# Toxic erythema of chemotherapy induced by liposomal doxorubicin, a clinical case

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## Abstract

A 76-year-old woman presented to the medical oncology outpatient clinic with painful, burning, pruritic erythematous plaques involving both palms and axillae that had suddenly appeared five days before. Examination revealed no additional relevant findings and laboratory studies did not show any alteration. The patient had been recently diagnosed with a high-grade angiosarcoma of the breast (probably radiation induced) and after frequent local recurrences, was being treated with liposomal doxorubicin (three cycles were administered, the last of which was seven days before the appearance of the mentioned lesions). Oral corticosteroids were started, treatment with liposomal doxorubicin was stopped, and cutaneous biopsies performed that revealed features compatible with toxic erythema of chemotherapy induced by liposomal doxorubicin. Complete resolution of the cutaneous lesions was verified one month after. No signs of recurrence of angiosarcoma were documented at follow-up three months later.

*Keywords: angiosarcoma, chemotherapy, liposomal doxorubicin, toxic erythema*

## Introduction

Chemotherapy may lead to the development of a wide spectrum of cutaneous manifestations. Palmar-plantar erythrodysesthesia was first described subsequent to treatment with mitotane in 1974 by Zuehlke [1]. During the following decades diverse diagnostic designations have been used to name these chemotherapy-induced cutaneous eruptive lesions until the clinically descriptive term toxic erythema of chemotherapy (TEC) was proposed in 2008 by Bolognia et al. and widely adopted [2]. Hunjan et al. performed the most recent comprehensive review of the clinical and histopathological features of TEC, based on 40 cases of patients who have had the diagnosis of TEC and have undergone allogeneic hematopoietic cell transplantation [3]. We report a 76-year-old woman with a known diagnosis of a radiation-induced breast angiosarcoma, accordingly treated with liposomal doxorubicin (LPD), that developed severe toxic erythema secondary to LPD.

## Case Synopsis

A 76-year-old woman presented to our medical oncology outpatient clinic on the 28th of June 2021

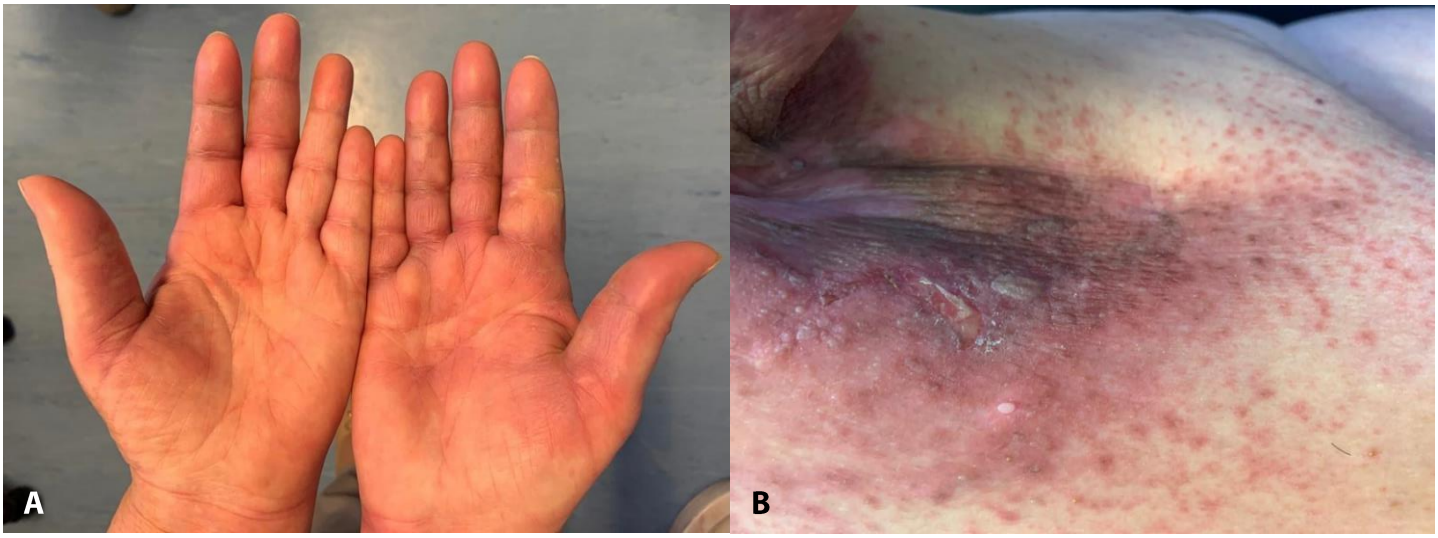


**Figure 1**. *Toxic erythema of chemotherapy induced by liposomal doxorubicin: lesions of the **A)** palms, and **B)** left axilla.*

with painful, burning, pruritic erythematous and edematous plaques covering both palms and erythematous plaques involving the intertriginous zones (both axillar regions) that had suddenly appeared five days before (**Figure 1**).

The patient had a past medical history of breast cancer, which was diagnosed in 2013 and subsequently treated in another hospital. The treatment involved a conservative surgical approach (lumpectomy) followed by adjuvant radiotherapy (whole breast irradiation, conventional fractioning, total dose of 50Gy, 25 fractions of two Gy each) that the patient completed during 2013 and adjuvant endocrine therapy with an aromatase inhibitor for a period of five years. She remained under clinical surveillance afterwards.

Eight years after completing adjuvant radiotherapy and three years after ending adjuvant endocrine therapy, the patient noted the appearance of fast-growing violaceous nodules in the lumpectomy scar of the right breast. A mammary magnetic resonance imaging was performed showing a de novo heterogenous lesion (7.5×1.8cm, contacting and invading the pectoralis major) and an adjacent de novo nodule (1.0×0.9cm) in the upper outer quadrant of the right breast (BIRADS assessment density 6). A core needle biopsy was performed allowing the diagnosis of an angiosarcoma of the right breast.

The patient was referred to our oncology outpatient clinic for further evaluation in January 2021. A computed tomography scan of the chest, abdomen, and pelvis did not show any signs of distant disease. A radical mastectomy was suggested and accepted by the patient. The surgery took place uneventfully and tumor-free surgical margins were obtained.

Two months after the mastectomy, three new violaceous nodules were noted in the mastectomy scar bed. These nodules were clinically suspicious for recurrent angiosarcoma. The patient was once again referred to the general surgery team for enlargement of margins, which was performed one week after. The histopathological examination of the surgical sample was compatible with angiosarcoma and revealed tumor-free surgical margins.

Two months after the above-mentioned surgical enlargement of margins, a large erythematous patch involving the areas surrounding the most recent scar appeared, together with numerous violaceous nodules in the periphery of the patch. These features were compatible with an exuberant local recurrence and systemic treatment with LPD was proposed.

The patient began a regimen of LPD (40mg/m$^2$—dose reduction of 50% regarding comorbidities and performance status by the time chemotherapy was started—every twenty-one days) on the 6$^{th}$ of May 2021. The second and third cycles were administered on the 28$^{th}$ of May 2021 and the 16$^{th}$ of June 2021.

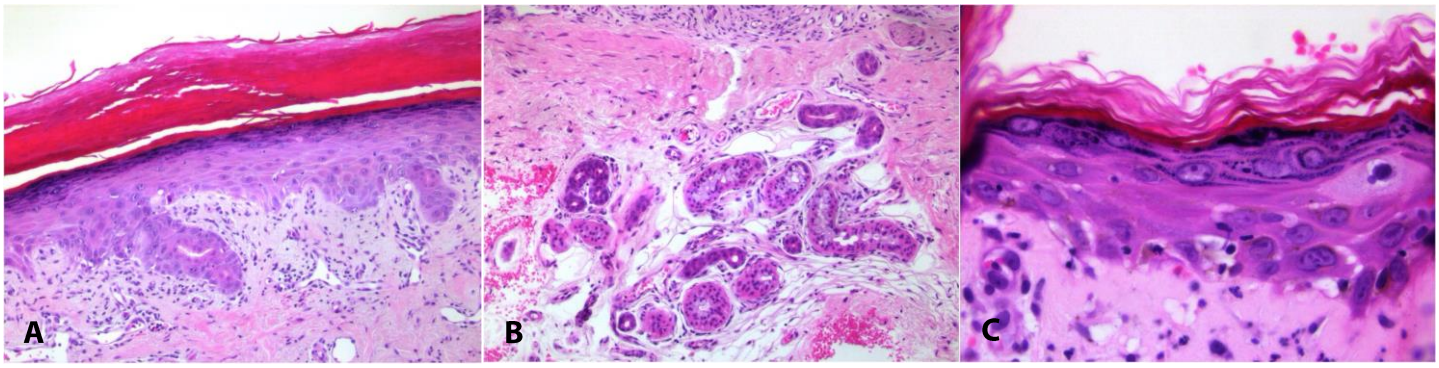


**Figure 2**. ***A)*** *Toxic erythema of chemotherapy induced by liposomal doxorubicin: cutaneous biopsy of the palm. Lentiginous hyperplasia of epidermis with digitiform elongation of epidermal crests and large keratinocytes. H&E, 100×.* ***B)*** *Cutaneous biopsy of the palm showing features of eccrine squamous syringometaplasia.* ***C)*** *Cutaneous biopsy of the palm showing amplification of a dyskeratotic keratinocyte. H&E, 400×.*

Twelve days after the third cycle of LPD, the patient came to our outpatient clinic with the previously mentioned complaints. Blood tests were performed and did not show any relevant findings. The patient was observed in the dermatology clinic in the same day. Skin biopsies were taken from both palms.

Toxic erythema secondary to LPD was considered the most likely diagnosis and the patient was medicated with oral corticosteroids (prednisone, 40mg daily). Treatment with LPD was suspended given the presence of a grade three adverse event (by Common Terminology Criteria for Adverse Events, Version 5.0).

Skin biopsies showed an interface dermatitis, large and pleomorphic keratinocytes, some dyskeratotic cells, focal basal cell liquefactive degeneration, and features of eccrine squamous syringometaplasia. In the upper dermis there was scant edema, vascular dilatation, and a mild superficial perivascular lymphohistiocytic inflammatory infiltrate. These histological features were consistent with a TEC related to LPD (**Figure 2**).

The patient was re-evaluated one month later and resolution of intertriginous lesions, along with significant improvement of palms lesions were observed. Concomitantly, the erythematous patch and violaceous nodules had completely disappeared after the three cycles of LPD with dose reduction. One month later, the patient was once again observed and complete resolution of the palms lesions was verified and there were no signs of recurrence of angiosarcoma. The patient is now under a rigorous schedule for tapering of oral corticosteroids and will be closely observed.

## Case Discussion

Our case describes a woman with a recent diagnosis of a high-grade angiosarcoma of the breast, probably radiation induced. Angiosarcoma is a highly aggressive malignant neoplasm that originates from lymphatic or vascular-endothelial cells and whose main etiological factors are 1) ionizing radiation exposure, specifically, radiation-induced breast sarcomas which show a long latency period post radiation exposure, with a median disease-free interval of 5-10 years, 2) chronic lymphedema (Stewart-Treves syndrome), 3) environmental carcinogens, and 4) genetic syndromes [4]. Given the past history of breast cancer with consequent radiotherapy treatment and the time hiatus between the end of radiotherapy (2013) and the diagnosis of angiosarcoma (2021) it is plausible to assume that this patient's angiosarcoma was radiation induced.

This patient was treated with mastectomy after the breast angiosarcoma diagnosis. The posterior local recurrences were managed with a surgical enlargement of margins and subsequently with a first-line chemotherapeutic agent (LPD) in accordance with the most recent international guidelines. The backbone of treatment of angiosarcoma is radical surgery, whereas radiotherapy and chemotherapy (primary agents include anthracyclines, namely doxorubicin,

liposomal doxorubicin, and taxanes) may play a role in the management of recurrent or metastatic disease [4].

The administration of chemotherapy may prompt the development of different skin manifestations, such as drug-specific dermatologic findings (doxorubicin radiation recall phenomenon, fluorouracil-induced lupus erythematosus, and topotecan sclerodermiform syndromes), immunosuppression-related skin complications, and true immunologic, and toxic reactions to particular agents.

The development of this patient's lesions after a cumulative exposition to LPD (after three cycles, even with a 50% dose reduction), the temporal link between their development and the last LPD administration (7 days) suggest the existence of a correlation between their appearance and treatment with LPD. Additionally, their macroscopic characteristics (erythematous and edematous plaques), the topographic distribution (palms and intertriginous zones), and the accompanying symptoms (pain, burning, and pruritus) sharply point towards the hypothesis of a TEC induced by LPD.

Toxic erythema of chemotherapy is a group of toxic dermatologic reactions that typically develop during a two-to three-week period following treatment with cytotoxic agents and that are characterized by erythematous patches or edematous plaques that normally affect hands and feet, intertriginous zones, and less frequently, elbows, knees, and ears [2]. These lesions may be bullous, are usually self-limited, and often resolve with desquamation and post-inflammatory hyperpigmentation [2]. Severe pain, burning, paresthesias, pruritus, and tenderness are frequent accompanying symptoms [2]. The lesions may recur if the same or higher dose of the same cytotoxic agent is administered [2].

It is critical to appropriately recognize this entity since the lesions arise in a period of active chemotherapeutic treatment with diverse medications. At these times patients are at high-risk for infections and treating physicians do not want to mistake these reactions for drug allergies to needed medications such as antibiotics [2].

Different explanations for the pathophysiology behind toxic erythema have been discussed (temperature gradient, vascularity, trauma, friction), but toxic damage of the cells of the straight portion of the eccrine duct and the acrosyringium and the epidermis is the most widely accepted theory [2]. Excretion of chemotherapeutic agents via eccrine sweat offers a conceivable explanation [2]. Sites of predilection could be related to the high density of eccrine glands on the palms and soles, and by sweating plus occlusive phenomenon in intertriginous areas [2]. The demonstration by laser scanning microscopy of the accumulation of chemotherapeutic agents in eccrine glands in these locations [5] and the development of circumscribed areas of eccrine squamous syringometaplasia at the sites of extravasation of doxorubicin constitutes additional evidence of a toxic insult [2].

Liposomal doxorubicin and its metabolites reach the skin by sweat [2,6]. Liposomal doxorubicin has higher and longer accumulation concentrations in vivo when compared with doxorubicin [6]. The half-life of doxorubicin in patients' palms and soles is significantly lengthened with LPD and its hydrophilic liposomal coating augments drug excretion through sweat, leading to accumulation of drug in the ducts of eccrine glands [6,7]. The stratum corneum layer of skin may serve as a drug reservoir, culminating in heightened drug concentrations, which ultimately lead to free radical generation [6]. Significant levels of free radicals may decrease the skin's antioxidant capacity, potentially leading to TEC [6]. The use of LPD in animals resulted in the production of reactive oxygen species, which may induce damage to keratinocytes and release inflammatory cytokines that cause keratinocyte apoptosis [6,8].

Moreover, the concomitant involvement of palms and intertriginous zones is particularly interesting, since the coexistence of features of hand-foot syndrome and malignant intertrigo in the same patient is uncommon [9,10]. Typically, the most common form of presentation of TEC is hand-foot syndrome [9]. Specifically, regarding the patterns of skin toxicity secondary to DLP, hand-foot syndrome is the most common form of presentation, followed by diffuse follicular rash and intertrigo-like eruption

**Table 1**. *Demographics of patients engaging in teledermatology from March 30, 2020 to May 30, 2020 at a single urban academic medical center.*

| | Hand-foot syndrome | Malignant intertrigo |
|---|---|---|
| Most frequent related drugs | Capecitabine, 5-fluorouracil, doxorubicin, L-doxorubicin, docetaxel | Docetaxel, paclitaxel, cytarabine |
| Clinical manifestations | Well-defined symmetrical purplish to erythematous plaques on palms and soles, typically associated with prodromal symptoms characterized by dysesthesia associated with pain or burning sensation | Painful sharply, demarcated, erythematous-to-dusky patches and plaques with focal scaling, crusting and erosions |
| Histopathological findings | Atypical large individual keratinocytes with pleomorphic nuclei at different levels of the epidermis, increased mitotic figures, dyskeratosis and apoptosis. May associate neutrophilic eccrine hidradenitis and / or eccrine syringometaplasia. Coarse stratum corneum of palms or soles can be identified. | |

[10]. A comparison between causative pharmacological agents and clinical manifestations of both hand-foot syndrome and malignant intertrigo is shown in **Table 1**.

The cutaneous biopsy features (interface dermatitis, large, pleomorphic and dyskeratotic keratinocytes, focal basal cell liquefactive degeneration, and features of eccrine squamous syringometaplasia) are also compatible with TEC induced by LPD.

Interface dermatitis represents the most frequently encountered histologic appearance in chemotherapy adverse drug reactions [11,12]. Pegylated LPD, capecitabine, docetaxel, and doxorubicin are now the most implicated drugs in TEC [11,12]. In addition to the epidermis, both follicular and sweat gland/duct epithelium may be affected [2,11,12]. The combination of interface changes with severe maturation arrest (dysmaturation) is pathognomonic of chemotherapy-related reactions [2,11,12]. In addition to impaired maturation, the epidermis appears disorganized and individual keratinocytes are enlarged with pleomorphic nuclei [2,11,12]. In the case of pegylated LPD the histologic features include basal cell liquefactive degeneration, keratinocyte necrosis, and mild spongiosis [2,11,12]. There is papillary dermal edema, vascular dilatation, and a mild superficial perivascular lymphohistiocytic infiltrate [2,11,12]. Features of squamous syringometaplasia are rarely seen [2,11,12]. Cutaneous biopsies of the axillae were not obtained but similar histopathological findings were expected since the histological features of both palmar and intertriginous lesions are normally superimposable as shown in **Table 1**. Finally, the progressive resolution of the eruptions with corticosteroids and LPD interruption confirm the effectiveness of the proposed measures for mitigation of these toxic dermatological reactions, supporting the TEC induced by LPD diagnosis.

It is important to reinforce that there is no specific treatment for TEC [13], but several measures may be taken for the prevention or mitigation of these adverse reactions such as pre-medication patient education. Avoidance of any activity that may increase blood flow to the mucous membranes or skin, like ingestion of hot drinks or running long distances, for several days following each cycle of treatment is recommended [14]). Local cooling (applying ice packs to wrist and ankle joints with LPD administration) causes vasoconstriction, decreases drug accumulation in limbs, and diminishes the incidence of hand-foot syndrome [15]. Intake of vitamin B6 concurrent with LPD administration [16], or intake of vitamin E after LPD administration [17] have been suggested. Concurrent treatment with corticosteroids (namely dexamethasone) has been suggested [18]. Topical application of 99% dimethyl sulfoxide (four times per day for fourteen days) may be helpful. Dimethyl sulfoxide carries free doxorubicin into the circulatory system and acts as an antioxidant avoiding doxorubicin toxicity in soft tissue [19,20]. Finally, liposomal doxorubicin dose reduction, lengthening the interval between cycles, or discontinuation of the offending agent may be required [2].

## Conclusion

This case embodies an example of TED induced by LPD with the peculiarity of concurrence of features of hand-foot syndrome and malignant intertrigo at presentation. The combination of characteristics facilitated the recognition of this entity. Toxic erythema incorporates a group of dermatologic reactions to chemotherapy that should be differentiated from other cutaneous conditions that may affect cancer patients following cytotoxic treatment. The correlation with cumulative exposure to certain drugs, the parallel close temporal association between skin lesion development and specific drugs exposure, the clinical appearance and topographic pattern of the dermatologic findings, the associated symptoms, and the histologic trademark features together may allow an accurate diagnosis, and the assumption of proper measures to mitigate the reaction.

## Potential conflicts of interest

The authors declare no conflicts of interest.

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