# Skin toxicity in a patient with ovarian cancer treated with pegylated liposomal doxorubicin: A case report and review of the literature

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**Abstract.** Pegylated liposomal doxorubicin (PLD) is a form of doxorubicin enclosed in pegylated liposomes. In contrast to conventional doxorubicin, PLD is characterized by a lower incidence of cardiotoxicity and myelosuppression. However, it induces specific mucocutaneous side effects, particularly palmar-plantar erythrodysesthesia (PPE). Other dermal manifestations, such as intertrigo-like dermatitis, diffuse follicular rash, melanotic macules, maculopapular rash or recall phenomenon are less common. Mechanisms that lead to skin toxicity remain unclear, however, certain reports indicate that drug excretion in sweat, host-vs.-altered-host reactions and local mechanical microtrauma play an important role in the development of cutaneous disorders. Effective preventive and curative management has not yet been established. The current study reports a case of a 55-year-old patient with advanced ovarian cancer who developed an uncommon diffuse maculopapular rash and severe PPE during treatment with PLD. Complete regression of the skin disorder was observed after 4 weeks. At present, palliative chemotherapy provides the opportunity to prolong life and alleviate disease symptoms, nonetheless it produces a number of adverse effects. Dermal complications may affect patient quality of life and cause therapy interruption. In the light of widespread use of PLD, skin toxicity associated with this drug creates a major problem.

## Introduction

Conventional doxorubicin is used actively in various malignant tumors, however, it produces a number of serious side effects, including cardiotoxicity and myelosuppression (1). A new form of this chemotherapeutic agent enclosed in pegylated liposomes was developed to reduce these organ toxicities (1). Liposome encapsulation prevents doxorubicin from penetration to compartments with tight endothelial cells junctions and facilitates its distribution to tissues with abnormal blood vessels (1). This results in higher drug accumulation within the tumor when compared with normal tissues (2). Consequently, a decreased incidence of cardiac and hematological toxicity is observed. Pegylated liposomal doxorubicin (PLD) has the ability to deposit itself within the skin and to induce specific mucocutaneous reactions. There are six types of PLD-related dermal disorders, and the most common is palmar-plantar erythrodysesthesia (PPE). Other, less frequent manifestations are intertrigo-like dermatitis, a diffuse follicular rash, a maculopapular rash, melanotic macules or a recall phenomenon (3). The symptoms of PPE develop usually within 2 to 12 days after the infusion of chemotherapy (4). Initially, dysesthesia, erythema or edema of the palms and plantae is noticed. These symptoms may progress to desquamation, blistering and ulceration. The soles are less often affected than the palms (5).

The current study presents the case of a patient with advanced ovarian cancer treated with PLD who developed severe hand-foot syndrome and a diffuse maculopapular rash, which is rarely reported in the literature. Complete resolution of the skin lesions was observed after 4 weeks. Due to ovarian cancer progression, the patient was disqualified from further chemotherapy.

## Case report

A 55-year-old patient without any relevant medical history underwent suboptimal cytoreductive surgery involving a hysterectomy, bilateral salpingo-oophorectomy, omentectomy and appendectomy in November 7, 2011 at the Polish Mother's Memorial Hospital Research Institute (Lodz, Poland), and was accordingly diagnosed with stage IIIC ovarian cancer based on the tumor-node-metastasis classification criteria (6). The patient received 6 cycles of intravenous paclitaxel (175 mg/m$^2$) and carboplatin [area under the curve (AUC), 5], administered every 3 weeks, and then follow-up surgery with cervical amputation. The disease was considered to be in complete remission until November 2012, when rapid progression with accompanying intestinal obstruction was observed. The patient underwent ileostomy formation, and due to significant loss in body weight, started parenteral nutrition. Subsequently,

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from January to June 2013, 2 cycles of cisplatin (70 mg/m$^2$ every 3 weeks) were administered, followed by 6 cycles of carboplatin (AUC, 5). Cisplatin was discontinued due to renal insufficiency. A partial response to chemotherapy was observed. During this time, no skin toxicity was noted. When the ovarian cancer progressed again, therapy with 50 mg/m$^2$ PLD administered every 4 weeks was initiated. No prevention strategies for PPE were implemented. At 3 weeks after the second cycle of chemotherapy, the patient developed a rash localized on the trunk and severe skin lesions on the hands. Dermatological evaluation revealed painful desquamative erythema with ulceration on the palms (Fig. 1) and mild erythema on the soles. Non-pruriginous, non-painful maculopapular eruption accompanied by peeling was present on the trunk (Fig. 2). Oral mucous membranes and other areas of the skin were not affected. The patient was classified with grade 3 PPE (according to the basic scale from the Common Terminology Criteria for Adverse Events, version 4), as difficulties were exhibited in self-care activities, and a grade 3 maculopapular rash (7). Upon admission on October 25, 2013, the patient was apyretic and in a good general condition (Eastern Cooperative Oncology Group performance status 2), with the main complaint being of pain due to ulcerative cutaneous lesions. No previous episodes of drug allergies were reported. The patient started 100 mg tramadol and 100 mg doxycycline, administered twice daily, and prophylactic antifungal treatment with 50 mg fluconazole, administered daily. Amelioration of the skin lesions was observed after 5 days of therapy, and complete regression was apparent after 4 weeks. In November 2013, there was a sudden deterioration in the patient's general condition. Follow-up abdominal ultrasound and laboratory blood tests [carbohydrate antigen-125, 4,495 U/ml (normal range, <35 U/ml); and bilirubin, 4.3 mg/dl (normal range, 0.3-1.2 mg/dl)] revealed dynamic progression of the malignancy. The patient was therefore disqualified from further chemotherapy and referred to a palliative care specialist. The patient succumbed to cancer progression in December 2013.

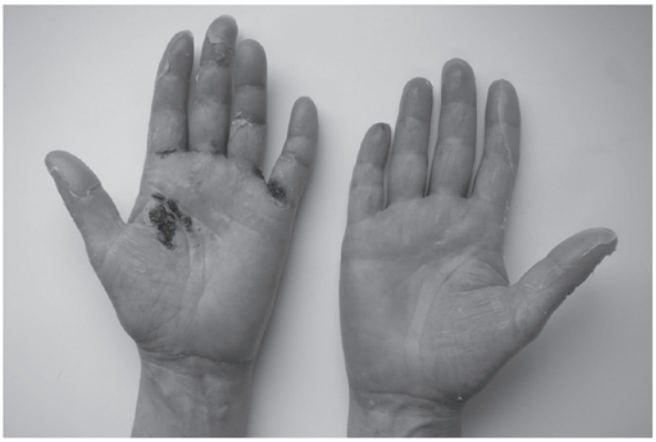

Figure 1. Clinical manifestation of palmar-plantar erytrodysesthesia: Erythema, desquamation and ulceration on the palmar sides of the hands.

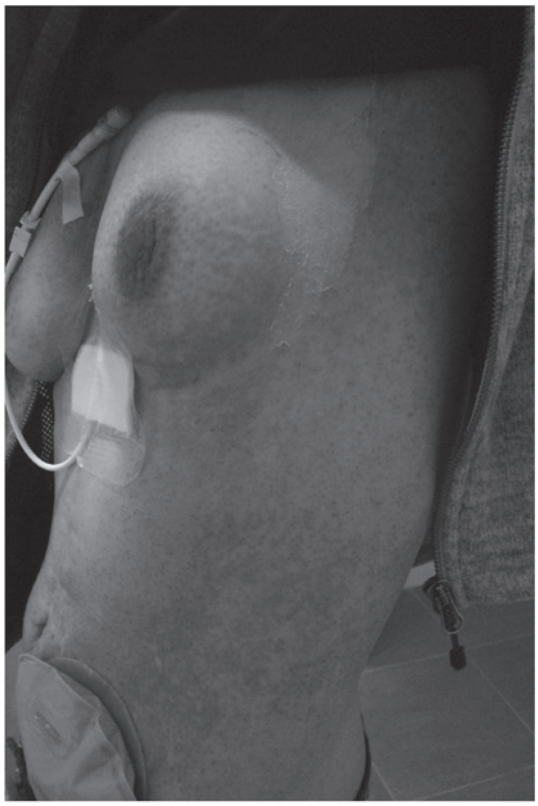

Figure 2. Clinical appearance: Maculopapular rash on the trunk.

## Discussion

Dermal toxicity is the most common adverse reaction limiting PLD therapy. Skin lesions usually appear in regions prone to trauma, such as the palms and soles. PPE of any grade is observed in up to 50% of individuals treated with PLD, while grade 3 is noted in ~20% of patients (when using a PLD dose of 50 mg/m$^2$ every 4 weeks) (8). Less frequently intertriginous areas, such as axillary folds, are affected. The maculopapular rash present in the current patient has rarely been reported in the literature (9-11).

The pathophysiology of this cutaneous syndrome is widely debated. It is presumed that drug excretion in sweat and local microtrauma are responsible for the development of PPE (12). Certain data have indicated that PLD may penetrate through the damaged vessels and impair keratinocytes, which are particularly susceptible to anticancer drugs (13). An elevated PLD concentration found in the skin of the palms and plantae supports the hypothesis that the chemotherapeutic agent is excreted in the sweat. Jacobi *et al* (14) reported the appearance of PPE only in patients with hyperhidrosis of these regions. Another hypothesis is that PPE develops due to an excessive concentration of toxic doxorubicin within the skin and its reaction with metal ions (particularly copper ions) (15). An underlying mechanism for the development of other skin disorders is poorly known. Skelton *et al* (9), on the basis of the late outbreak of dermal lesions and lymphocytic inflammation affecting keratinocytes found in the skin biopsies of 3 patients with PLD-induced maculopapular rash, suggested the possibility of host-vs.-altered-host reaction as a key factor responsible for the development of cutaneous syndromes. Optimal management of PLD-related skin reactions remains undefined. It may appear that numerous clinical trials have been performed, but in fact, the majority of them have limited value (5). Preventive approaches for PPE, including administration of moisturizers, regional cooling of

the skin, and avoidance of excessive activities associated with overheating or trauma, have been evaluated in non-randomized trials (4,16). The use of topical antiperspirant with a beneficial effect has also been reported in the literature (17). Pyridoxine appeared to be a promising agent for the prevention of PPE, but in randomized controlled trials, it proved to be ineffective (18,19). In a meta-analysis conducted by Macedo *et al* (16), celecoxib exclusively demonstrated a 53% risk reduction (odds ratio, 0.47; 95% confidence interval, 0.29-0.78; P=0.003) of any grade PPE. Certain studies have indicated that dimethyl sulfoxide (20) or corticosteroids (21,22) may be beneficial in the treatment of PLD-induced dermal complications, as they accelerate skin recovery, but in fact, the only well-established preventive management includes dose intensity modification or complete chemotherapy discontinuation (11).

In conclusion, apart from PPE, other skin toxicities associated with PLD treatment are less frequent and not well known. The aforementioned prophylactic and curative strategies for PLD-induced dermal toxicity require further investigation, and their usage in routine clinical practice is unsupported. As mucocutaneous side effects are an important cause of PLD dose modification or treatment withdrawal, it is essential to conduct prospective randomized controlled clinical trials in order to strictly define the preventive and curative management of this complication.

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