Case Report

Liposomal Doxorubicin Induced Severe Palmar-Plantar Erythrodysesthesia

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Abstract

Observations: Pegylated liposomal doxorubicin (PLD) is a more recent form of doxorubicin which is a highly effective chemotherapeutic agent for the treatment of ovarian carcinoma. This form enables to use higher concentrations of the drug with less systemic side effects. The most important side effects that have been reported to occur during treatment with PLD are palmar and plantar erythrodysesthesia (PPE) (hand-foot syndrome) and stomatitis.

A patient with severe form of PPE due to liposomal doxorubicin which has been given for the treatment of recurrent ovarian carcinoma is presented. Her complaints had begun with generalized and painful erythema after the third course of chemotherapy and progressed to a more toxic clinical picture with gross hemorrhagic bullae and ulcerations involving the palms, the soles, axillar and inguinal folds.

She also had neurofibromas and café au lait macules and a family history of neurofibromatosis type I whereas no correlation was found between two conditions.

It is noteworthy to point out that the patient exhibited the involvement of occasional sites, such as trunk and flexural sites along with the palmoplantar lesions. This clinical picture was consistent with Grade IV PPE which is characterized by diffuse or local blistering and ulceration causing bedridden state. The patient completely recovered after systemic treatment with corticosteroids and pyridoxine within 6 weeks.

Introduction

Palmar-plantar erythrodysesthesia (PPE) or hand-foot syndrome is a characteristic cutaneous toxicity manifested by approximately 25% of patients with protracted 5-fluorouracil or pegylated liposomal doxorubicin (PLD) infusion [1]. PLD has been shown to be a useful second or third line antineoplastic agent for the management of platinum-resistant or refractory ovarian carcinoma. The risk for the occurrence of liposomal doxorubicin associated PPE have been reported to be increased by the use of higher concentrations of drug (>50mg/m²) and maintenance of treatment courses with relatively short intervals (less than 4 weeks) [2].

PPE is generally seen after a couple of courses of treatment but it may also occur earlier [3]. Grade IV PPE which is a relatively uncommon complication, represents the most severe form of skin toxicity with the highest morbidity.
Case Report

A 62 year old female with poorly differentiated papillary serous ovarian carcinoma had total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy. Subsequently she received chemotherapy with cisplatin and cyclophosphamide for six courses and remained disease-free for three years. However she quitted her periodic follow-up and underwent a surgical intervention due to ileus induced by a pelvic mass 3 years later.

Histopathological evaluation of the mass revealed a recurrent poorly differentiated papillary serous carcinoma. Chemotherapy with carboplatin and cyclophosphamide was initiated and a remissional state for 2 years was established after six courses.

In March 2004 the patient received a third line chemotherapy regimen consisting of carboplatin and paclitaxel for peritoneal recurrence. Four months later chemotherapy was completed and the patient was followed up without treatment for 14 months. In October 2005 a rise in CA-125 antigen level to 354 units/ml occurred and examination by computerized tomography revealed multiple enlarged lymph nodes at retroperitoneal and left supraclavicular regions. Thereafter a fourth line chemotherapy regimen containing liposomal doxorubicin (50 mg/m² q4w) was started. At the thirteenth day of the third course of PLD a generalized and painful erythema which was more severe at the palms, soles, axillary and inguinial folds occurred. The patient was especially complaining about intensive sensation of burning on her palms and soles. She needed to be hospitalized in the department of dermatology very soon since large areas of blistering started at these parts along with the ulcerations at the axillar and inguinal sites. There were erosions at the interscapular and pubic area. Nasal mucosa showed hemorrhagic crusts and Grade II erosive mucositis of the oral cavity was also present. Large blisters at the palms and soles had serohemorrhagic character. (Figures 1 and 2) The clinical picture was found to be consistent with Grade IV PPE. Dermatologic examination revealed multiple nodular tumors with a varying diameter of 1 to 2 cm. on the trunk and extremities and cafe au lait macules less than 5 cm. After resolution of skin toxicity, axillary folds appeared normal and showed no freckling. She gave a family history of classical cutaneous type of neurofibromatosis (NF-1). Systemic examination including ophthalmologic evaluation and laboratory test including whole blood counts, blood chemistry, ECG and chest X-ray revealed normal findings except for increased level of CA 125, high sedimentation rate (99 mm/h) and CRP level (167 mg/dl).

Histopathologic examination of the skin biopsy, taken from the erythematosus margin of a blistering area from the right ankle showed orthohyperkeratosis, hypergranulosis, dyskeratotic and apoptotic cells in the epidermis and hydropic degeneration of the basal layer. There was marked edema in the papillary dermis, interstitial and perivasular neutrophil rich inflammatory infiltration and pigmented macrophages in the upper dermis (Figure 3). These findings were consistent with palmar-plantar erythrodysesthesia.

Systemic treatment was started with oral methylprednisolone, 48 mg/day, antibiotic (levo-
floxacin) and oral pyridoxine (100 mg/day). Topical treatment with wet dressings of potassium permanganate solution (1: 4000) and beclomethasone dipropionate ointment was applied to support systemic treatment and control oedema and seropurulent discharge from ulcerated and eroded areas. The symptoms gradually improved within 15 days. We tapered corticosteroid dose 8 mg weekly. She recovered completely in six weeks and is still disease free.

**Discussion**

The advent of polyethylene glycol-coated liposomal doxorubicin hydrochloride has allowed delivery of higher concentration of the chemotherapy to the target tissue, with potentially fewer systemic toxic effects. However, the change in the drug’s pharmacokinetics has been accompanied by the appearance of new cutaneous toxic reactions [4]. Palmar-plantar erythrodysesthesia (hand-foot syndrome) is a common dose and schedule related adverse effect associated with liposomal doxorubicin [3]. PPE has also been reported with other chemotherapeutics including capecitabine, cytara- bine, doxorubicin, gemcitabine, vinorelbine and docetaxel.¹ The pathophysiology of PPE, is not well understood as it occurs with any drug. It has been hypothesized that, following the local trauma associated with routine activities, PLD may extravasate from the deeper microcapillaries in the hands and feet; PLD has been detected in elevated concentrations in eccrine sweat glands in palms and soles, where it accumulates perhaps facilitated by the hydrophilic coating of the liposomes, and the higher number of eccrine glands in hands and feet could explain the preferred body localizations of the syndrome [5]. Occurrence of PPE is related to prolonged drug exposure as with continuous intravenous infusion, daily ingestion, or with liposomal encapsulation which prolongs drug half-life.

The earliest sign is painful erythema of the palms, soles and fingers that later becomes edematous, changes color to violet, then dries off and desquamates. In severe cases, blisters develop later leaving erosive surfaces, with considerable impairment in function [6]. Histologically, PPE shows a few specific findings. Mild spongiosis, scattered necrotic and dyskeratotic keratinocytes and hydroptic degeneration of the basal layer are reported. Dermal changes in most cases include dilated blood vessels, papillary edema, and a sparse superficial perivascular lymphohistiocytic infiltrate [7]. Among this findings, dyskeratotic cells in the epidermis and hydroptic degeneration in the basal layer, edema in the papillary dermis were seen in the skin biopsy of our case. The common toxic effects criteria of the National Cancer Institute was used to evaluate the skin lesions.

- **Grade 1:** Scattered asymptomatic lesions,
- **Grade 2:** Scattered symptomatic lesions without functional impairment,
- **Grade 3:** Generalized eruption with functional impairment,
- **Grade 4:** Erosive or ulcerated lesions.

This scale was modified for palmar-plantar erythrodysesthesia as follows

- **Grade 1:** Asymptomatic, mild erythema, swelling, and desquamation,
- **Grade 2:** Painful erythema, swelling, and desquamation not precluding normal physical activity,
- **Grade 3:** Blistering, ulceration, or swelling interfering with regular activity, including ability to wear clothing,
- **Grade 4:** Diffuse or local blistering and ulceration causing infections or bedridden state.

Definitive prevention and treatment strategies for PPE have not been established. With the onset of clinically significant PPE, recommendations are to stop the agent to prevent progression of symptoms. Subsequently, depending upon the severity of PPE consideration is given to dose reduction and/or delay of treatment.¹ In some cases the symptoms are mild and tend to resolve within 1-2 weeks so it is not necessary to stop or delay the treatment. Treatment of PPE is mainly palliative. There are few supportive measures that have proven effectiveness at controlling symptoms. Supportive treatments such as topical wound care, elevation, and cold compresses may help to relieve the pain. Symptoms can often be relieved by immersing the hands and feet in cool water, avoiding extremes of temperature, pressure, and friction on the skin and by cushioning sore skin with soft pads [8].

Systemic corticosteroids are also used in the prophylaxis and treatment of PPE. While the exact mechanism by which corti-
costeroids affects PPE occurrence is unknown, it may be related to the reduction of inflammatory-mediated, premature liposomal leaks, which have been suggested as an etiology for the syndrome. Drake et al. demonstrated that the use of oral dexamethasone is effective in attenuating or eliminating PLE induced PPE and the use of the dexamethasone regimen prevents treatment delay and dose reduction [9].

There have been a number of small studies and anecdotal reports that oral pyridoxine delays the onset of drug induced PPE. Oral pyridoxine has also been shown to be beneficial in the prevention and treatment of PPE in small groups of patients at doses varying from 50 to 300 mg/day [10].

One pharmacologic topical agent, dimethyl sulfoxide (DMSO), has been investigated for its potential benefit in PPE management because of its potent free-radical scavenging properties. DMSO rapidly penetrates tissues following topical application and has been used successfully to treat extravasation of conventional doxorubicin [5]. Also oral administration of vitamin E was found to be effective in the treatment of docetaxel-capecitabine induced PPE. Studies in rats showed that pretreatment of animals with yeast enriched by the antioxidants selenium and vitamin E, C, and A prevented the loss of cutaneous reductase activity after the administration of doxorubicin. Therefore, supplementation with antioxidants may diminish the cutaneous cytotoxic effects of doxorubicin [4].

Our patient developed a severe form of PPE which involved unoccasional sites, like trunk together with palmar, plantar, inguinal involvement. Her lesions were consistent with grade 4 skin toxicity. The lesions were resolved with effective symptomatic treatment. We could not find any correlation between her constitutional skin lesions and the occurrence of the drug eruption. The patient received no more PLD. She had 2 more recurrences since then and received 2 more lines of other chemotherapies without any skin toxicity. She is alive, well and still in another remission period.

References

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