Fixed Erythrodysaesthesia Plaque due to Gemcitabine and Epirubicin Treatment

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Sir,

Fixed erythrodysaesthesia plaque (FEP) is a unique cutaneous reaction due to intravenous injection of docetaxel. It presents as fixed erythematous plaque(s) unrelated to extravasation or previous skin injury (1). Gemcitabine (difluorodeoxycytidine, 2',2'-difluorodeoxycytidine; dFdC) is a deoxycytidine analogue with structural and metabolic similarities to cytarabine (ara-C) (2). It mimics the structure of the natural nucleoside and, following phosphorylation, is incorporated into DNA (3). Several previous reports have shown that gemcitabine alone or in combination with cisplatin is active against non-small-cell lung cancer (NSCLC) with little cutaneous toxicities (4–6). Epirubicin is the 4' epimer of the anthracycline antibiotic doxorubicin (7). A combination of epirubicin and gemcitabine has been reported to be effective in treating patients with advanced NSCLC (8). We report the development of FEP on both forearms of a patient treated with gemcitabine and epirubicin.

CASE REPORT

A 60-year-old man was diagnosed as having stage IV adenocarcinoma of the lung with bone metastasis and left pleural effusion in 1999. His body surface area was 2.0 m^2. Chemotherapy was administered with intravenous infusion of gemcitabine 1000 mg/m^2 for 30 min on days 1, 8 and 15 as well as intravenous infusion of cisplatin 80 mg/m^2 on day 15 since 1999. The premedications were intravenous infusion of granisetron, dexamethasone sodium phosphate and furosemide on day 15 before administration of cisplatin. The dosage of gemcitabine was decreased to 900 mg/m^2 on day 8 of the first cycle due to grade 2 leukopenia and grade 3 thrombocytopenia. Because cisplatin-induced sodium-losing nephropathy was noted, cisplatin was changed to intravenous infusion of epirubicin 120 mg on day 15 at the second cycle. One week after the infusion of gemcitabine and epirubicin, a well-demarcated, palm-sized, erythematous plaque with a preceding dysaesthesia (a tingling, painful sensation) was noted over the right forearm. Erysipelas was the initial impression at that time, and oral dicloxacillin was administered for 2 weeks. He received further treatment of gemcitabine and epirubicin, and 3 other similar plaques developed on his left arm one month later (Fig. 1), while the right arm lesion persisted. There was neither a history of previous skin injury over these areas nor extravasation during infusion of gemcitabine and epirubicin. Furthermore, the patient had no clinical picture of acral erythema. One skin biopsy undertaken on the left arm lesion showed epidermal dysmaturation, frequent dyskeratosis, interface dermatitis, pigment incontinence and a superficial dermal perivascular mononuclear cell infiltrate (Fig. 2). Betamethasone valerate cream and salicylate ointment were given as topical therapy. The plaques became desquamated, crusted and their colour darkened to brown. One month later, all the skin lesions resolved with only slight hyperpigmentation. No recurrence of the skin lesions was noted even though the patient

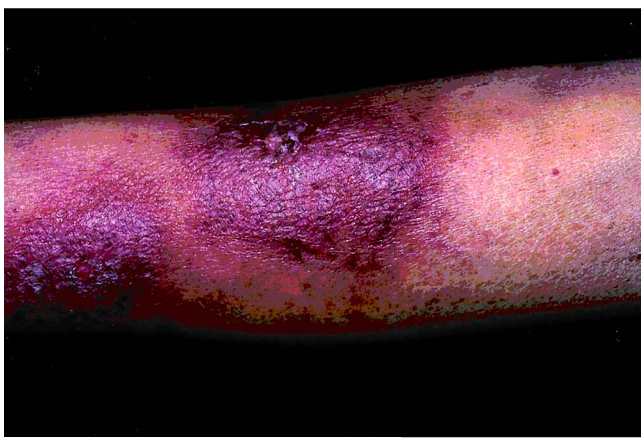

Fig. 1. Hen-egg-sized, erythematous to brownish, infiltrated plaques presented on the left forearm.

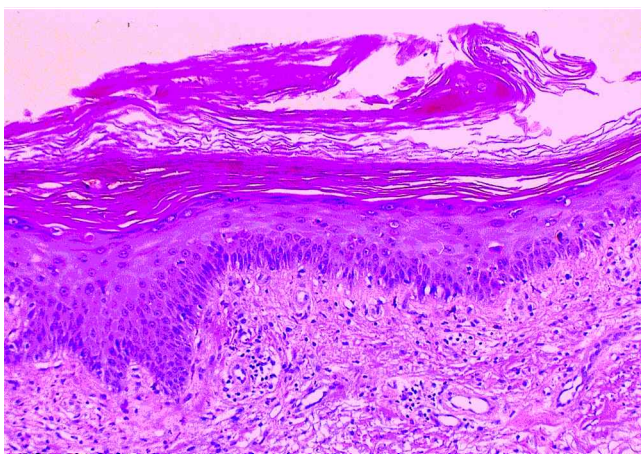

Fig. 2. Histopathological study showed epidermal dysmaturation, frequent dyskeratosis, interface dermatitis, pigment incontinence and a superficial dermal perivascular mononuclear cell infiltrate (haematoxylin and eosin; original magnification ×100).

received two further cycles of gemcitabine and epirubicin.

DISCUSSION

FEP is a docetaxel-induced cutaneous reaction presenting as fixed erythematous plaque(s) unrelated to extravasation or previous skin injury. Its histopathological findings are similar to those of acral erythema (1). We propose that it is a special form of acral erythema without involvement of the palms and soles. It usually develops 7–14 days after the first injection of the second cycle of docetaxel, and then resolves with desquamation, leaving hyperpigmentation 5–6 weeks later. The reaction usually does not recur even though patients receive further treatment courses of docetaxel (1).

The skin reactions of gemcitabine included a maculopapular eruption and alopecia, which were rarely reported (4, 9). Epirubicin can induce several types of skin reaction, such as urticaria/angioedema, both irritant and vesicant type reactions of extravasation, and alopecia (10). Acral erythema due to gemcitabine or epirubicin treatment has not been reported (10). Although cisplatin-induced acral erythema is a well-known skin reaction (10), development of the patient's skin lesions after discontinuation of cisplatin makes it unlikely to be the causative agent. The patient did not receive other alternative remedies, such as Chinese herbal medicine. Till now, we have seen that only one patient receiving gemcitabine and epirubicin treatment developed FEP. No other chemotherapeutic agents used in our hospital, except docetaxel, had been noted to induce FEP. Therefore procedure-related adverse drug reactions could be excluded. Based on the patient's history and the previous report, gemcitabine seems to be the most likely cause of FEP, since the skin reaction developed about 7 days after the third injection of the first cycle of gemcitabine (1). However, the possibility that FEP was induced by epirubicin still cannot be ruled out.

The mechanism of developing FEP is not clear, but the absence of recurrent lesions makes an allergic basis for the reaction unlikely (1). In addition, previous reports about the cutaneous reactions of docetaxel treatment from the United States (11) and Portugal (12) have also described a similar reaction in 3 and 2 of their patients, respectively, suggesting that patients from different genetic backgrounds do not have different susceptibility to this unique drug reaction.

This is the first report of FEP due to chemotherapeutic agents other than docetaxel. We surmise that FEP is not a cutaneous reaction induced by docetaxel alone, but a special form of cutaneous reaction that could be induced by other antineoplastic agents.

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