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Antineoplastic Therapy–Induced Palmar Plantar Erythrodysesthesia ('Hand-Foot') Syndrome

Incidence, Recognition and Management

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Contents

Abstract

Palmar plantar erythrodysesthesia (PPE) is a distinctive and relatively frequent toxic reaction related to some chemotherapeutic agents. Doxorubicin, cytarabine, docetaxel, and fluorouracil are the most frequently implicated agents. PPE seems to be dose dependent and both peak drug concentration and total cumulative dose determine its occurrence.

PPE presents as a painful erythema, often preceded by paresthesia, located on the palms and soles in the context of treatment with chemotherapy. Histologically, PPE shows few specific findings. Mild spongiosis, scattered necrotic and dyskeratotic keratinocytes and vacuolar degeneration of the basal layer is seen. Dermal changes in most cases include dilated blood vessels, papillary edema, and a sparse superficial perivascular lymphohistiocytic infiltrate can be found in varying degrees in the epidermis.

Withdrawal or dose reduction of the implicated drug usually gives rise to amelioration of the symptoms. Supportive treatments such as topical wound care, elevation, and cold compresses may help to relieve the pain. Use of systemic corticosteroids, pyridoxine (vitamin B6), blood flow reduction, and, recently, topical 99% dimethyl-sulfoxide have been used with variable outcomes. It could be of interest to consider them as preventive measures when drugs with a strong association with PPE are going to be administered.

Table I. Agents that have been associated with palmar plantar erythrodysesthesia

Most frequently associated
Cytarabine
Docetaxel
Doxorubicin and liposome-encapsulated doxorubicin
Fluorouracil
Less frequently associated
Capecitabine
Cisplatin
Cyclophosphamide
Daunorubicin
Doxifluridine
Etoposide
Floxuridine
Hydroxyurea (hydroxycarbamide)
Mercaptopurine
Methotrexate
Mitotane
Paclitaxel
Tegafur
Vinorelbine

1. Incidence

Palmar plantar erythrodysesthesia (PPE) is a cutaneous drug reaction that is most often induced by chemotherapeutic agents. It is important to be aware of this reaction since it can be a dose-limiting toxicity.

PPE was firstly described by Zuehlke in 1974 associated with mitotane therapy for hypernephroma.[1] Subsequently, many reports, using different terms for the condition (acral erythema, hand-foot syndrome, palmar-plantar erythema, Burgdorf's reaction, and toxic erythema of the palms and soles), have appeared in the literature.[2]

Many drugs have been implicated as causing PPE. Cytarabine, doxorubicin, fluorouracil, and docetaxel are the most commonly involved drugs, although many others have also been reported to cause this condition (table I).[1-89] Nevertheless, it is very difficult to assess the real relationship between PPE and some agents since most cases are described in the context of different multidrug regimens.

The actual incidence of PPE is very difficult to determine because most reports in literature are isolated case reports or short case series, and when a drug is evaluated by oncologists in large series, its cutaneous reactions are usually mentioned with few details. However, an estimation can be made by considering some case series in which PPE has been found to occurs in 6 to 64% of patients treated with different chemotherapy regimens.[34,89] In most cases (nearly 80%), patients present with less severe grades of PPE [1 and 2 of WHO criteria and 1 of the National Cancer Institute (NCI) criteria (these criteria are described in section 2)],[18,62] although the severity is very variable depending on the chemotherapy regimen, and some series have reported more frequent severe toxicity.[57]

We review herein some of the major aspects of PPE and detailed information in those drugs which are more frequently associated with this reaction. To this end, we have systematically reviewed articles obtained from MEDLINE published between 1966 and March 2000 using all the synonymous for PPE mentioned earlier as key words.

2. Clinical Presentation

Whatever the causative agent, the clinical presentation of PPE is very similar and is distinct from other adverse skin reactions.[8,19,23,26,27,34,38,55,59,65,66,73,88-91]

Most patients present with a prodrome of dysesthesia, usually a tingling sensation of the palms and soles. In a few days, it progresses to a burning pain in conjunction with well-defined swelling and erythema. The erythema is symmetric, and sometimes more marked over the pads of the distal phalanges. Some patients may develop alternating bands of erythema over joint surfaces or have periungual skin involvement. The hands are usually more severely affected than the feet, and may be the only area involved (figs 1 and 2). Rarely, erythema may also be noted outside the palmar and plantar regions.[29,47] Some patients may only present with fine desquamation with or without erythema. A bullous variant has also been described, specifically associated with cytarab-

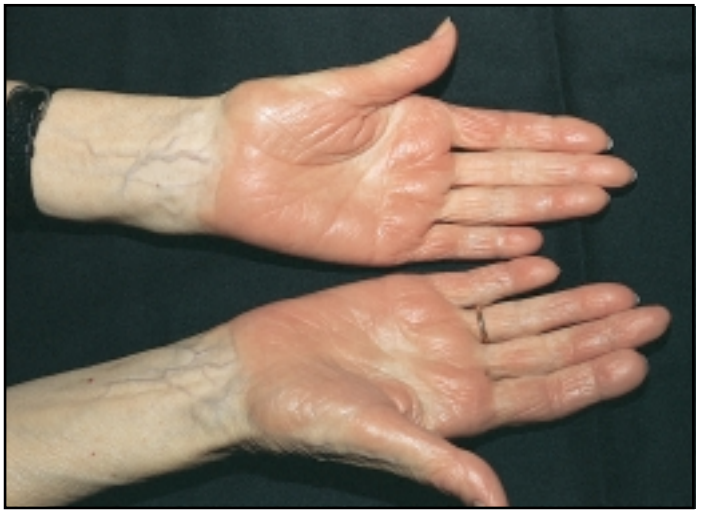

Fig. 1. Palmar edema and erythema, with fine desquamation (palmar plantar erythrodysesthesia WHO grade 2).

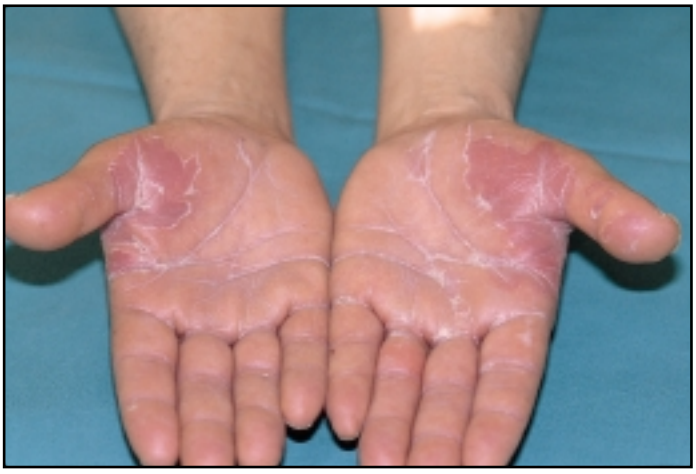

Fig. 2. Palmar erythema, with fissuration (palmar plantar erythrodysesthesia WHO grade 3).

ine or methotrexate.[39,76] However, in our experience, bullous PPE may appear with other agents such as fluorouracil or doxorubicin (fig. 3). Bullous PPE is merely a severe form of this entity. The lesions tend to worsen if therapy is continued, and tenderness and associated edema may cause restriction of the fine movements of the fingers.[37] The erythema becomes darker or violaceous, and spreads to involve the entire surface of the palms and soles. The pain may be so severe that daily activities are limited. If the drug responsible is stopped within a few days of the reactions appearing a gradual clearing of symptoms will occur over a period of 2 weeks. Areas of pallor with blisters develop, and eventually desquamate with extensive, but superficial, exfoliation. In some patients, when treatment is continued despite the appearance of the PPE, lesions may evolve into a palmoplantar keratoderma.[44,65] In rare instances, long term sequelae may occur despite cessation of chemotherapy, with persistence of abnormal sensation and appearance of the affected digits.[7]

PPE seems to be dose dependent. Both peak drug concentration and total cumulative dose determine its occurrence because regimens with either bolus (short term) infusions or continuous low dosage administration can induce the reaction in a dose-dependent manner.[6,40,47,51] In general, the reaction happens sooner (from 24 hours to 2 or 3 weeks) and more severely with bolus or short term chemotherapy than with low-dose continuous infusions (up to 2 to 10 months). Rechallenge of patients with the causative chemotherapeutic agents using similar dosage schedules has lead to recurrence of the reaction in most but not all patients.[25,29,52,61]

There are a number of different classifications for grading the degree of severity of PPE, but the two most often used are those from WHO and NCI (table II). These classifications are of interest because, according to some protocols, a high degree of severity may necessitate a dose reduction for some drugs. When WHO grade 3 or 4 or NCI grade 3 toxicity first appears, or WHO grade 2 toxicity appears repeatedly, the dosage should be decreased to 50 or 75% of the initial dosage, or the drug discontinued. Drug withdrawal is preferable if toxicity of these grades recurs even after the dosage is decreased.

3. Pathology

There are no studies with a large series which describe histologic findings. However, some case reports include histologic evaluation (table III).[8,15,19,23,24,26,27,34,38,50,59,63,65,66,73,79,87-90,92]

PPE is a clinical variant of a cytotoxic reaction that primarily affects keratinocytes, and the histopathologic findings are similar to those seen with direct toxic reactions, such as radiation recall dermatitis, localized epidermal necrolysis or generalized epidermal necrolysis. All these adverse skin reactions demonstrate the same basic histologic pattern of an interface dermatitis with a cell-poor infiltrate and a variable degree of epidermal necrosis.[92]

Early or mild cytotoxic reactions (PPE WHO grades 1 and 2) show isolated necrotic basal keratinocytes (fig. 4). In severe cytotoxic reactions (WHO grades 3 and 4) the entire basal layer is destroyed, and a blister may form together with complete epidermal necrosis (fig. 5).[15]

Dermal changes in most cases include dilated blood vessels, papillary edema, and a sparse superficial perivascular lymphohistiocytic infiltrate. Eccrine glands may also be involved in some

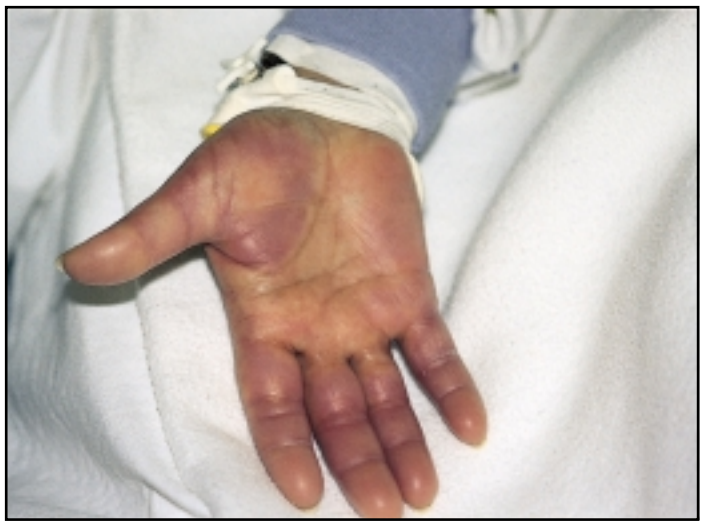

Fig. 3. Palmar edema, erythema, and blisters in the lateral aspects of the digits (palmar plantar erythrodysesthesia WHO grade 4).

Table II. Classification of palmar plantar erythrodysesthesia severity according to WHO and National Cancer Institute (NCI) criteria

WHO criteria		NCI criteria	
grade	definition	grade	definition
1	Dysesthesia/paresthesia, tingling in the hands and feet	1	Skin changes or dermatitis without pain (e.g., erythema, peeling)
2	Discomfort in holding objects and upon walking, painless swelling or erythema		
3	Painful erythema and swelling of palms and soles, periungual erythema and swelling	2	Skin changes with pain, not interfering with function
4	Desquamation, ulceration, blistering, severe pain	3	Skin changes with pain interfering with function

cases. Eccrine squamous syringometaplasia may also be seen in some cases of severe PPE (WHO grades 3 and 4) (fig. 6).[66,90]

4. Pathogenesis

The cause of PPE is currently unknown. Formerly, as there are some clinical and histologic similarities between PPE and acute graft-versus-host disease (AGVHD) it has been suggested that chemotherapeutic drug-induced changes in cell surface receptors might be able to induce host-versus-altered host changes.[9] However, currently, the most likely and accepted hypothesis is a direct toxic effect of the chemotherapeutic drug against epidermal cells because of the dose-relationship and the common histopathologic findings with other entities produced by direct toxicity.[92,93] It is of interest that PPE is a dose-limiting factor in some treatment regimens, when other toxicities can be modulated. Nevertheless, there is not a clear explanation for its particular distribution. Specific features of the hands and feet could play a role in its location. The thick stratum corneum, the temperature gradient, the vascular anatomy, the rapidly dividing epidermis, the absence of sebaceous glands and hairs follicles, the high concentration of eccrine glands, and wide dermal papillae may all be important in the pathogenesis.[88,89] Other traits must be involved since there is no direct relationship between drug, dosage, and severity in all patients. Concomitant drug therapy, transfusions, blood transfusions, and the metabolic status of the patient may contribute as well.[24,89]

5. Differential Diagnosis

Although the diagnosis is usually evident, it may be difficult to differentiate PPE from AGVHD when the reaction occurs in a patient who has received a bone marrow transplant.[89-90] Moreover, both disorders may occur simultaneously. Other signs of the disease may provide clues in the case of AGVHD, such as gastrointestinal abnormalities (including diarrhea and abdominal pain), elevated liver enzymes levels, and a rapid decline in the T helper cell/suppressor cell ratio.[90] However, in the absence of extracutaneous involvement, AGVHD can appear identical to PPE.[89] The involvement of the palms and soles in AGVHD is usually a diffuse macular erythema which may form papules, in contrast to the areas of well-defined intense erythema and edema that are seen in PPE.[90] Histologically, both PPE and AGVHD are indistinguishable in their early stages. Serial biopsies may sometimes be needed to differentiate between them.[24] The presence of degenerate keratinocytes, at all levels of the epidermis and associated with adjacent lymphocytes (satellite cell necrosis), are characteristic of AGVHD.[94] In contrast, the finding of squamous syringometaplasia suggests PPE.[90]

It is important to distinguish between these 2 entities because they require different treatment. Moreover, cyclosporine infusion, which is one of the most important treatments for AGVHD, is reported to worsen the pain of PPE possibly due the alcohol present in the infusion.[45]

6. Specific Comments on Relevant Drugs

In this section we describe the more relevant and specific characteristics displayed by the drugs associated with a high in-

Table III. Histologic grades with their corresponding clinical expression (related to WHO criteria)

Grade	Clinical lesion	Histologic findings
1	Erythema	Dilated blood vessels of the superficial dermal plexus
2	1 + edema	
3	2 + fissuration	Isolated necrotic keratinocytes in higher layer of the epidermis
4	3 + blister	Complete epidermal necrosis

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