Influence of Mechanical Stress on Palmoplantar Erythrodysesthesia – a Case Report

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Established Facts

- A possible influence of mechanical pressure on palmoplantar erythrodysesthesia (PPE) has been discussed for skin lesions on the palms of the hands and soles of the feet.
- In the literature, several therapeutic options are described, but most of them have not yielded sufficient therapeutic results regarding grade 3 PPE. So far, the most effective strategy has been the discontinuation or postponement of chemotherapeutic treatment.

Novel Insights

- We present an unusual case of extensive mechanically induced PPE skin lesions affecting various areas of the body during treatment with pegylated liposomal doxorubicin.
- We demonstrate the successful treatment of extensive PPE grade 3 allowing continuation of the scheduled chemotherapy. Our case shows the importance and effectiveness of patient education and compliance in combination with local application of an antioxidant-containing ointment as a therapeutic option for high-grade PPE patients.

Keywords

Adverse events, cutaneous · Anthracyclines · Chemotherapy · Doxorubicin, pegylated liposomal · Skin care

Summary

Background: Cutaneous adverse events can have an important negative influence on quality of life and compliance in affected patients. Palmoplantar erythrodysesthesia (PPE; hand-foot syndrome) is a cutaneous toxicity associated with chemotherapeutic treatment, which necessitates treatment interruption or dose reduction in severe cases. This case report of pegylated liposomal doxorubicin-induced PPE shows the influence of mechanical stress on the development of skin lesions in various locations and the importance of patient education and compliance. Case Report: We present the case of a 43-year-old female patient diagnosed with ovarian cancer and having undergone surgical and chemotherapeutic treatment. The development of extensive grade 3 PPE affecting numerous areas of the body particularly exposed to mechanical pressure necessitated dermatological treatment. The combination of local application of an antioxidant-containing ointment and the patient’s compliance made it possible to continue chemotherapy without interruption or dose reduction. Conclusion: The development of PPE often limits the use of chemotherapeutic agents, and this case report can provide a possible therapeutic and preventive strategy for affected patients.
Introduction

Palmoplantar erythrodysesthesia (PPE) or hand-foot syndrome is a frequent side effect of common chemotherapeutic agents such as multikinase inhibitors, anthracyclines, and taxanes [1–3]. The symptoms of grade 1–3 PPE vary from mild edema, erythema, numbness, and paresthesia to painful blisters, rhagades, and skin detachment. The severity of the disease is graded according to the U.S. National Cancer Institute classification [4]. Skin lesions mainly occur on the palms of the hands and soles of the feet; nevertheless, other areas, such as the axillary or submammary region, can also be affected by correspondent inflammatory skin lesions. Data on the incidence of PPE vary in the literature, ranging from 23 to 78% for PPE associated with pegylated (PEG) liposomal doxorubicin [5–7] and up to 89% for the combination of doxorubicin and 5-fluourouracil (FU) [8, 9]. Even though symptomatic treatment strategies for skin lesions in the form of cooling of the affected areas and use of pyridoxine, topical dimethylsulfoxide, oral and topical corticosteroids and other anti-inflammatory substances have already been explored and implemented [10–13], so far no causative treatment of PPE has been established as such. Furthermore, dose reductions and postponement or cessation of the chemotherapeutic treatment are often resorted to as the final therapeutic option. Moreover, the pathogenesis of PPE has also not yet been fully ascertained; a graft-versus-host-like reaction had been discussed, whereas histopathologic and clinical findings suggest a toxic effect on epidermal keratinocytes [14–16]. It has been shown that doxorubicin is excreted through the sweat glands after intravenous application and is spread on the dermal surface where it can penetrate into the skin and accumulate during the course of chemotherapy [17–19]. The thickness of the epidermal layer as well as the high density of sweat glands in the palmar and plantar area could explain the characteristic dominance of symptoms in acral sites. Hence, PPE symptoms could be explained as a local toxic effect of doxorubicin on epidermal keratinocytes.

A number of reports have suggested that PPE might be correlated with improved therapeutic effects and higher survival rates based on enhanced exposure to the chemotherapeutic agent [14, 20]. Recently, Lademann et al. [3, 21] showed that continuous local application of an ointment containing highly concentrated antioxidants exhibiting a radical protection factor of at least 4,000 (patent WO 2008023064 A2) is an effective prevention strategy against PPE providing even therapeutic effects.

Several enhancing effects for PPE development under chemotherapeutic treatment have been discussed, such as heat exposure, chemical noxae, hyperhidrosis, excessive ultraviolet radiation, and mechanical stress [10, 22]. Within this report, a case of extensive PEG doxorubicin-induced PPE in mechanically stressed areas of the body is described. Local treatment resulting in partial regression of the symptoms improved the quality of life in this patient and enabled her to finish the scheduled chemotherapeutic treatment without interruption or dose reduction.

Case Report

Here, we report the case of a 43-year-old female patient treated with PEG liposomal doxorubicin. The patient was initially diagnosed with ovarian cancer in 1999, followed by surgical intervention and chemotherapeutical treatment with carboplatin and paclitaxel. After a relapse in 2009, peritoneal and hepatic metastases were diagnosed which necessitated further surgery including tumor debulking, radical hysterectomy, lymphonodectomy, and partial peritoneal resection. The patient was subsequently treated with a combination of carboplatin and gemcitabine in 2010, followed by 6 cycles of topotecan in 2012. Prior to that, in 2009, the patient’s lower left leg had to be amputated due to the occurrence of compartment syndrome with occlusion of the left femoral artery, necessitating the use of a wheelchair and an above-the-knee prosthesis from that point onward. In 2013, a therapy with PEG doxorubicin, 40 mg/m² every 4 weeks, was initiated in an outpatient setting.

The treatment was initially well tolerated by the patient and did not show significant side effects except for mild fatigue, intermittent diarrhea, and lack of appetite during the first 3 chemotherapy cycles. After the 3rd cycle of PEG doxorubicin, the patient described tingling and pruritic sensations in different areas with emphasis on the palmar finger tips and plantar-dorsal and medial areas of the right foot concordant with PPE grade 1, which did not notably impair the patient’s daily activities. Moreover, the patient showed PPE grade 2 on the left hand in the area of her wedding ring, from which she felt a burning sensation when manually moving her wheelchair. The patient was advised to refrain from wearing the ring during further treatment with PEG doxorubicin in order to reduce mechanical stress, and to ensure appropriate application of the ointment. After the 4th cycle of PEG doxorubicin, the patient developed PPE grade 2–3 in various sites. The affected regions were mostly areas exposed to significant mechanical stress due to the patient’s sitting position in the wheelchair and the use of a prosthesis. Most of the affected skin areas were in direct contact with the wheelchair or frequently under mechanical strain. The medical examination showed painful erythema and rhagades on the palms of the hands, which worsened when the patient moved about more extensively with her wheelchair. Furthermore, painful erythema, maculopapular rash, and erosions were found on the elbows and dorsal forearms, the dorsal upper arms, and the upper back and dorsal thigh, which can all be described as areas of mechanical pressure while sitting in the wheelchair. Moreover, the sternum as well as the interdigital areas of the right foot showed painful weeping erosions concordant with PPE grade 3. The large surface and dissemination of the skin lesions significantly impaired the quality of life in this patient and restricted her daily activities, leading to a need for additional support regarding home care and personal care.

After 3 days of local treatment (3 times daily) of the affected areas with an antioxidant-containing ointment (Mapisal® medac GmbH, Hamburg, Germany) providing a high radical protection factor (RPF), the PPE grade 3 symptoms improved to grade 1–2. The infraestrernal skin lesions completely disappeared after 1 week of local treatment. Motivated by these positive results, the patient showed increased compliance applying the cream up to 10 times per day to the affected areas. Reducing mechanical stress was only partially feasible due to the patient’s physical condition and personal circumstances. Although new skin lesions developed, especially in border areas of present skin lesions which had not been treated with the antioxidant formulation before, all existent PPE lesions remained stable at grade 1–2 under the described topical treatment. This had several advantages for the patient. It not only lead to a notable improvement in her quality of life, but also made it possible for her to continue the chemotherapeutical treatment for 2 more cycles without dose reduction or postponement of infusions. The skin lesions remarkably improved after termination of the chemotherapy and showed complete regression 6 weeks after the last cycle of PEG doxorubicin.

Conclusion

Efficient treatment and prevention of PPE can significantly improve patients’ quality of life during chemotherapy. In this case report, the importance of mechanical stress and pressure for the de-
velopment of PPE was shown, underlining the importance of education regarding behavioral prevention strategies and avoidable triggers. Moreover, this case shows that awareness and self-observation of the patient also play an important role in the progression of PPE symptoms; our patient independently performed the topical treatment of additionally affected areas at an early stage without first consulting a physician during the 4-week intervals between appointments. Hence, patient education and monitoring play an essential role in the prevention of PPE, ensuring that early intervention strategies are implemented as needed.

Once PPE skin lesions have developed, the healing process takes up to several weeks until the complete resolution of skin symptoms, especially while chemotherapy is ongoing. Therefore, a combined prevention strategy is recommended consisting of adequate behavioral measures and application of an antioxidant-containing cream providing a high RPF during the entire period of chemotherapeutic treatment. The efficiency of oral or topical antioxidant substances in the treatment of PPE has been shown in previous studies [3, 21, 23, 24] favoring the assumption of a pathomechanism based on the topical formation of free radicals in the skin after excretion of the chemotherapeutic agent [18, 19]. The high RPF and the continuous topical application of ointment enhance the antioxidant efficiency at the site of application. Topical ointment not only leads to immediate neutralization of free radicals but also serves as a protective film impeding the accumulation of the chemotherapeutic agent in the stratum corneum [3, 19, 21, 25]. Since topical antioxidant application in PPE patients has been investigated only recently, the available data is limited. Further randomized controlled trials are needed to confirm the preventive and therapeutic effects.

In conclusion, it can be stated that diligent medical observation as well as adequate patient education on cutaneous side effects combined with the topical application of a preventive antioxidant formulation can enhance the quality of life in cancer patients at risk of PPE, and avoid interruption or discontinuation of cancer therapy as the final treatment option.

Disclosure Statement

The authors declare no conflict of interest.

References


