

Erythrodysesthesia-like skin eruption due to docetaxel with a nonimmediate positive intradermal skin test result

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Clinical Implications

- We report a case of delayed maculopapular exanthema with swelling of the hands, acral erythema, and onycholysis due to docetaxel with a nonimmediate positive intradermal test result and histopathologic features that suggest a type IV hypersensitivity mechanism.

TO THE EDITOR:

Docetaxel is a frequently used chemotherapeutic agent belonging to the taxane family. It was first discovered in 1986 and is a semi-synthetic compound derived from the needles of the European yew (*Taxus baccata*). These cytotoxic agents are commonly associated with cutaneous adverse reactions such as urticaria, maculopapular exanthemas, pruritus, mucositis, and palmoplantar erythrodysesthesia (PPE).¹ Usually, skin tests are not useful for diagnosis in these patients.

We report the case of a 77-year-old man without a personal history of allergy. He had a history of several primary tumors: colon (1990), bladder (2005), and prostate (2008).

In 2008, he underwent a transurethral resection for treatment of prostate carcinoma. Because of a poor response to treatment with hormonal therapy, in August 2011 he began systemic chemotherapy with docetaxel, with a positive response.

Twenty-four hours after the seventh cycle of chemotherapy with docetaxel, he developed a micropapular chest exanthema and swelling of the hands, which was treated with topical betamethasone. Seven days later he was seen in the emergency department because he began to suffer paresthesias and pain in the upper and lower limbs, accompanied by functional limitation. The physical examination showed a marked violaceous erythema and swelling of hands and feet (without vesicles, blisters, or necrosis) accompanied by hyperpigmentation and onycholysis. The palms and soles were also affected, but with less intensity. He was treated with topical steroids with resolution of symptoms and improvement after 4 weeks, with skin desquamation of the affected areas.

He was diagnosed with PPE grade 3 according to the National Cancer Institute scale.² One month later, we performed an allergy study: intradermal skin test (IDT) with optimal and nonirritant docetaxel concentrations³ (0.1 and 1 mg/mL), the result for which was negative at immediate and delayed readings day 2 (D2) and 4 (D4) and turned positive at D6, with 2 erythematous-violaceous macules with well-defined lines that turned more purple on D8 (Figure 1). After the results, we proposed the study with paclitaxel, but the patient did not provide consent for performing more tests. These IDT dilutions are used in patients suspected of a hypersensitivity reaction to docetaxel, and we have only 1 positive late-reading test result, which was in the present patient.

Skin biopsy of these lesions showed a moderately acanthotic epidermis with frequent necrotic keratinocytes in the basal layers, accompanied by a marked vacuolar degeneration of the basal layer. In the underlying dermis, a moderate perivascular inflammatory lymphoid infiltrate and marked perivascular extravasation of erythrocytes was seen. There were no signs of vasculitis, fibrinoid necrosis of the vessel wall, or acute infiltrates (Figure 2). It was suggestive of lichenoid dermatitis consistent with fixed drug eruption.



FIGURE 1. Nonimmediate (sixth and eighth days) positive IDT results with docetaxel at concentrations of 0.1 and 1 mg/mL.

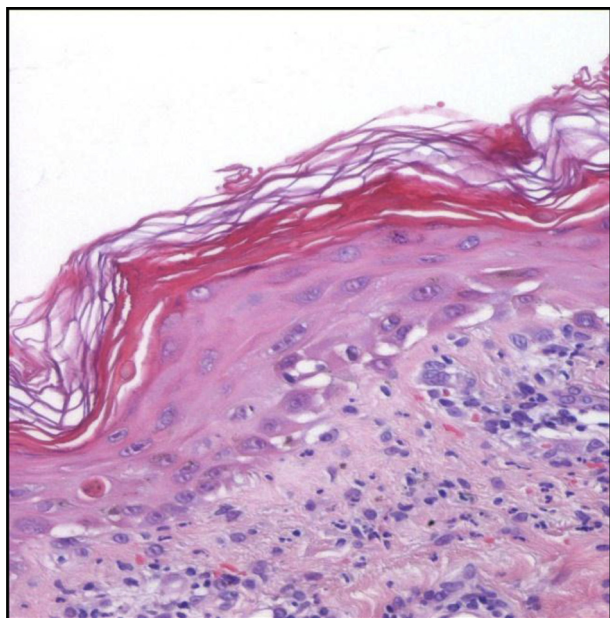


FIGURE 2. Biopsy of the lesions showed acanthotic epidermis, keratinocytes in the basal layers, marked vacuolar degeneration of the basal, perivascular inflammatory infiltrate lymphoid, and marked perivascular extravasation of erythrocytes.

PPE, also called acral erythema or hand-foot syndrome, was described in 1984 by Lokich and Moore.⁴ PPE is characterized by painful erythematous lesions that mainly affect palmoplantar surfaces. Patients may experience palmoplantar dysesthesia. Symptoms include burning pain and sharply demarcated erythema with edematous swelling, which may develop into blistering, desquamation of the horny layer, and subsequent ulceration or erosions.⁵ It is a clinical pattern that has been described only with chemotherapeutic agents, typically with 5-fluoracil, doxorubicin, capecitabine, docetaxel, and methotrexate.⁶ In some patients, it is a cause of dose reduction or even withdrawal of the drug. Cross-hypersensitivity reactions between paclitaxel and docetaxel occurred in a significant proportion of patients, around 90%.⁷

The pathophysiological mechanism in PPE is not entirely clear, but it seems to be dose dependent and its occurrence is related to both peak drug concentration and total cumulative dose. The acral location of the lesions is probably due to several factors, such as the accumulation of metabolites excreted by eccrine sweat glands favored by hyperhidrosis of these areas, extravasation microcapillary on palms and soles, and deposits in the stratum corneum of the skin.⁸ Also, it has been suggested to be a local inflammatory tissue reaction, probably mediated by cyclooxygenase. In some reports, treatment with the cyclooxygenase-2 inhibitor celecoxib, along with the chemotherapy agent, has been effective in reducing the number of cases of PPE.^{9,10}

In some other cases reported in the literature with docetaxel, the eruption became more widespread to include the thorax.¹¹ In such patients, it has been suggested to use the term erythrodysesthesia

instead of acral erythema. PPE can also manifest like a solitary erythematous plaque or fixed erythrodysesthesia plaque in the dorsum of the hands and forearms.¹² In our patient, the IDT is compatible with this cutaneous pattern and the histopathology of the lesion is reminiscent of a fixed drug eruption, which would suggest the existence of a possible type IV hypersensitivity reaction mediated by T cells in the pathogenesis.

This is a novel case of delayed maculopapular exanthema with swelling of the hands, acral erythema, and onycholysis due to docetaxel, with a nonimmediate positive IDT result. These data suggest a type IV hypersensitivity reaction. To our knowledge, it is the first time that a positive skin test result has been demonstrated with this reaction. Therefore, although skin test results are assumed to be negative in taxane-induced nonimmediate hypersensitivity reactions, we recommend performing skin tests with this group of drugs with delayed readings, which may help clarify the pathogenetic mechanism of this clinical entity.

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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REFERENCES

- Price KS, Castells MC. Taxol reactions. *Allergy Asthma Proc* 2002;23:205-8.
- National Cancer Institute. Common toxicity criteria. Cancer Therapy Evaluation Programme; 1999. National Cancer Institute. Cancer Therapy Evaluation Program. Common Toxicity Criteria Manual, Version 2.0; June 1, 1999. CTEP Website. <http://ctep.info.nih.gov>. Accessed November 9, 2015.
- Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002;57:45-51.
- Lokich JJ, Moore C. Chemotherapy-associated palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1984;101:798-9.
- Degen A, Alter M, Schenck F, Satzger I, Völker B, Kapp A, et al. The hand-foot-syndrome associated with medical tumor therapy—classification and management [in English, German]. *J Dtsch Dermatol Ges* 2010;8: 652-61.
- Eich D, Scharffetter-Kochanek K, Eich HT, Tantcheva-Poor I, Krieg T. Acral erythrodysesthesia syndrome caused by intravenous infusion of docetaxel in breast cancer. *Am J Clin Oncol* 2002;25:599-602.
- Dizon DS, Schwartz J, Rojan A, Miller J. Cross-sensitivity between paclitaxel and docetaxel in women's cancers programs. *Gynecol Oncol* 2006;100: 149-51.
- Lorusso D, Di Stefano A, Carone V, Fagotti A, Pisconti S, Scambia G. Pegylated liposomal doxorubicin-related palmar-plantar erythrodysesthesia ('hand-foot' syndrome). *Ann Oncol* 2007;18:1159-64.
- Lin E, Morris JS, Ayers GD. Effect of celecoxib on capecitabine-induced hand-foot syndrome and antitumor activity. *Oncology (Williston Park)* 2002;16:31-7.
- Kara IO, Sahin B, Erkiş M. Palmar-plantar erythrodysesthesia due to docetaxel-capecitabine therapy is treated with vitamin E without dose reduction. *Breast* 2006;15:414-24.
- Zimmerman GC, Keeling JH, Burris HA, Cook G, Irvin R, Kuhn J, et al. Acute cutaneous reactions to docetaxel, a new chemotherapeutic agents. *Arch Dermatol* 1995;131:202-6.
- Chu CY, Yang CH, Yang CY, Hsiao GH, Chiu HC. Fixed erythrodysesthesia plaque due to intravenous injection of docetaxel. *Br J Dermatol* 2000;14:808-11.

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