Chemotherapy-induced Acral Erythema

Sir,

Chemotherapy-induced acral erythema (CIAE) is a cytotoxic drug reaction to certain systemic chemotherapeutic agents, such as fluorouracil, doxorubicin, and especially cytosine arabinoside (1). Following discontinuation of chemotherapy, cutaneous lesions subside in 1–2 weeks with eventual desquamation. Rechallenge of patients with similar chemotherapeutic agents has reproduced the reaction in most but not all cases.

PATIENTS AND METHODS

Between August 1985 and February 1998, a total of 15 patients admitted to our institution developed CIAE after receiving different chemotherapeutic regimens for solid tumours and haematological malignancies (Table I).

RESULTS

All 15 patients initially experienced a prodrome of dysesthesia (referred as a burning or tingling sensation), followed in a few days by a painful (11 patients) or mildly to severe pruriginous (4 patients) and symmetrical, swelling and erythema of the palms (Fig. 1). In 12 patients the plantar surfaces were also affected. Clinical lesions were diffuse and well defined in most cases (9 patients), whereas some patients (6 cases) developed erythematous to violaceous plaques with sparing areas. Extension over the dorsa of the hands was noticed in 2 patients. In 6 patients (5

Table I. *Clinical features of patients with CIAE*

Patients (number/sex/age in years)	Diagnosis	Treatment chemotherapy/BMT	Clinical lesions	Onset after chemotherapy/BMT (days)	Resolution (days)
1/F/58	Colon carcinoma	Tegafur	DPP Keratodermia	60	10
2/F/57	Gastric carcinoma	Tegafur	DPP	90	7–10
3/F/42	Breast cancer	Fluorouracil	PPP	3	7–10
4/F/27	CML	Cytarabine, daunorubicine, cyclosporin, methotrexate/BMT	DPP Mobilliform eruption	21/–4	10
5/M/61	AML	Cytarabine, daunorubicine	Palmar erythematous plaques	11	14
6/F/34	Hodgkin disease	Etoposide, cyclophosphamide carmustine/BMT	DPP Dorsae of hands Morbilliform eruption	9/+1	12
7/F/27	Hodgkin disease	Etoposide, cyclophosphamide carmustine/BMT	DPP Morbilliform eruption Flexural lesions	2/–2	10
8/F/24	ALL	Etoposide, melphalan, cyclosporin, methotrexate/PBSCT	DPP Morbilliform eruption Flexural lesions	7/–1	10
9/F/56	Vesical urothelioma	Mitomycin	Palmar diffuse Morbilliform eruption	1–3	14
10/F/27	CML	Hydroxyurea	Palmar erythematous plaques	30	10
11/F/40	CML	Busulfan, cyclophosphamide cyclosporin, methotrexate/BMT	PPP	26/+15	12
12/M/44	Multiple myeloma	Busulfan, cyclophosphamide thiotepa, cyclosporin methotrexate/BMT	Palmar diffuse Morbilliform eruption Flexural lesions	9/+1	10
13/M/49	Myelodysplastic syndrome	Busulfan, cyclophosphamide cyclosporin, methotrexate/BMT	PPP Flexural lesions	23/+16	7
14/F/47	ALL	cyclophosphamide cyclosporin, methrotexate, TBI/BMT	DPP Flexural lesions	10/+4	8
15/F/48	Ovarian carcinoma	cisplatin, Taxol	PPP Dorsae of hands and forearms	7	21

CML, chronic myelogenous leukaemia; AML, acute myelogenous leukaemia; ALL, acute lymphocytic leukaemia; CT, chemotherapy; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; DPP, diffuse palmoplantar erythema; PPP, palmoplantar erythematous plaques.

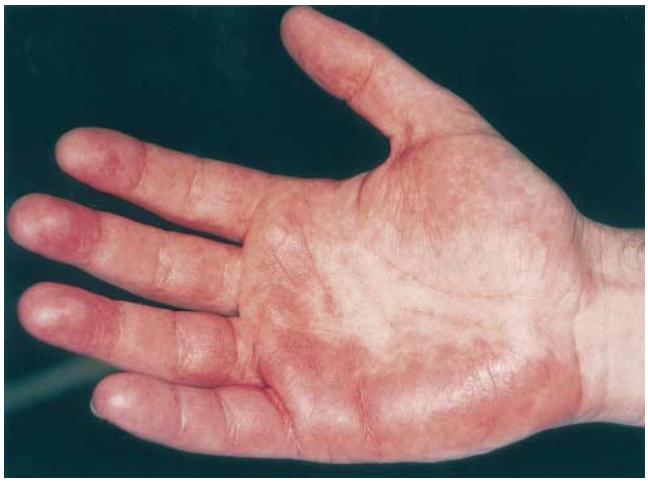

Fig. 1. Edematous erythematous plaques on the palmar surface of the hand.

with polychemotherapy and case 9 receiving only mytomicine) a generalized morbilliform eruption on the face, trunk and extremities appeared simultaneously to acral erythema. Five patients with polychemotherapy also developed concomitantly to acral affection an erythematous to brown confluent papular eruption affecting the flexural regions (axillae and groin in 3 patients, and only the groin in 2 cases). Onset of cutaneous lesions ranged from 1 to 90 days after chemotherapy, was before BMT in 3 patients, and soon after BMT (1 – 16 days) in 5 patients. Cutaneous lesions cleared spontaneously within 2 to 3 weeks of discontinuation of chemotherapy in 14 patients, while patient 11 required systemic administration of corticosteroids (prednisone 1 mg/kg). Residual keratoderma was seen in 1 patient who received fluorouracil (case 1).

Skin biopsies were obtained for 13 patients. Common histological findings in most patients were those of cytotoxic reactions: vacuolar alteration of basal layer; abnormalities of keratinocyte maturation and necrosis; and sparse interface and perivascular infiltrate of lymphocytes. Eccrine sweat gland changes were evidenced in histological samples of 9 patients, with 6 cases showing a reaction of eccrine squamous syringometaplasia and duct cellular atypia (Fig. 2), while in 3 only duct cellular atypia was noticed. None of the 15 patients

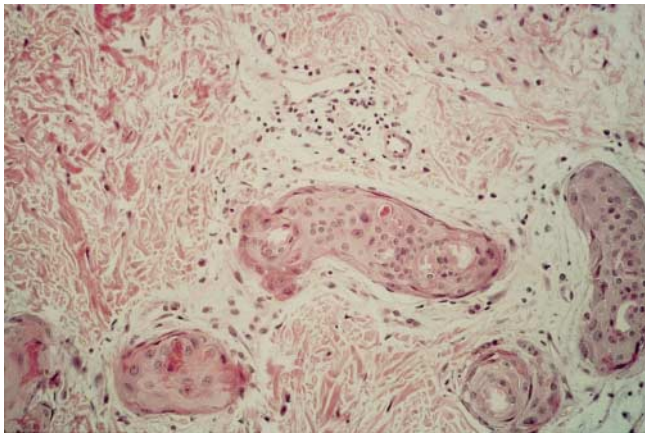

Fig. 2. Syringosquamous metaplasia with focal necrosis of the eccrine ductular epithelium.

with CIAE developed gastrointestinal or liver function abnormalities consistent with acute GVHD.

DISCUSSION

CIAE represents a drug-induced response to certain systemic chemotherapeutic agents that appears to be dose-dependent, with the reaction occurring sooner and more severely with bolus or short-term chemotherapy (from 24 h to 3 weeks) than with low-dose continuous infusion (up to 10 months). The incidence has been reported to be between 6% and 42% in different series (2, 3).

Several physiopathological mechanisms have been suggested, including anatomical characteristics of acral regions, direct toxic effect of drugs and immunological factors. As in our patients, current administration of these agents in combination chemotherapy makes it difficult to attribute the cutaneous reaction to a particular agent or combination of these drugs. All patients developed a variable degree of acral affection (palmar and plantar surfaces) after introduction of chemotherapy. Although the clinical lesions of CIAE are typically described as sharply-defined swelling and erythema of the palms and soles, some cases (as in most of our patients) may display a variable degree of affection (diffuse swelling and erythema, erythematous edematous plaques, alternating bands of erythema and sparing, extension over the dorsa of the hands and feet, and a mild erythema or morbilliform eruption accompanying the acral response). This may be due in part to different patterns of reaction depending on the nature of chemotherapeutic protocols and on the individual patient response to those regimens. Common histological findings in biopsies obtained from acral lesions in 13 patients were non-specific and showed features of a cytotoxic chemotherapy reaction (4). Biopsies obtained from all patients with affected flexural regions (patients 7, 8, 12, 13 and 14) and from 1 case with a generalized eruption (case 15), revealed histological changes of eccrine squamous syringometaplasia (ESS). Eccrine duct cellular atypia without ESS was seen in 3 other patients without flexural lesions.

ESS has been recently recognized in patients who receive chemotherapy in various combinations, as part of a clinicopathological spectrum of toxic phenomena affecting the eccrine apparatus, and has been described to occur in association with CIAE (5, 6). ESS is characterized by an erythematous, papular, confluent, localized or generalized eruption with histopathological findings of squamous metaplasia of the eccrine ducts, periductal oedema, fibrosis, and variable epithelial necrosis. In bone marrow transplant patients, differential diagnosis of CIAE with early stages of acute GVHD may be extremely difficult, clinical and histopathologically (7). In 3 patients of the 8 with BMT, the clinical picture of CIAE appeared before transplantation. The rapid onset of cutaneous lesions after introduction of chemotherapy (less than 3 weeks), the absence of extracutaneous involvement and rapid resolution of lesions upon chemotherapy discontinuation in the 5 other patients receiving BMT (patients with ESS findings in flexural lesions), render a diagnosis of acute GVHD improbable.

Histological findings of chemotherapy sweat gland toxicity, as in 9 of our patients, may be another clue in the differential diagnosis of CIAE with incipient cutaneous lesions of acute GVHD.

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