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CLINICAL REPORT

Gemcitabine-induced Acute Lipodermatosclerosis-like Reaction

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Gemcitabine is considered to be a well-tolerated and safe cytostatic drug because of the relative lack of side effects. Cutaneous reactions due to gemcitabine treatment, including alopecia and maculopapular eruption, are well known. We report one patient with squamous cell carcinoma of the lung who developed a gemcitabine-induced cutaneous reaction mimicking acute lipodermatosclerosis. This case has never been reported in the literature before. ***Key words: Gemzar® ; lipomembranous change; lipomembranous fat necrosis; skin toxicity.***

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Gemcitabine (difluorodeoxycytidine, 2′,2′-difluorodeoxycytidine; dFdC) is a deoxycytidine analogue with structural and metabolic similarities to cytarabine (ara-C) (1). It mimics the structure of the natural nucleoside and, following phosphorylation, is incorporated into DNA (2). Several previous reports have shown that gemcitabine alone or in combination with cisplatin is active against non-small-cell lung cancer with little cutaneous toxicities (2, 3). Gemcitabine is considered to be a well-tolerated and safe cytostatic drug because of the relative lack of side effects, which include nausea, emesis, myelosuppression, general weakness, peripheral oedema and flu-like symptoms (4). Its cutaneous reactions, such as alopecia and a maculopapular rash, are well documented (4–7). A phase II randomized study of gemcitabine treatment in inoperable non-small-cell lung cancer conducted in Taiwan revealed the occurrence of World Health Organization (WHO) grade I and grade II skin toxicities in 33.3% of the total 27 patients (5). Reports from the United States, the United Kingdom and Denmark also revealed that the incidence of cutaneous toxicity due to gemcitabine treatment was about 25.7–39% (6, 7). The skin toxicity was a transient rash which tended to be macular and did not occur with every course of therapy (7). Here, we report a case of gemcitabine-induced cutaneous reaction mimicking acute lipodermatosclerosis (LDS). To the best of our knowledge, it is the first report of acute LDS-like reaction due to an antineoplastic agent.

CASE REPORT

A 70-year-old male was diagnosed as having stage IIIb squamous cell carcinoma of the lung in 1999. His body surface area was 1.8 m^2. Chemotherapy had been 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 120 mg 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 second cycle of treatment was postponed, with the dosage of gemcitabine reduced to 888 mg/m^2 due to persistent thrombocytopenia. Three days after the first injection of gemcitabine of the second cycle, diffuse erythema, swelling, tenderness and local heat were noted on both the patient's lower legs. Oral amoxicillin was administered for 10 days under the impression of cellulitis, and the leg symptoms improved slightly. However, the patient received a further 3 injections of gemcitabine. The skin reactions recurred each time about 2–3 days after the injection and showed a minimal response to a course of oral antibiotic treatment for 5–7 days, but would gradually fade out later. Physical examination at the acute phase revealed erythema and induration on the medial aspect of both his lower legs (Fig. 1). There was neither a history of previous



Fig. 1. An erythematous, indurated plaque on the left leg above the medial malleolus.

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skin injury over this area nor extravasation during infusion of gemcitabine and cisplatin. A skin biopsy specimen taken from the erythematous, indurated plaque showed pictures of stasis dermatitis with capillary proliferation in the upper dermis, as well as hyalinized sclerosis, septal fibrosis and remarkable lipomembranous change in the subcutis (Fig. 2). The laboratory studies revealed fibrinogen 550 mg/dl (normal 214–474), 3 P test 2+ (normal negative), fibrin degradation products (FDP) 20–40 μg/ml (normal <10), D-dimer test 2–4 μg/ml (normal <0.5), plasminogen 120% (normal 75–140), antithrombin III antigen level 98% (normal 82–168) and function level 102% (normal 84–132), protein C antigen level 81% (normal 70–174) and function level 63% (normal 70–192), protein S antigen level total 150% (normal 80–180), free 94% (normal 70–180) and function level 97% (normal 66–155). The antiphospholipid antibody level, anticardiolipin antibody level and lupus anticoagulant test were all within the normal limits. Leg venous Doppler flow studies did not show any evidence of venous obstruction. Another skin biopsy specimen taken from the same area when the skin lesions subsided showed only stasis changes and persistent fibroplasia without the characteristic lipomembranous change. According to the characteristic clinical and pathological features, we diagnosed the patient as having acute LDS-like reaction induced by gemcitabine treatment. The skin reactions recurred seven times when the patient received further injections of gemcitabine. After completing all 6 courses of gemcitabine and cisplatin treatment, there was brownish pigmentation and induration of both lower legs with no recurrence of acute LDS during the following 5-month follow-up period. Poor wound healing of the biopsy sites was also noted. The patient expired, due to progression of the disease, with respiratory failure.

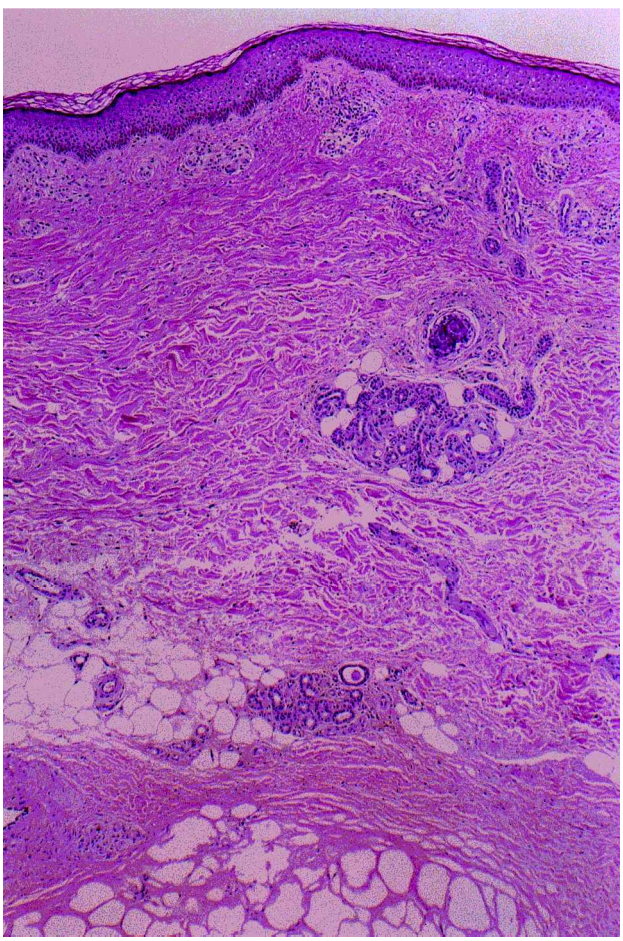


Fig. 2. Capillary proliferation in the upper dermis; septal fibrosis and lipomembranous change in the subcutis (haematoxylin and eosin; original magnification ×40).

DISCUSSION

Lipodermatosclerosis, also called hypodermitis sclerodermiformis or sclerosing panniculitis, is skin induration and hyperpigmentation of the legs that often occurs in patients who have venous insufficiency (8–11). It can be divided into at least two phases of presentation (8, 9). The acute phase of LDS can occur without any obvious clinical signs of venous disease (8). The patients usually have pain and intense discomfort in the medial leg above the medial malleolus. The area is erythematous, tender, warm and sometimes scaling. The sharp demarcation of hardness noted in chronic LDS is usually absent (8). The diagnostic criteria of acute LDS has been proposed as: (i) persistent pain, tenderness and redness of the medial aspect of the leg; (ii) no local or systemic evidence of cellulitis; (iii) no evidence of phlebitis; and (iv) clinical findings inconsistent with other types of panniculitis or with morphea (9). The mechanism of LDS is unknown, but venous insufficiency with reduced fibrinolytic activity might play an important role (8). The fibrinolytic abnormalities in patients of LDS are evidenced by increased plasma levels of D-dimer, D-monomer and fibrin monomer (8). Besides, abnormally low plasma levels of protein C or protein S has been documented in patients with LDS (12, 13). The histopathological features of LDS could be divided into early, intermediate and well-developed changes (11). The most characteristic features are stasis changes with dermal sclerosis, subcutaneous septal fibroplasia, hyalinized sclerosis and lipomembranous change. Although lipomembranous fat necrosis is a non-specific form of ischaemic fat degeneration that could be induced by conditions such as erythema nodosum, morphea profunda, lupus panniculitis, necrobiosis lipoidica, polyarteritis nodosa, necrotizing vasculitis and erysipelas, it is most prominent and most commonly found in venous stasis-associated chronic sclerotic plaques that are typically seen in middle-aged obese women (14).

The patient had no clinical evidence of venous insufficiency, but the histopathological studies revealed proliferation of dermal capillaries, which was a typical stasis change. In addition, the positive 3 P test result, increased levels of fibrinogen, FDP and D-dimer, as well as a low functional level of protein C, all pointed to an underlying venous thrombotic state.

Since gemcitabine is closely related to cytarabine, a drug that is well known to induce acral erythema (15–18), the skin reactions in this patient could be acral erythema (erythrodysaesthesia syndrome) localized to the area of LDS. In addition, fixed drug eruption could be another possible diagnosis. Nevertheless, both can easily be excluded in lacking the characteristic histologic features, such as vacuolar degeneration of the basal layer and scattered necrotic and dyskeratotic keratinocytes (15). The patient could have acute LDS *per se* due to the chronic stasis change disclosed by the histopathological examination of the leg skin. But the lack of previous

attack history, the close relationship between administration of chemotherapeutic agents and onset of the skin lesions, as well as no recurrence of them after discontinuation of chemotherapy, all led to the suspicion of a chemotherapy-induced skin reaction. Although cisplatin can induce several kinds of cutaneous reactions (16), the time course between disease onset and cisplatin treatment makes it unlikely to be the causative agent. Strikingly, the acute LDS-like reaction developed 11 times immediately after administration of gemcitabine. Based on the clinical features and the characteristic histopathological findings, a diagnosis of acute LDS-like reaction caused by gemcitabine was established. In reviewing the mucocutaneous reactions to chemotherapy, no such LDS-like reaction had been reported (16).

The mechanism of LDS-like reaction induced by gemcitabine is unclear. Histopathologically, the patient's leg skin showed a chronic stasis change, which was unlikely the effect of gemcitabine because the injections of gemcitabine were started only one month before the biopsy. In addition, there was no previous report of gemcitabine-induced venous insufficiency. We surmise that, in patients in a chronic stasis state, injury of venous endothelium due to gemcitabine might lead to further activation of a local coagulation process, and result in acute lipodermatosclerosis change.

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