Penile Ulceration During Pegylated Doxorubicin Chemotherapy of Classical Kaposi's Sarcoma

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Sir,
Kaposi's sarcoma (KS) is a multifocal angiolymphoproliferative disease with variable clinical course; widespread cutaneous lesions and/or lymph nodal or visceral involvement are an indication for systemic chemotherapy (1, 2). A new class of drugs, called liposomal anthracyclines, appears to be effective and tolerable, with fewer toxic side-effects than many conventional cytotoxic drugs. Among liposomal anthracyclines, pegylated liposomal doxorubicin (PLD) has become the treatment of choice of classical KS, both as first-line therapy and in previously treated patients (3). This therapy is potentially associated with several mucocutaneous toxic effects, including palmar-plantar erythrodysesthesia (PPE), also known as hand-foot syndrome, follicular rash, intertrigo-like eruption, melanotic macules, stomatitis and recall phenomenon (4, 5). To the best of our knowledge, penile ulceration in the course of PLD chemotherapy has not been previously reported in the literature.

CASE REPORT

An otherwise healthy 64-year-old man with classical KS of 3 years' duration presented with multiple reddish-blue papules and plaques widely distributed on the distal upper and lower extremities, abdomen and face. Mediastinic and abdominal lymphadenopathy was detected by computed tomography (CT). He had received chemotherapy with etoposide 100 mg/m^2 on day 1 every 21 days; after 10 cycles of first-line therapy, clinical examination revealed progression of cutaneous manifestations with no substantial effect on lymph node involvement by CT. Second-line chemotherapy with methoxypolyethylene-glycol-coated liposomal doxorubicin hydrochloride (Caelyx, SP Europe, Bruxelles, Belgium) 30 mg/m^2 on day 1 every 21 days was therefore started to stabilize the disease. Twelve days after the seventh cycle, the patient developed sudden onset of grade III (according to the National Cancer Institute criteria for skin toxicity) palmar-plantar dysesthesia and penile ulceration. Physical examination revealed an irregularly shaped painful erosion on the dorsal surface of the glans, 1 cm in diameter, with erythematous borders and a yellowish smooth clean base (Fig. 1). No inguinal lymph-node involvement was clinically detectable. There were no associated systemic or urinary tract symptoms and no relevant history of recent trauma or pruritus in the genital region. The patient had an active sexual life with a stable partner and no history of sexually transmissible diseases. Urine cultures were clear, and viral cultures, as well as serological investigations for syphilis and human immunodeficiency virus, were negative. He was not currently on other medications. An incisional biopsy specimen revealed an eroded epidermis and a perivascular inflammatory infiltrate in the dermis, composed mainly of lymphocytes. PLD was discontinued, and the patient received supportive care, including the application of wet dressings and high-potency topical corticosteroids to the palmar-plantar lesions. The genital ulcer was treated with topical application of ozonated vegetable oil, with gradual and progressive *restitutio ad integrum* within 5 weeks. With the patient's consent, re-challenge with the implicated drug was not performed and chemotherapy with etoposide was restarted, with no episodes of skin toxicity.

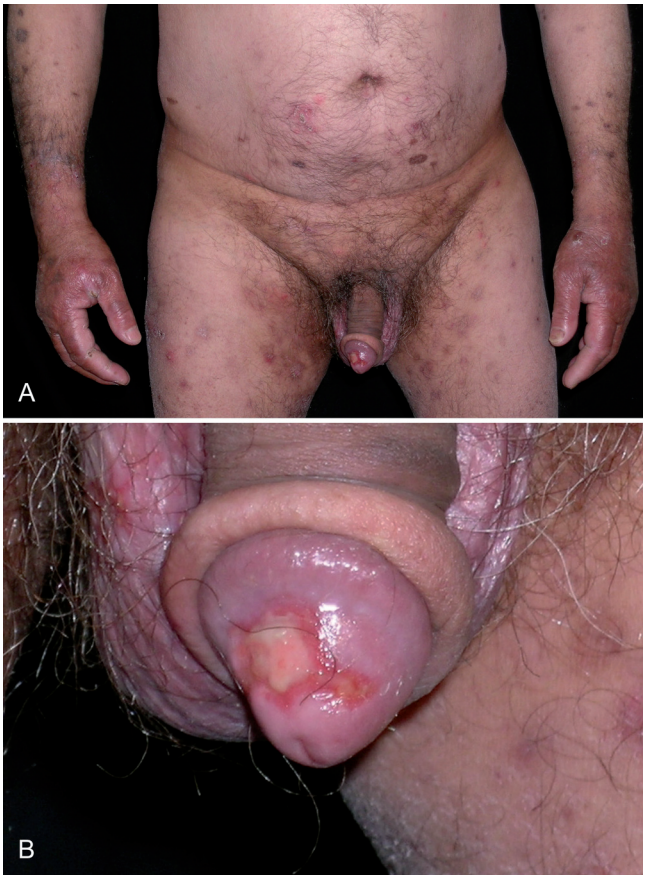

Fig. 1. (A) Glans ulcer with hand-foot syndrome in a patient with Kaposi's sarcoma. (B) Close-up of the genital lesion.

DISCUSSION

Liposome encapsulation of doxorubicin offers many advantages with respect to the soluble form of the drug, noticeably reducing myelosuppression, alopecia and myocardial damage; on the other hand, the altered pharmacokinetics of PLD accounts for the frequent, often dose-limiting, skin toxic effects, mainly represented by PPE. It is characterized by dysesthesia and tingling, with symmetrical painful erythema and swelling of the palms and soles followed by desquamation and exfoliation; in severe cases, patients may experience blister formation, especially on the feet, with considerable functional impairment. Its development is both dose- and schedule-dependent, and the reaction tends to recur with increasing intensity on re-exposure (6). Less common cutaneous manifestations are diffuse follicular rash, characterized by a non-pruritic scaly erythematous accentuation of hair follicles over the lateral limbs and trunk and intertrigo-like eruption: this eruption, resembling a true intertrigo, consists of erythematous patches over skin folds (groin, axillae, waist) and other areas of friction, often complicated by painful erosions, that may require dose reduction (4). Involvement of the oral mucosa is another well-known major side-effect of PLD, especially for dosage ranging between 60 and 70 mg/m^2; nevertheless with lower doses, as those employed for KS treatment, most patients experienced only grades I to II stomatitis (3, 4). Unlike oral manifestations, ulceration of the glans mucosa is a very rare cause of morbidity in cancer chemotherapy, and its occurrence has never been described during PLD therapy. In our case, the temporal connection between the drug administration and the onset of the phagedenic ulcer, the simultaneous presence of other typical skin toxicity manifestations (hand-foot syndrome) and the progressive healing after PLD discontinuation render a casual link likely, as confirmed by the Naranjo algorithm (total score: 6, "probable") for adverse drug reactions probability assessment (7). Differential diagnoses, including fixed drug eruption, erosive lichen planus and infections (genital herpes, syphilis), were excluded on the basis of histological findings and results of cultural and serological investigations. The relevant side-effect described in our patient may, at least in part, be explained in the light of the peculiar vascular anatomy and glandular structure of the glans and of the biodistribution of pegylated doxorubicin. Compared with the soluble form, PLD has an extremely long circulation time and tends to accumulate in the skin, especially in the distal extremities, according to a regional temperature gradient (8). Repeated friction and microtrauma, as will occur in a sexual active man like our patient, may have precipitated penile skin toxicity by increasing blood flow leading to a local high concentration of the drug, responsible for the observed cytotoxic effect.

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