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Palmar-plantar erythrodysesthesia (PPE), also called hand-foot syndrome (HFS), is a distinctive and relatively frequent dermatological toxic reaction associated with certain chemotherapeutic agents: pegylated liposomal doxorubicin, capecitabine, a long-circulating formulation of doxorubicin, cytosine arabinoside, interleukin 2. HFS typically presents with dysaesthesia and tingling in the hands and feet. Dysaesthesias and erythema may occur on several other body surfaces, especially in areas where pressure or increased warmth occurs, such as on the buttocks, groin, under pendulous breasts, and in the axillae. We present the case of a 56-year-old woman with HFS in the axillae, inguen and on the skin of the back and abdomen during treatment with pegylated liposomal doxorubicin for metastatic breast cancer. After four cycles of chemotherapy, treatment was interrupted due to HFS (G3 according to NCI CTC). Palmar-plantar erythrodysaesthesia is an oppressive complication after chemotherapy; it often makes normal daily activity impossible, deteriorates the patient's quality of life and frequently limits chances of effective treatment.

Key words: palmar-plantar erythrodysaesthesia, hand and foot syndrome, HFS.

Palmar-plantar erythrodysaesthesia during pegylated liposomal doxorubicin treatment – case report

Bożena Cybulska-Stopa, Marek Ziobro, Marta Skoczek, Ida Cedrych

Department of Systemic and Generalized Malignancies, Department of Centre of Oncology Maria Sklodowska-Curie Memorial Centre, Krakow, Poland

Introduction

Palmar-plantar erythrodysaesthesia (PPE), otherwise known as the hand-foot syndrome, is a characteristic dermatological complication which may occur after administration of certain cytotoxic drugs. It was observed and described for the first time in 1974 after administration of mitotane [1]. Later there was an increase in reports concerning the development of PPE after prolonged infusions of 5-fluorouracil [2]. At the moment it is known that palmar-plantar erythrodysaesthesia can be caused by a number of other anticancer drugs. It is most frequently observed after administration of capecitabine [3], pegylated liposomal doxorubicin (PLD) [4], sorafenib [5], sunitinib [5], 5-fluorouracil [8], vinorelbine [8], tegafur [6], emitefur [7] and after prolonged exposure to irinotecan [8], doxorubicin [8], cytarabine [8], floxuridine [8], and high doses of interleukin [4], or gemcitabine [4].

The precise mechanism which leads to the onset of the PPE associated with the administration of certain drugs is not yet known. It was observed that pegylated liposomal form of doxorubicin (PLD) accumulates in greater amounts in the eccrine sweat glands, located mainly on the palms and soles of the feet, which may explain the frequent location of the skin changes in this area [4, 9]. An individual tendency to excessive sweating of hands and feet can also contribute to the occurrence of PPE [10]. It is hypothesized that PLD emerges from the capillaries in the deeper layers of the skin due to the local trauma associated with daily activities, which may explain the occurrence of PPE in other areas of the body such as the axillary, inguinal, and sacral region [11].

Clinical signs of PPE are: dysaesthesia defined as unpleasant sensory sensations, tingling, itching, connected with swelling and redness (erythema) of the palms of the hands and soles of the feet, appearing about 2-12 days after initiation of chemotherapy. These symptoms may worsen within 3-4 days after onset, leading to blistering, painful skin cracking and deep ulcerations. Dysaesthesia and erythema may also occur in other areas of the body, particularly those exposed to pressure or higher temperature, but it is much less frequent.

Histological examination of the affected foot skin reveals hyperkeratosis and parakeratosis in the cornified layer (stratum corneum) of the epidermis and intercellular oedema (spongiosis) with numerous pyknotic cells without associated lymphocytes in the Malpighian layer. A focal vacuolization in the basal layer, perivascular lymphocytic infiltration and deposits of melanin in the dermis are also observed [12].

Description

We report a case of palmar-plantar erythrodysaesthesia in a 56-year-old breast cancer patient with metastatic lesions located in the liver and lungs, treated with pegylated liposomal doxorubicin. During the second cycle of the cytotoxic therapy the patient developed a classic form of hand-foot skin lesions with the clinical features of erythrodysaesthesia located on the skin of the armpit, groin, back and the abdomen.

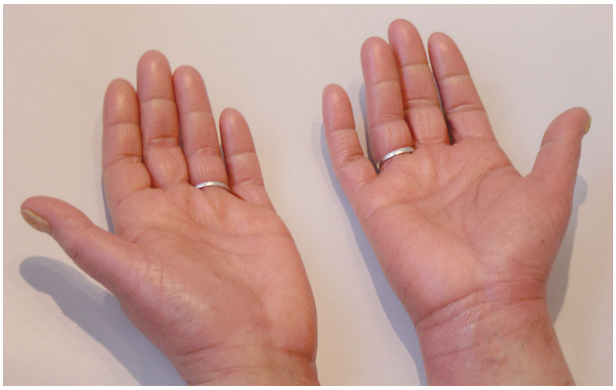

Fig. 1. Palmar-plantar erythrodysaesthesia (PPE) – grade 1

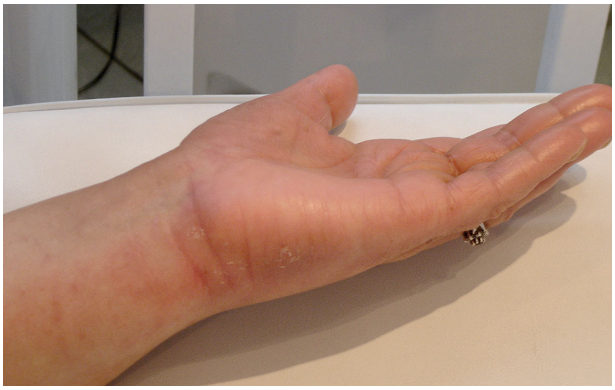

Fig. 2. Palmar-plantar erythrodysaesthesia (PPE) – grade 1

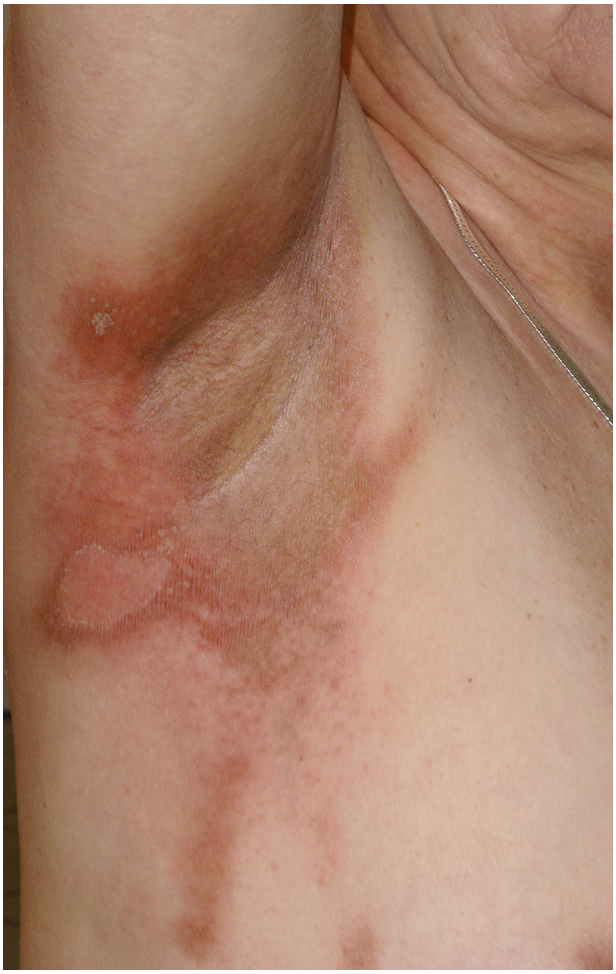

Fig. 3. Manifestation of PPE in axillary region – grade 3

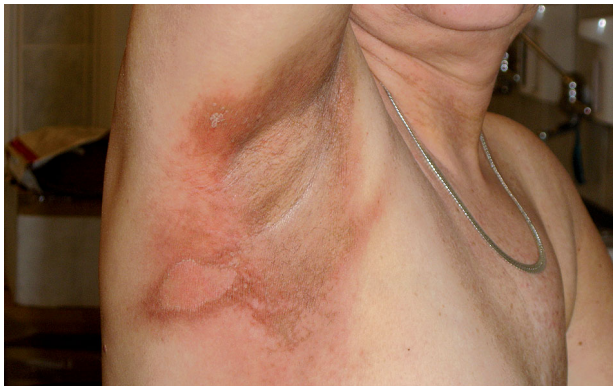

Fig. 4. Manifestation of PPE in axillary region – grade 3

The patient started treatment with pegylated liposomal doxorubicin and docetaxel at doses of 30 mg/m^2 and 75 mg/m^2 respectively, administered in 3-week intervals. Since the initiation of the chemotherapy, vitamin B_6 (pyridoxine) in a dose of 100 mg twice daily as a hand-foot syndrome prevention, and dexamethasone in doses of 2 × 8 mg on three consecutive days, as a premedication for dace taxel were administered. After three series of the chemotherapy the patient developed grade 1 hand-foot syndrome (according to the NCI CTCAE v3 scale) [17]. Initially the changes were limited to the hands and feet and were described as dysaesthesia (unpleasant sensory experiences) and tingling, with redness and swollen, cyanosed areas on the hands and feet (Fig. 1). The application of a skin barrier cream and cooling of the changed areas was recommended, which gave relief to the patient. The chemotherapy was continued in full doses, until the worsening of the skin lesions. Redness and desquamation of the skin on the palm appeared (Fig. 2), followed by changes around the armpits, groin, and on the skin of the back and abdomen (Fig. 3, 4). The described symptoms were connected with severe pain. Due to the severity of the changes – grade 3 (according to the NCI CTCv3 scale) [17], after the fourth cycle the chemotherapy was stopped and symptomatic treatment to relieve the pain was implemented. The topical application of the grease cream a few times a day and ice-cooling of the hands and feet was continued. To relieve the pain we used non-steroidal anti-inflammatory drugs, as well as oral formulations of morphine. The skin changes of such sever-

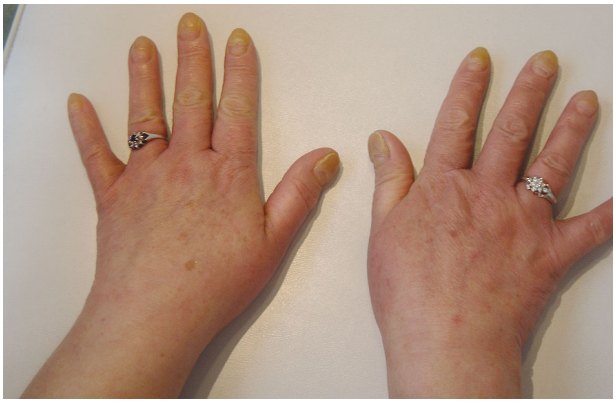

Fig. 5. Palmar-plantar erythrodysaesthesia (PPE) – grade 1

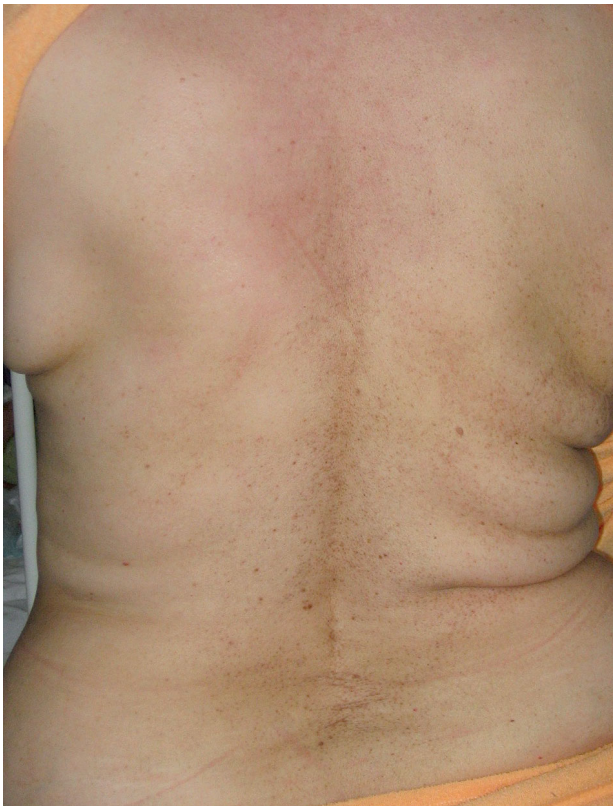

Fig. 7. The symptoms resolved in about three weeks after the end of treatment, leaving a brown discoloration that remained for a period of several months

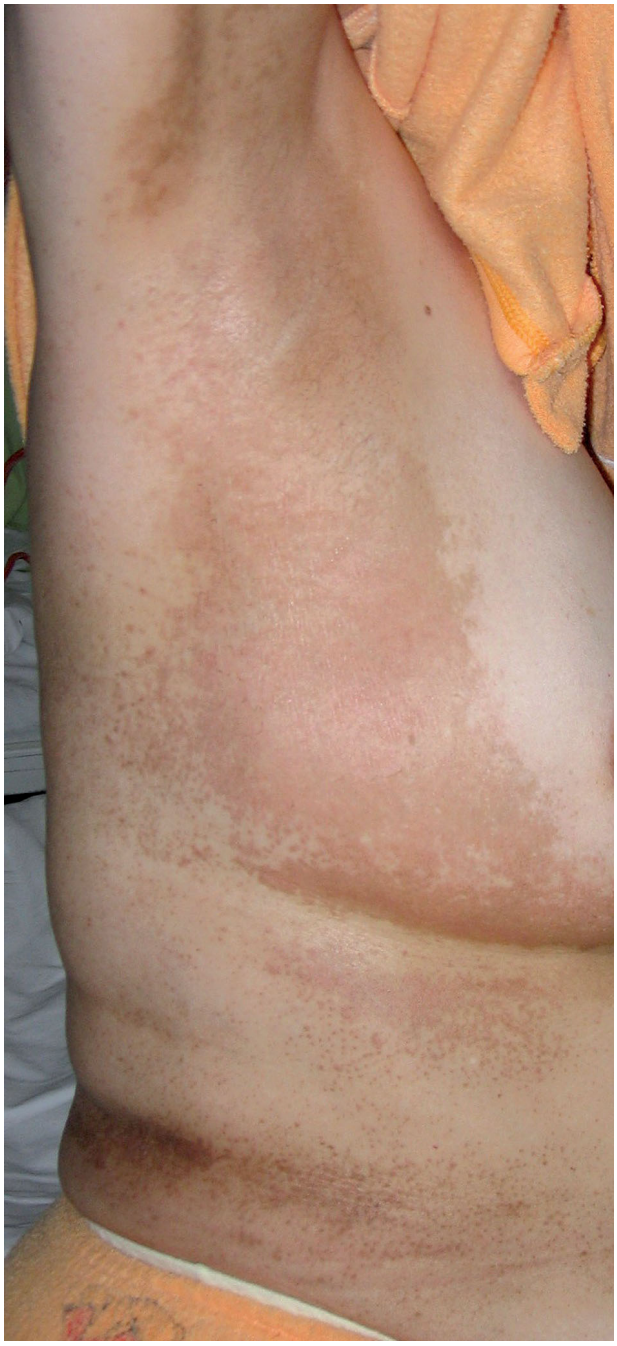

Fig. 6. The symptoms resolved in about three weeks after the end of treatment, leaving a brown discoloration that remained for a periodof several months

ity lasted for about four weeks. After this time, a decrease in symptoms to grade 1 was observed (only local erythema and paraesthesia) (Fig. 5). Chemotherapy was resumed with doses reduced by 25% in accordance with the recommendations for dose modification (Table 1). The chemotherapy was continued for a further four courses, after which, due to worsening of skin symptoms on the hands, armpits and abdomen, the therapy was completed. We administered the symptomatic treatment as mentioned above. The symptoms resolved in about three weeks after the end of treatment, leaving a brown discoloration that remained for a period of several months (Fig. 6, 7).

Summary

Palmar-plantar erythrodysaesthesia in most cases is confined to the hands and feet, but dysaesthesia, erythema, skin desquamation and sores may appear in other areas of the body, especially those exposed to pressure or increased temperature [11]. In the presented case the PPE affected the axillary and inguinal region, the skin of the back and abdomen. These changes, however, may also appear on the buttocks, inframammary region, vulva or scrotum [13], deteriorating the quality of life of the patient, and impairing normal activities of daily living. Prevention strategies of palmar-plantar erythrodysaesthesia onset include the patient's education

Table 1. Recommendations for dose modification of PLD in case of palmar-plantar dysaesthesia [16]

Toxicity grade	Dose modification
1 – mild erythema, swelling, or desquamation of the skin, not interfering with daily activities	Continue treatment if the patient has not previously experienced grade 3/4 toxicity. Otherwise, delay the treatment up to two weeks and reduce the dose by 25%. Return to original dose interval
2 – erythema, desquamation of the skin or swelling interfering with but not precluding normal physical activities, small blisters or ulcerations with a diameter < 2 cm	Delay treatment up to 2 weeks or until resolved to grade 0/1, and if after 2 weeks there is no resolution of the symptoms, PLD should be discontinued
3 – blisters, ulcerations or swelling interfering with walking or normal daily activities; the patient cannot wear regular clothing	Delay treatment up to 2 weeks or until resolved to grade 0/1 Reduce the dose by 25% and return to original dose interval If after 2 weeks there is no resolution of the symptoms, PLD should be discontinued
4 – diffuse or local process causing infectious complications or bedridden state or hospitalization	Delay treatment up to 2 weeks or until resolved to grade 0/1 Reduce the dose by 25% and return to original dose interval If after 2 weeks there is no resolution of the symptoms, PLD should be discontinued

on the care of the body areas most exposed to the hand-foot changes, which includes: to avoid pressure, skin abrasions and circumstances leading to vasodilatation such as hot baths and solar radiation [9]. The use of moisturizing creams, cool baths and wearing loose clothing and footwear are also recommended [9, 15]. The list of pharmacological agents includes vitamin B6 (pyridoxine) and oral corticosteroids; however, the efficacy of these drugs in the prevention of PPE has not been confirmed by randomized clinical trials [9].

Treatment delay or chemotherapy dose reductions in accordance with the recommendations for dose modification remain the most important action in PPE treatment. Adequate hygiene of the affected skin areas, the use of moisturizing creams (containing petrolatum and lanolin), the application of antibiotic ointment in case of infection and analgesic drugs is also crucial [9]. Palmar-plantar erythrodysaesthesia is a common and very inconvenient complication of chemotherapy, which significantly impairs the patient's quality of life. Unfortunately there are no effective methods of prevention and treatment of this complication, so we are forced to lengthen the time interval between courses and reduce drug doses, which often limits the possibility of effective treatment of oncological patients.

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Address for correspondence

Bożena Cybulska-Stopa
Department of Systemic and Generalized Malignancies
Department of Centre of Oncology
Maria Sklodowska-Curie Memorial Centre
Garncarska 11
31-115 Kraków, Poland
e-mail: bcybulskastopa@vp.pl