LIPOSOMAL DOXORUBICIN-RELATED PALMAR-PLANTAR ERTHRODYSESTHESIA (HAND-AND FOOT SYNDROME): REPORT OF A CASE

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SUMMARY

Palmar-plantar erthrodyesthesıa (PPE) (hand and foot syndrome) is a dermatological toxic reaction related to some chemotherapeutic agents. Liposomal doxorubicin is the long-acting formula of doxorubisin and it causes PPE in 50% of the patients when used with the dosage of 50 mg/m^2. The disease causes burning sensation in the hands and feet and then shows progression by edema and erythema. After the disease is estbalished the treatment consists of lowering the drug dosage, prolonging the dose intervals or discontinuing the drug as well as using topical agents.

Key words: *liposomal doxorubicin, palmar-plantar erthrodyesthesıa*

Journal of Turkish Society of Obstetrics and Gynecology, (J Turk Soc Obstet Gynecol), *2011; Vol: 8 Issue: 1 Pages: 62- 6*

ÖZET

LİPOZOMAL DOKSORUBİSİN İLE İLİŞKİLİ PALMAR-PLANTAR ERİTRODİSESTEZİ (EL-AYAK SENDROMU): OLGU SUNUMU VE DERLEME

Palmar-plantar eritrodisestezi (PPE) (el-ayak sendromu) bazı kemoteropotik ilaçlar ile ilişkili dermotolojik toksik reaksiyondur. Lipozomal doksorubisin konvansiyonel doksorubisinin uzun salınımlı bir formülüdür ve 4 haftada bir 50 mg/m^2 kullanıldığında hastaların %50'sinde PPE görülmektedir. Hastalık özellikle el ve ayaklarda yanma hissi ile ortaya çıkmakta, daha sonra ilerleyerek ödem ve eritem meydana gelmektedir. Hastalık geliştikten sonra ise tedavi ilaç dozunun azaltılması, doz aralıklarının uzatılması ya da ilacın kesilmesiyle birlikte çeşitli topikal ajanların kullanılması şeklindedir.

Anahtar kelimeler: *lipozomal doksorubisin, palmar-plantar eritrodisestezi*

Türk Jinekoloji ve Obstetrik Derneği Dergisi, (J Turk Soc Obstet Gynecol), *2011; Cilt: 8 Sayı: 1 Sayfa: 62- 6*

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Received: 28 January 2010, revised: 31 March 2010, accepted: 14 April 2010, online publication: 15 December 2010

DOI ID: 10.5505/tjod.2011.87059

INTRODUCTION

Palmar-plantar erythrodysesthesia (PPE) or hand-foot syndrome is a relatively frequent dermatologic toxic reaction that is associated with a number of chemotherapeutic drugs[1]. This syndrome was first described by Lokich and Moore in 1984 on a patient receiving continuous infusion of 5-FU[2]. Peglated liposomal doxorubicin (PLD) is an extended-release formula of conventional doxorubicin and when the PLD is used with the current proven dose as 50 mg/m^2 in every 4 weeks PPE is seen in 50% of patients and 20% of these cases appear to be grade 3 PPE[3,4]. Ensuring the safety of PLD, which is an important agent in the advanced ovarian cancer use, would improve the quality of life of patients with ovarian cancer.

CASE

57-year-old female patient, in postmenopausal period for 11 years and has 2 vaginal birth. In 2001, the patient was admitted to our clinic because of abdominal distension and in her sonography a 93 x 130 mm sized tumoral mass with lobules that fills the whole abdomen and extends to the umbilical level was detected. The patient was operated with the diagnosis of ovarian cancer due to patient's CA 125: 27,933 U/ml. The patient's post-operative pathological diagnos was papillary serous and mucinous mixt type ovarian surface epithelial carcinoma with histologic grade III. The patient received 6 cycles of paclitaxel-cisplatin chemotherapy. After the chemotherapy has been completed without any problems patient was followed-up. After approximately 2.5 years of follow-up the rise of CA125: 216 U / ml and detection of 1 pathological lymph node in the pelvic CT scan the patient was evaluated as recurrence and received 9 cycles of docetaxel-carboplatin 6 AUC chemotherapy. Afterwards, the patient was followed with tamoxifen. The patient was followed approximately 1 year and increase of CA125: 256 U / ml and detection of more than one lymph nodes in pelvic CT scan was evaluated as recurrence, and the patient received 6 cycles of paclitaxel-carboplatin 6 AUC chemotherapy. After about 2 years in remission detection of a mass in pelvic tomography which is consistent with relapse and increase of CA125: 258 U / ml the patient received 6 more cycles of topotecan chemotherapy. At the end of chemotherapy, control pelvic tomography revealed tumor implants in the mesenteric root and peritoneum and the levels of CA125: 340 U / ml the therapy of pegilated liposomal doxorubicin 50 mg/m^2 every 4 weeks was decided. Following the initiation of the drug at the end of 3.cycle dysesthesias-like symptoms in hands and feet appeared which was followed by erythematous plaques accompanied by edema (Figure 1). The drug was stopped because despite local cold application and steroid treatment during drug infusion patient's symptoms deteriorated. Following the discontinuation of the drug lesions on hands and feet disappeared within a few weeks (Figure 2).

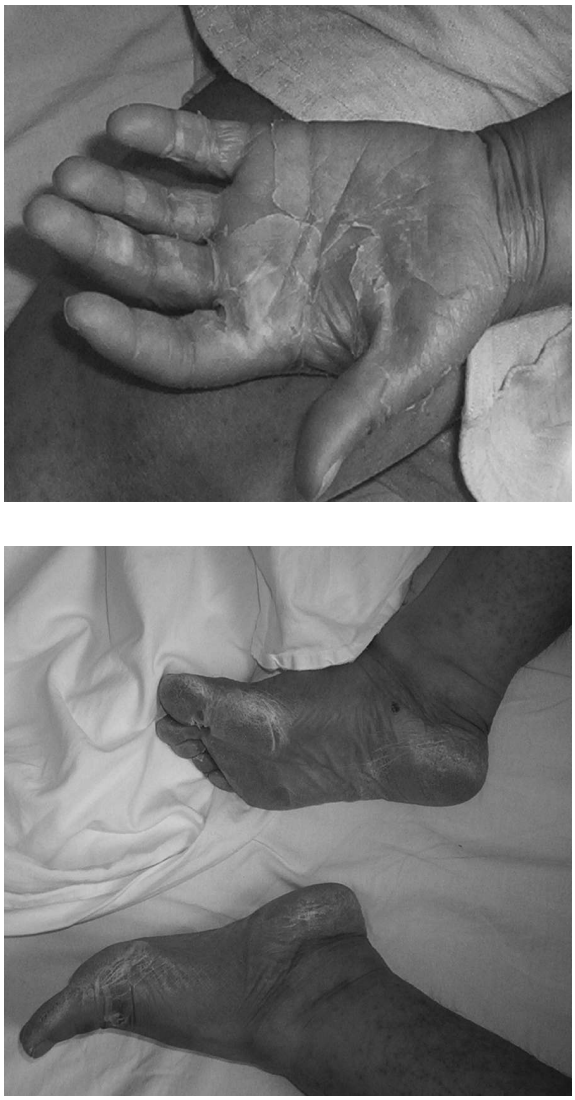
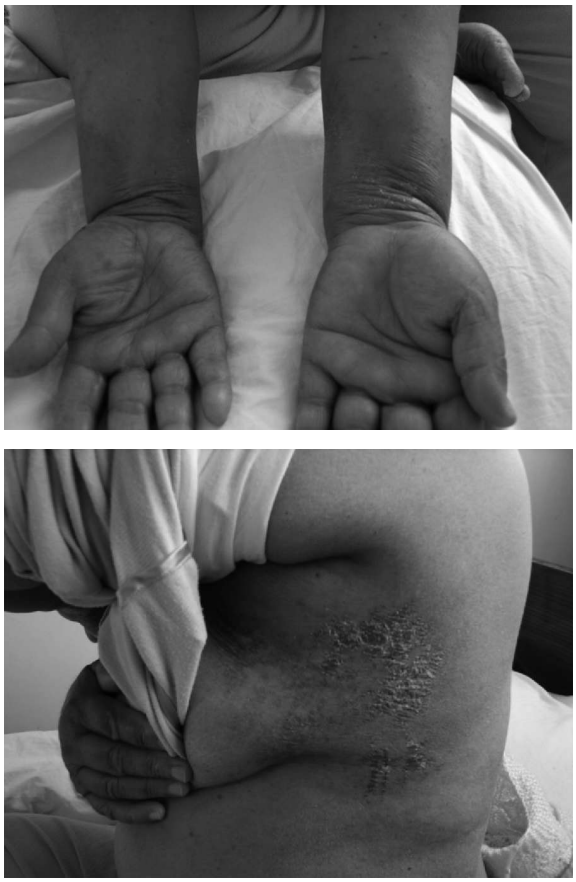


Figure 1: *Erythematous and desquamating lesions involving the hands and feet.*



Fifure 2: *Lesions showing significant regression a few weeks after drug withdrawal.*

DISCUSSION

Palmar-plantar erythrodysesthesia (PPE) or hand-foot syndrome is a relatively frequent dermatologic toxic reaction that is associated with a number of chemotherapeutic drugs[1]. PPE usually appears 2-12 days after initiation of chemotherapy as dysesthesia and tingling, and after 3-4 days these symptoms progress to symmetrical edema and erythema in palms, soles. Erythematous plaques and edema in the palms, soles of the feet and other areas exposed to pressure soften and dissolve within 1-2 weeks. If the next dose of chemotherapy is not postponed or the dose is not decreased blistering, peeling, crusting, ulceration and epidermal necrosis might occur with the progression of PPE. Dysesthesia and erythema might be seen could be seen in other parts of the body that are exposed to pressure with increased heat such as calf, groin, breast, axilla. İngunal, scrotal and labial areas might be affected as well.

Histologically, with the plantar punch biopsies, hyperkeratosis of the stratum corneum layer of the epidermis, parakeratosis and numerous picnotic cells and spongiosis that are not associated with the lymphocytes located in stratum Malpighi were shown. Vacuolised areas in the basal layer, perivascular lymphocytic infiltration in the dermis and deposits of melanin are contained. Dermal changes include dilated blood vessels, papillary edema and superficial perivascular lymphohistiocytic infiltration[1].

PLD is an extended release formulation of doxorubicin hydrochlorid buried within the peglated liposome. This formula is being used for metastatic breast cancer patients with increased cardiac risk, advanced ovarian cancer patients for whom platinum-based chemotherapy had failed (as in our case), and for immune deficiency syndromes associated with Kaposi's sarcoma. Embedding of doxorubicin into liposomes causes a change in pharmacokinetic and biodistrubition of the drug, and as a result toxic effects caused by doxorubicin in particular cardiac toxicity is reduced[3-5]. The incidence of PPE in patients receiving PLD is higher compared to patients receiving conventional doxorubicin[3-5]. Studies have shown that when the effective dose of PLD 50 mg/m^2 is used for 4 weeks, PPE was observed in 50% of the patients and 20% of these cases were grade 3 PPE[3-4].

Pathophysiology of the drugs causing PPE is poorly understood. PLD might cause extravasation from the microcapillary following local trauma caused by routine activity. Increased concentration of PLD have been identified in the eccrine sweat glands of hands and feet. Coverage of hydrophilic liposomes in these areas might facilitate the accumulation and occurrence of the syndrome in hands and feet might be explained by high amounts of eccrine glands in these regions[6].

In a study, doxorubicin was observed in the sweat of extrator channels of eccrine sweat glands in 10 patients received PLD for various malignancies[6]. In the same study, only 5 patients with hyperhidrosis in the hands and feet developed PPE[6]. Regional temperature gradient in the lower extremities, rapid cell proliferation, gravitational force and the vascular anatomy contribute to the development of typical localization of this syndrome in the palms and soles of the feet[7,8]. In another study, contribution of local pressure and skin trauma was examined[9]. In a study, Lyass and colleagues showed that in 45 patients with metastatic breast cancer receiving different doses of PLD might develop PPE in different parts of the body that are exposed to micro

trauma and pressure except hands and feet (axilla, groin, and sacral region, etc.) as well.

The early diagnosis of PPE is valuable as it allows early interventions and prevents worsen of the symptoms. Education of the patient is important for early diagnosis of PPE in minimizing signs and symptoms. In order to prevent the progression of PPE treatment should be initiated as soon as possible.

Prevention strategies of PPE include various pharmacological and non-pharmacological treatments such as avoiding excessive pressure or rubbing the skin and avoiding situations that cause dilation of blood vessels (such as hot showers or sun exposure)[10]. In a retrospective study, in 17 women application of regional cold to hands and ankles and consumption of cold drinks during PLD infusion reduced the severity and incidence of PPE compared to 3 women that did not receive the same treatment[11]. The effect of cold application occurs as a result of reduction of drug circulation in the lower extremities due to vasoconstriction. This causes reduced drug extravasation and tissue toxicity in the surrounding tissue. At the same time, low temperature leads to a decrease in the concentration of uncapsulated doxorubicin by stabilizing the liposomal configuration [11].

One of the investigated agents for prophylaxis of PPE is pyridoxine, because in rodents with pyridoxal phosphate deficiency acrodini, a PPE-like situation, was observed[12], and in an uncontrolled study it has been shown that pyridoxine might reduce the incidence and severity of PPE develops due to 5-FU infusion[13].

Many researchers evaluated dexamethasone in the prophylaxis of PPE. In a prospective study evaluating the dexamethasone premedication[14] 23 patients received PLD 50 mg/m2 every 28 days without dexamethasone because of recurrent gynecologic malignancies. 9 patients developed grade 2-4 PPE and PPE treatment was stopped untıl PPE disappeared and then started again. Once the treatment was started again 6 out of nine patients received 8 mg dexamethasone twice a day 5 days before the start of infusion and the given dose was discontinued by reducing in the next 2 days. All of the 6 patients received dexamethasone did not need to delay or reduce the dose of the therapy for an average of 7 cycles of chemotherapy, but patients that did not reveived dexamethasone needed dose reduction or delay of the therapy.

Another agent investigated for the prophylaxis of PPE is amiphostine. Lyass and colleagues[15] reported that in 22 patients receiving 45 to 60 mg/m^2 PLD in every 21 days the risk of developing grade 3-4 PPE is reduced compared to control groups when intravenous amifostine 500 mg is given on the 1st, 3rd or 4th, 8th days.

There are non-pharmacological methods in the treatment of PPE, as well. These are emollient creams, lotions with aloe vera, moisturizing creams (such as bag balm), lanolin-based ointments that include antiseptic hidroksiquinoline sulfate and to maintain the integrity of the skin. Thses might reduce the current symptoms. Since dimethyl sülfokside (DMSO) a topical pharmacological agent has properties as a potent free radical scavenging it has been were investigated for potential benefit in PPE. Following the topical application DMSO rapidly penetrates the tissues and could be successfully used in the treatment of conventional doxorubicin extravasation[16].

The properties of administration and pharmacokinetics of PLD seem to influence the severity and incidence of PPE. Clinical data showed that after multiple injections of PPE the development of PLD increases [9]. In their studies, Lyass and colleagues[9], and Ranson and colleagues[7] investigated the effect of different doses and tariffs on PPE incidence in patients with breast cancer. These studies showed that applications in the short term (meaning short-term of dose ranges) are associated with more toxicity. This effect seems to be independent of the dose intensity. When the dose and pharmacokinetic parameters of PLD are analyzed stomatitis and decreasein leukocyte count were found strongly correlated with dose and Cmax, while the severity of PPE was correlated only with the half-life ($t_{1/2}$)[18]. Previous preclinical data indicate that there there is a relationship between severity of PPE and dose intensity[19]. On the other hand, the impact of changing the dose intensity on clinical outcomes is not clear. Rose et al.[20]. compared 40 mg/m^2 every 4 weeks (dose intensity 10 mg/m^2/week) versus 50 mg/m^2 every 4 weeks (dose intensity 12.5 mg/m^2/week) in a retrospective analysis of 78 patients with platinum refractory ovarian, peritoneal, tubal carcinoma. Similar response rates in patients receiving different PLD doses were observed: one complete and 4 partial response in the group receiving 40 mg/m^2, 1 complete and 2 partial response in the patients group receiving 50 mg/m^2. In a prospective study[21], when 40 mg/m^2 of dose was applied to 49 patients with platinum and

paclitaxel resistance ovarian cancer (phase 2 study), 4 out of 44 patients (9%) showed an objective response. The rate of PPE in any grade was 18%. Grade 3 or higher grade of PPE was not observed. 6 patients (12%) required dose reduction due to treatment-related toxic effects. Based on this information, supported by sufficient clinical evidence many authors believe that the modified dose of PLD is 40 mg/m^2 every 4 weeks in patients with recurrent or relapsed ovarian cancer. Even though, currently, the accepted dose of PLD is 50 mg/m^2 every 4 weeks, minimal toxicity related to drug and optimal clinical effectiveness with different drug doses are shown in the literature. Developing the safe chronic use of PLD in the ovarian cancer would lead to an improvement in the life quality of patients with advanced ovarian cancer.

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