and dermis (D) intact. **c** Actinic keratosis, left arch. Prominent hyperkeratosis (HK) and parakeratosis (PK) is associated with papillomatous acanthosis (PA) and focal hypergranulosis (HG). Focal loss of maturation progression is present, and occasional keratinocytes appear atypical (A) with hyperchromatic nuclei. **d** Palmar keratosis, right palm. Hyperkeratosis (HK), predominantly compact orthokeratotic in nature. The epidermis demonstrates light acanthosis with preservation of the granular layer (G). **a**–**c** H&E-stained section, 4× magnification. **d** H&E-stained section, 2× magnification

was treated with acitretin and photodynamic therapy, with improvement in keratosis over the next year.

After 2 years of stable disease not requiring therapy for angiosarcoma, he had progression in the right atrium and again had surgical resection. Hyperkeratotic papules on the hands and feet persisted, though no evidence of malignant transformation occurred. A year later, he developed liver metastases from angiosarcoma, and PLD was restarted. This treatment was continued for an additional 12 months with good response (total lifetime dose of PLD = 1775 mg/m^2). Disease then progressed with widespread metastases to the bones, lungs, and brain; he was treated with several chemotherapy regimens before enrolling in hospice.

Case 2

A 45-year-old previously healthy woman presented with pruritic, waxing and waning crusting plaques on the central face and extremities. Biopsy showed cutaneous T-cell lymphoma (CTCL), folliculocentric type, and evaluation for systemic disease was negative. She had improvement with skin-directed therapy of bexarotene gel, psoralen and ultraviolet-A light, and electron beam radiation to the larger lesions.

Two years after diagnosis she abruptly developed a more diffuse and intensely pruritic rash. Skin biopsy showed disease transformation to a CD30-positive large cell lymphoma, and chemotherapy with cyclophosphamide, vincristine, and prednisone (CVP) was initiated. After initial improvement her symptoms would recur late in each cycle, demonstrating kinetic failure of CVP. Therefore, doxorubicin was added. Because of its longer half-life, lower cardiotoxicity, and less myelosuppression, PLD was substituted for doxorubicin in the 4th cycle at a dose of 20 mg/m^2 every 2 weeks. She completed five cycles of CVP plus PLD with an excellent response, then transitioned to narrowband ultraviolet-B (UVB) light three times weekly as maintenance therapy.

After 4 months on maintenance narrowband UVB, her disease relapsed with worsening skin lesions. PLD was started and she received 34 cycles with occasional dose delays for HFS symptoms manifest mostly as oral mucositis with some mild skin symptoms mostly on the soles of the feet. Therapy was eventually changed to the CD30 monoclonal antibody brentuximab and continued for 26 cycles until the development of significant neuropathy.

After briefly resuming PLD, she noted a right lateral tongue ulcer. A biopsy showed invasive SCC, and PLD was discontinued. She had a right partial glossectomy and neck dissection, with adjuvant radiation for pathologic stage II (T2N0M0) oral cavity SCC.

Three months after surgery, nearly 6 years after starting PLD, a painful hyperkeratotic papule on her right heel was biopsied and showed an invasive, well-differentiated SCC (Fig. 2). This was treated with Mohs surgery. Her lymphoma then progressed while on brentuximab, and several months later she enrolled in hospice.

Discussion

An association between PLD and cutaneous SCC has not, to our knowledge, been described. The detection of PLD in sweat glands and upper layers of the skin several hours after infusion is a proposed mechanism of the HFS caused by PLD [1]. Whether chronic inflammation associated with HFS or a direct toxic effect of PLD on keratinocytes is more important in the development of cutaneous SCC in our patients is unknown. Cases of cutaneous SCC with sorafenib, which also causes HFS, have been reported [8–10]. These cutaneous effects are not observed with bolus-free doxorubicin, as the biodistribution of PLD favors accumulation in skin because of increased circulatory time and hydrophilic liposomes accessing the sweat glands [1, 2].

Prolonged treatment with PLD has been associated with the development of secondary oral mucosal SCC in a number of case reports, including patients treated for ovarian carcinoma [11] and uterine carcinoma [12]. Importantly, none of the patients had a smoking history. Our patient in this report with SCC of the tongue also was a non-smoker.

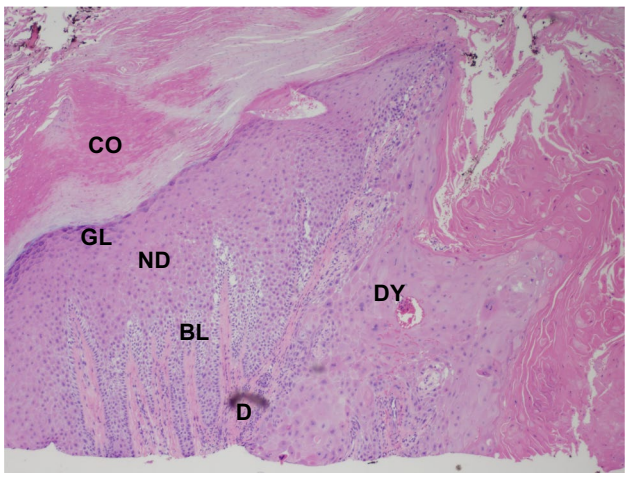

Fig. 2 Case 2, invasive well-differentiated squamous cell carcinoma, right heel. H&E-stained section, 4× magnification. Non-dysplastic (ND) squamous epithelium on the left showing intact maturation from basal layer (BL) to granular layer (GL) and covered by compact orthokeratosis (CO) typical of plantar skin. There is abrupt transition to dysplastic (DY) eosinophilic epidermal cells that proliferate downward to invade the dermis (D) and extend to the base of the specimen (deep margin)

This lends support for PLD as a potential etiology of her oral cavity SCC, although XRT to the right face 6 years earlier was an additional risk factor.

The cumulative doses of PLD in our patients before the development of SCC were 1350 mg/m^2 and 1142 mg/m^2 respectively, indicating that, similar to the reported associated cases of oral SCC, prolonged administration is necessary. After the diagnosis of cutaneous SCC, both patients received additional PLD without development of further SCC; however, their limited survival time after the events precludes assessment on the safety of continuing PLD after a diagnosis of SCC.

Cutaneous SCC is a common malignancy and generally non-invasive, although about 2% of cases metastasize locally and distantly [13]. The incidence has increased over the last several decades, likely from higher lifetime solar UV light exposure in an aging population [14]. Known iatrogenic causes of cutaneous SCC include immunosuppressive therapy for solid organ transplant, external radiation therapy (XRT), and the BRAF inhibitors vemurafenib and dabrafenib [15–17].

The unusual location on the plantar foot in both cases argues against an etiology related to UV light exposure. Chronic arsenic exposure, usually by use of traditional Chinese topical remedies or through well water contamination, is associated with hyperkeratosis and SCC of the palms and feet [18]. Neither of the patients presented here had a known history of arsenic exposure although the long latency period makes this difficult to completely exclude. Both patients received other chemotherapy agents, though none are associated with cutaneous SCC and case 1 only had paclitaxel before starting PLD.

The hyperkeratotic lesions on the palms and soles in case 1 are not a previously described skin reaction to PLD [2]. Whether hyperkeratosis is a precursor lesion to SCC, which seems likely given the presence of premalignant hypertrophic actinic keratosis, deserves further investigation.

The cases reported here call attention to the need for patients with long-term exposure to PLD to have regular oral cavity examinations along with complete skin examinations, including in non-sunlight-exposed areas, to screen for the potential complications of oral cavity and cutaneous SCC. This also raises the question as to whether prolonged HFS due to other anti-cancer drugs, in addition to sorafenib, may also be associated with an increased risk of cutaneous SCC.

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Compliance with ethical standards

Conflict of interest The authors have no potential conflicts of interests to report.

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