Complications mimicking lupus flare-up in a uremic patient undergoing pegylated liposomal doxorubicin therapy for cervical cancer

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Patients with systemic lupus erythematosus (SLE) have an increased risk for malignancy and end-stage renal disease itself might further augment the risk. Treating uremic patients with cervical cancer by cisplatin-based chemotherapy combined with radiation is hampered by the reduced renal excretion of cisplatin. Doxorubicin, a potential radiosensitizer with an established effect on carcinomas that arise in the ovary, uterine cervix and endometrium, might be applied in these cases. We describe a 36-year-old woman, who had a 9-year history of SLE and was maintained on dialysis, and who developed severe drug reaction manifesting as fever, skin rash and exfoliative dermatitis with positive lupus band test after infusion of pegylated liposomal doxorubicin therapy for advanced cervical cancer. These skin manifestations improved after i.v. methylprednisolone pulse therapy.
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Introduction

Previous investigations have shown that patients with systemic lupus erythematosus (SLE) have an increased risk of malignancy, especially non-Hodgkin lymphoma [1,2]. Notably, the incidence of cervical cancer, a papilloma virus-associated malignancy, has also been demonstrated to be increased in SLE women [1]. Several mechanisms have been hypothesized to be responsible for the increased risk, including impaired immunologic surveillance and an altered estrogen metabolism.

Patients maintained on dialysis are also potentially at increased risk of cancer for several reasons, including the presence of chronic infection, a weakened immune system, often previous immunosuppressive treatment and nutritional deficiencies. Maisonneuve *et al.* [3] reported an analysis from three dialysis registries in the USA, Europe and Australasia showing an overall increased risk of cancer in patients with end-stage renal disease (ESRD). High risks were observed for cancer of the genitourinary organs, and the standardized incidence ratio (SIR; the ratio of observed to expected cancers) of cancer of uterine cervix was between 1.6 and 4.0.

Treating the advanced cervical cancer in SLE patients with ESRD is challenging. The currently advocated therapeutic protocol for cervical cancer consists of radiotherapy alone or concurrent chemoradiotherapy [4]. Since some commonly used radiosensitizers, such as cisplatin, are prone to accumulate in ESRD patients, doxorubicin might turn out to be an alternative option [5]. In this article, we report a rare complication of pegylated liposomal doxorubicin in an SLE woman with ESRD and cervical cancer, which was diagnosed 5 years after starting regular dialysis.

Case presentation

A 36-year-old woman with ESRD due to SLE was admitted to the hospital because of advanced cervical cancer.

Nine years before this admission, she developed autoimmune hemolytic anemia with a positive direct Coombs test. The serum antinuclear antibody (ANA, homogenous type) was greater than 1:1280 and anti-double-stranded DNA (anti-dsDNA) was 1:1280. Oral steroid therapy was given followed by remission of hemolysis.

Eight years prior to the admission, she developed nephrotic syndrome. Serologic examination revealed that ANA titer was greater than 1:1280, C3 level 35.7 mg/dl (73–134 mg/dl) and C4 < 11.9 mg/dl (18.2–45.5 mg/dl). Her nephrotic syndrome was resistant to the i.v. methylprednisolone and cyclophosphamide therapy, and the renal function deteriorated progressively. Five years prior to this admission, she began to undergo maintenance hemodialysis (HD), which was shifted to continuous ambulatory peritoneal dialysis (CAPD) due to access problems. The dialysis course was uneventful except for the anemia, which showed poor response to recombinant human erythropoietin therapy. She was thus

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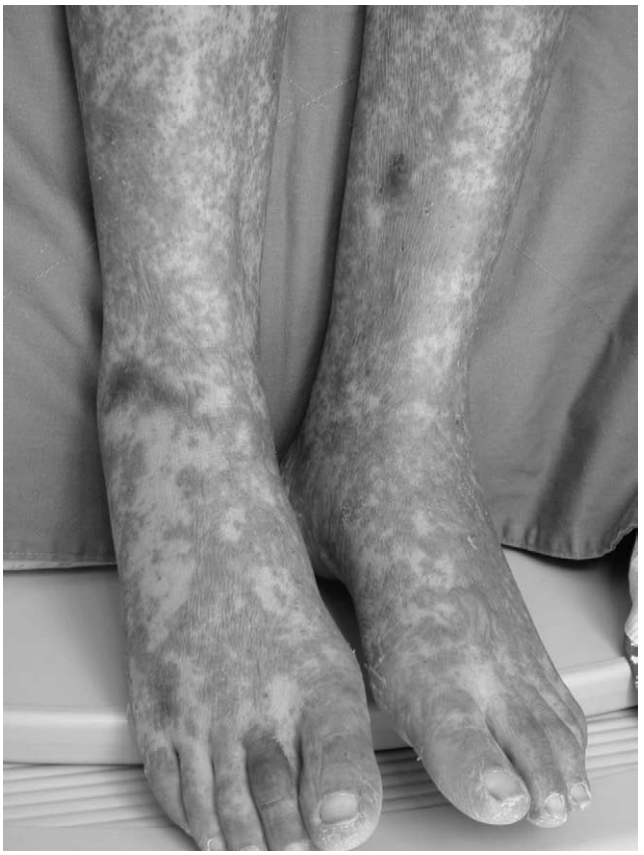
given intermittent oral prednisolone therapy, at a dose of 5–10 mg/day, to maintain the hematocrit at around 30%.

Throughout these 9 years, she had experienced several episodes of fever including urosepsis and arteriovenous shunt infection, and had been exposed to various antibiotics, including oxacillin, cefazolin, gentamicin, vancomycin and ceftriaxone. There were no demonstrated adverse effects, especially skin reactions, to these antibiotics.

Two weeks before this admission, she complained of heavy vaginal discharge with bloody spotting. The diagnostic procedure was a biopsy of the uterine cervix. The histopathologic examination showed squamous cell carcinoma with papillary growth of the cervix. Computed tomographic scanning revealed a $4 \times 5 \times 4.5$ cm mass of the uterine cervix protruding into the vaginal cavity, with involvement of the left parametrium and the left external iliac lymph node. A diagnosis of cervical cancer stage IIB was made and she was taken to the hospital. On the second day of admission, she developed CAPD-related peritonitis due to *Shewanella putrefaciens* infection, which was successfully treated with 14-day i.p. administration of vancomycin and amikacin. After the antibiotic therapy, one dose of Lipo-Dox (TTY BioPharm, Taipei, Taiwan) 60 mg was administrated i.v. before the scheduled irradiation for advanced cervical cancer. Lipo-Dox is a second-generation pegylated liposomal doxorubicin comprised of distearoyl phosphatidylcholine (DSPC)/cholesterol [6]. Thirteen days after the chemotherapy, high fever occurred without bacterial growth in blood culture. Several erythematous to violaceous atrophic plaques with erosion began to develop over the forehead, while vesicles appeared over the upper lip and bullae with erythematous scaling plaques over the ears. Subsequently, hyperpigmented skin and erythematous spots developed over the bilateral legs, followed by generalized skin rash (Fig. 1). Laboratory examination revealed leukopenia (WBC 1800/mm^3). Meanwhile, serologic examination showed C3 85.5 mg/dl, C4 36.7 mg/dl and anti-dsDNA 12 IU/ml (ELISA; < 35 IU/ml). A facial skin biopsy was performed demonstrating hyperkeratosis, follicular plugging and mononuclear cell infiltration in both the perivascular and periadnexal areas, which were consistent with lupus erythematosus (Fig. 2). The direct immunofluorescence study revealed a positive lupus band test, and granular IgG, IgM, IgA, C3 and C1q deposits in the dermoepidermal junction. Following 3-day i.v. methylprednisolone pulse therapy, at dose of a 500 mg/day, and the subsequent oral steroids, fever subsided and these severe skin lesions recovered completely within 2 weeks.

Fig. 1



Involvement of the legs and feet shows multiple erythematous to violaceous atrophic plaques with erosion.

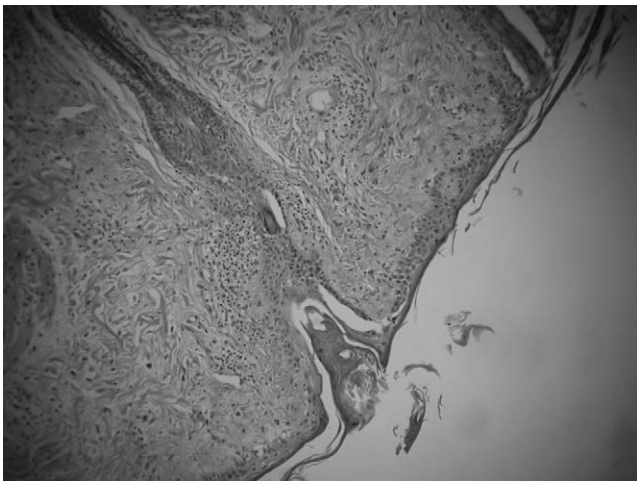
Discussion

This case suggests a causal relationship between chemotherapy with pegylated liposomal doxorubicin and development of skin reaction mimicking lupus flare-up.

Pegylated liposomal doxorubicin, a formulation of doxorubicin in poly(ethylene glycol)-coated liposome, has a prolonged circulation time and unique toxicity profile. Notably, pegylated liposomal doxorubicin is prone to accumulating in the skin and has a high incidence of cutaneous toxicity, particularly in the form of palmer–planter erythrodysesthesia (PPE) [5,7]. Clinically, PPE generally manifests by painful erythema and swelling primarily affecting contact pressure areas. These phenomena are followed by desquamation and, finally, re-epithelization. Skin toxicity is seldom observed after a single course of pegylated liposomal doxorubicin. Other reported skin manifestations include follicular rash, pigmentation spots and radiation recall reaction [8]. Our patient developed persistent high fever and skin reactions manifesting as erythema, hyperpigmentation, bullous formation, exfoliation and positive lupus band after a single dose of pegylated liposomal doxorubicin treatment. These adverse effects clearly differ from previously reported cases in the literature.

Lupus flare-up is another possibility causing these skin lesions. We speculate that doxorubicin therapy might

Fig. 2



The skin biopsy section reveals hyperkeratosis, follicular plugging and epidermal atrophy associated with vacuolar degeneration of the basal cells, and mononuclear cell infiltration in the perivascular and periadnexal areas (hematoxylin & eosin stain; original magnification × 100).

cause DNA structural change through interaction with topoisomerase II to form DNA-cleavable complexes, followed by the generation of autoantibody to DNA [7]. However, the fact that cytotoxic agents, such as cyclophosphamide, azathioprine and mycophenolate mofetil, are known to be effective for treating SLE makes these hypotheses less attractive, and the low serum anti-dsDNA titer and normal complement levels offer further evidence against this speculation. Furthermore, Brenner *et al.* [9] described a lupus patient with small cell anaplastic carcinoma of the lung. After chemotherapy with cisplatin etoposide, doxorubicin and cyclophosphamide, lung lesions and rash gradually disappeared, and no lupus flare-up was mentioned.

Another possible pathogenesis of these skin lesions is an abrupt and massive cytokine release caused by macrophage depletion after i.v. administration of pegylated liposomal doxorubicin. Daemen *et al.* [10] found the depletion and impairment of phagocytic activity of rat liver macrophages after i.v. administration of liposomal doxorubicin. Oussoren *et al.* [11] also demonstrated the localization of pegylated liposome within the macrophages of rat lymph nodes. As cytokines are synthesized and stored in macrophages, the depletion of cells might be accompanied by massive cytokine release. This massive release of cytokines could in turn induce worsening of the pre-existing SLE. High fever, leukopenia, generalized skin reactions and the rapid response to steroid therapy support this speculation.

In pegylated liposomal doxorubicin-treated cancer patients, the renal excretion of doxorubicin and its metabolites has a pattern similar to that reported for free doxorubicin. Only 5.5% of a single dose of pegylated liposomal doxorubicin is recovered in the urine as doxorubicin, doxorubicinol or other metabolites during the 72 h after injection [12]. However, in HD patients, Yoshida *et al.* [13] demonstrated a significant reduction of total body clearance of pegylated liposomal doxorubicin. The area under the curve for both doxorubicin and doxorubicinol showed increases of approximately 1.5 and 3 times in HD patients as compared with non-HD patients. Therefore, based on these pharmacokinetic studies, the contribution of a uremic condition *per se* to trigger the lupus-like reaction in this patient remains unclear.

In summary, pegylated liposomal doxorubicin may cause fever and severe skin reaction mimicking lupus flare-up in SLE patients with ESRD. However, caution should be exercised to extrapolate the results of DSPC pegylated liposomal doxorubicin to other similar products, because of their differences in lipid composition. Further investigation is required to elucidate the potential role of cytokines in this lupus-like adverse reaction.

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