Intertriginous Rash Caused by Pegylated Liposomal Doxorubicin

B. Monteagudo,[a] F.J. Afonso-Afonso,[b] M. Cabanillas,[a] and M.M. Used-Aznar[c]

[a]Servicio de Dermatología, [b]Servicio de Oncología, [c]Servicio de Anatomía Patológica, Complejo Hospitalario Arquitecto Marcide-Novoa Santos, Ferrol, A Coruña, Spain

To the Editor:

Doxorubicin is a chemotherapy agent of the anthracycline group. It is effective in many solid and hematological tumors, although use is limited by adverse effects—above all cardiotoxicity and myelosuppression. Use of pegylated liposomal doxorubicin (PLD) has recently become more common as it is effective against Kaposi sarcoma and ovarian cancer. This form of the drug has fewer adverse effects, but marked cutaneous toxicity still limits the dosage prescribed.[1] Common cutaneous reactions include palmoplantar erythrodysesthesia ("hand-foot" syndrome)[2,3] and stomatitis, and a diffuse follicular eruption or intertriginous rash is also highly characteristic of PLD use.[4,5]

We present a new case of an intertriginous rash caused by PLD in a 53-year-old woman with a history of clear cell ovarian cancer and histopathology findings that indicate epidermal dysmaturation. Only 3 similar cases including histopathological studies have been found in the dermatological literature.[6-8]

The patient was a 53-year-old woman with a history including depression, fibrocystic breast disease, lumbar and sciatic pain from herniated discs L4-L5 and L5-S1, cholecystectomy, and appendectomy. She was admitted for left popliteal deep vein thrombosis. Abdominal-pelvic computed tomography (CT) revealed a lobulated mass was observed in the pelvis minor with cancer antigen (CA) 15.3 levels of 189.4 U/mL (normal values: 0.0-38.6 U/mL) and CA 125 levels of 23.5 U/mL (normal values: 0.0-30.0 U/mL). A total hysterectomy, double adnexectomy, and partial omentectomy were performed. A left adnexal tumor of 8 cm in diameter was found and histopathology showed a poorly differentiated clear cell carcinoma. The postsurgical thoracic abdominal and pelvic CT was normal, but CA 15.3 values of 54 U/mL were found. As this was a stage 1A cancer, adjuvant chemotherapy was initiated with 4 cycles of paclitaxel and carboplatin, but CA 15.3 levels rose to 72 U/mL. A further CT was normal, but the positron emission tomography showed an area of intense uptake suggestive of an adenopathic conglomerate in the paraaortic region. A new course of therapy was started with PLD 50 mg/m^2 every 4 weeks. Three weeks after the second cycle of PLD the patient developed a pruriginous rash in the skin folds that was treated with 0.1% methylprednisolone aceponate emulsion for 10 days. The patient consulted at this point, presenting hyperpigmented plaques with scaly erythematous erosive and crusty areas on the axillas, groin, and waist (Figure 1).

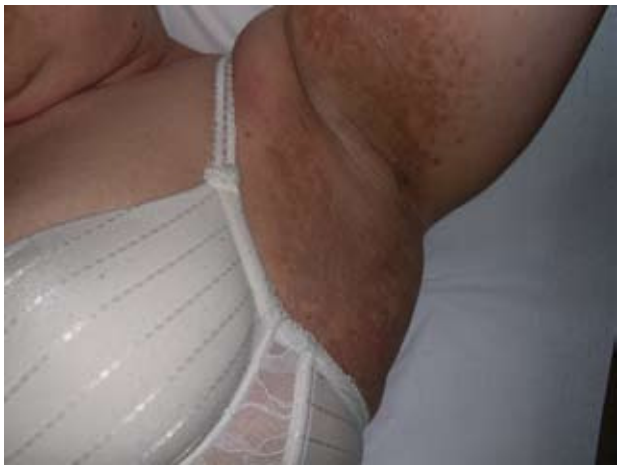

Figure 1. Scaly, erythematous and erosive areas on the left axilla.

A biopsy was taken from one of the lesions in the left axilla showing discrete hyperkeratosis and papillomatosis of the epidermis. There was a noticeable increase in size of the keratinocytes in the basal layer and middle layers, with enlarged atypical nuclei, occasional double nuclei, prominent nucleoli, and mitosis. Inflammatory infiltrate was present in a perivascular distribution in the middle papillary dermis. The infiltrate consisted of lymphocytes and scant neutrophils. This was in contact with the basal layer in some areas causing discrete disruptions and even penetrated into the epidermis in small groups (Figures 2 and 3).

A diagnosis was made of intertriginous rash with interphase dermatitis and epidermal dysmaturation caused by PLD, and treatment with the drug was continued at a reduced dosage of 40 mg/m^2. There was no recurrence of the complaint following the third infusion.

PLD frequently causes cutaneous toxicity. The most common reaction is palmoplantar erythrodysesthesia. This occurs in a third of all patients and consists of the development of erythematous lesions on the palms and plantar surfaces, accompanied by a sensation of dysesthesia.[2,3] There can also be a recall reaction in areas were sunburn, radiotherapy, or extravasation of cytostatic agents has occurred previously. Other reported effects include

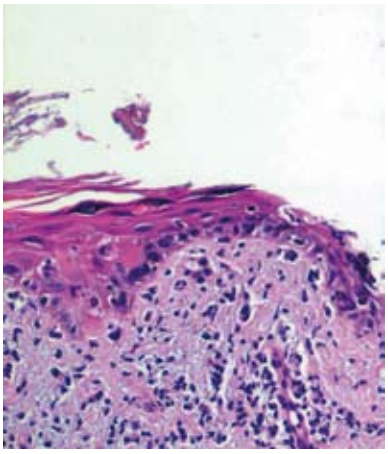

Figure 2. Epidermal cytological atypia and inflammatory infiltrate in the dermis (hematoxylin-eosin, ×400).

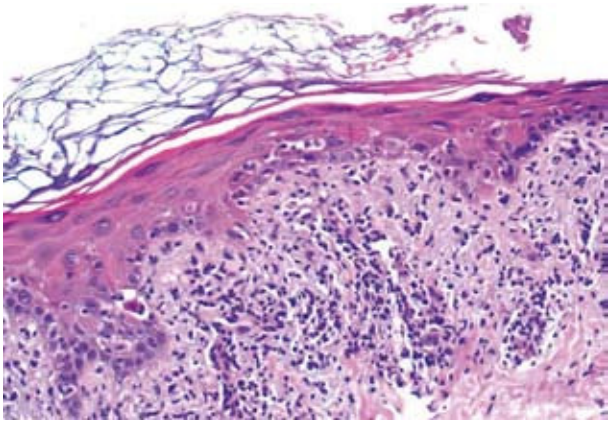

Figure 3. Apoptotic keratinocytes and inflammatory infiltrate in the dermis (hematoxylin-eosin, ×200).

the formation of new melanotic macules, stomatitis, or a diffuse symptomatic follicular eruption predominantly on the lateral surface of the extremities or trunk.[4,5] The histopathology in the latter case generally shows vacuolization of the basal layer and a lymphocytic infiltrate in the papillary dermis.

Although there are many reported cases of PLD inducing a similar intertriginous rash,[4,5] we have only found 3 articles describing the histopathological findings (Table).[6-8] The condition is denoted "dermatitis or an intertrigo-like eruption" in order to distinguish it as an independent morphological entity, even though the pathogenic mechanism may be identical to that of "hand-foot syndrome."[5,8] Erythematous plaques appear several weeks after the last infusion in all cases of treatment with PLD, often producing bilateral erosive, pruriginous or painful areas on the axillas, groin, and areas of friction with clothing. Histopathological study shows an interphase reaction with epidermal dysmaturation (cytological atypia with apoptotic/dyskeratotic keratinocytes). Epidermal dysmaturation often presents during treatment with other chemotherapy agents like cyclophosphamide,[10] and there have been many cases published recently of PLD-induced rashes with this histological pattern.[7,11] As in our case, reducing the drug dosage resolved the skin lesions leaving some residual postinflammatory hyperpigmentation but no subsequent recurrence.[6-8]

Correspondence:
Benigno Monteagudo Sánchez,
C/ Alegre, 83-85, 3.ºA,
15401 Ferrol, A Coruña, Spain
benims@hotmail.com

Conflicts of Interest
The authors declare no conflicts of interest.

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Table. Patients With Intertriginous Rash Caused by PLD and Histopathological Study

Reference	*Age/Sex*	*Cancer*	*Interval*[a]	*Site*	*Histologic Findings*
Skelton et al[6]	83 years/W	Ovary	21 days	Axillas and groin	Interphase dermatitis and apoptotic keratinocytes
English III et al[7]	64 years/W	Ovary	11 days	Axillas, side of breasts, and groin	Interphase dermatitis and apoptotic keratinocytes
Korver et al[8]	60 years/W	Breast	14 days	Axillas, groin, lower abdomen, and oral mucosa	Interphase dermatitis and dyskeratotic keratinocytes
Monteagudo et al (present case)	53 years/W	Ovary	21 days	Axillas, groin, and lower abdomen	Interphase dermatitis and dyskeratotic keratinocytes

[a] Interval between the last infusion of the drug and appearance of the rash.
W: woman.

mar-plantar erythrodysesthesia ('hand-foot' syndrome). Ann Oncol. 2007;18:1159-64.
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Merkel Cell Carcinoma at a Site of Vaccination

B. Monteagudo,[a] M. Cabanillas,[a] J.A. García-Rego,[b] and J.M. Cacharrón[a]

[a]Servicio de Dermatología, [b]Servicio de Anatomía Patológica, Complejo Hospitalario Arquitecto Marcide-Novoa Santos, Ferrol, A Coruña, Spain

To the Editor:

Adverse skin reactions from vaccination are very varied and can be local or generalized. Immediately after immunization, erythema, edema, pain, and induration may occur exclusively on the site of the injection, and these disappear spontaneously. Less frequently, papules or nodules appear that can persist for months or even years, consisting of nonspecific granulomatous or lymphoid reactions.[1,2]

Various tumors have also been described on the site of vaccine injections: basal cell carcinoma, squamous cell carcinoma, malignant melanoma, malignant fibrous histiocytoma, dermatofibrosarcoma protuberans (including the pigmented variant, Bednar tumor), dermatofibroma, and marginal zone B-cell lymphoma. The delay between vaccination and the appearance of the tumor varies widely, from days in the case of lymphomas, to more than 30 years in many patients with basal cell carcinoma.[3-5]

In this letter we report the case of an 84-year-old man who consulted with a tumor on the right arm that appeared a week after receiving an influenza vaccination in the same location. Histopathological and immunohistochemical studies provided the basis for a diagnosis of Merkel cell carcinoma (MCC).

The patient was an 84-year-old man with a history of Parkinson disease, referred to the Dermatology Department because of a fast-growing asymptomatic lesion in the right deltoid region present for 2 months. According to the patient and his family, the lesion first appeared on the site of the influenza vaccination received a week previously during the 2007 vaccination campaign (trivalent vaccine of inactive and fractionated viruses containing the following antigens: A/Solomon Islands/3/2006 [H1N1]-like strain, A/Wisconsin/67/2005 [H3N2]-like strain, and B/Malaysia/2506/2004-like strain). His physician initially diagnosed an abscess caused by administration of the vaccine, and prescribed oral antibiotics prior to draining.

Examination revealed a hard and poorly defined tumor, measuring 5 cm ×3 cm, located on the external surface of the right arm. The tumor surface showed many violaceous dome-shaped nodules (Figure).

A biopsy was taken to confirm a provisional diagnosis of pseudolymphoma or lymphoma caused by the vaccination and the ensuing histopathological study showed a tumoral infiltration of the dermis by rounded monomorphic cells of medium size with scant cytoplasm, round nuclei, and small nucleoli, forming solid masses or small trabecular structures. The mitotic index was high. Immunohistochemical study proved positive for cytokeratin 20, neuronal specific enolase, chromogranin A, and chromogranin B. There was no immunoreactivity to protein S-100, leukocyte common antigen, CD20, CD3, cytokeratin 7, or thyroid transcription factor 1. A diagnosis of MCC was made and the patient was referred to the Oncology Department.

MCC—first described by Toker in 1972—is a rare malignant cutaneous tumor of neuroendocrinal origin with poor prognosis and rapid progression. It tends to present as a fast-growing nodular erythematous lesion on the head, neck, or limbs in people aged over 65 years.[6,7]

The pathogenesis is unknown although various factors have been implicated: a) ultraviolet radiation—a greater