Inflammation of Seborrheic Keratoses due to Docetaxel Treatment

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Sir,
Cutaneous side effects of docetaxel include alopecia, an immediate hypersensitivity reaction, erythrodysesthesia, pruritus, radiation recall, urticaria, maculopapular eruptions and nail changes (1, 2). We herein report on a patient who developed inflammation of seborrheic keratoses after docetaxel treatment. To our knowledge, this has never been reported in the literature.

CASE REPORT

In December 1998, a 72-year-old woman was given a diagnosis of non-small-cell lung cancer. Previous treatment included left upper lobectomy with lymph node dissection followed by 4 cycles of chemotherapy with gemcitabine and cisplatin. Docetaxel was administered because of disease progression. The dosage schedule of each cycle was intravenous infusion of docetaxel for 30 min on days 1, 8 and 15 and the dosage was 45 mg/m^2 weekly for each injection. However, severe leukopenia following the first dose led to delayed administration of the second injection until day 19 after the first injection. Four days after the second injection, some pea- to bean-sized, itching, erythematous macules and patches developed on the right forearm and dorsum of the right hand. All of these lesions corresponded to the sites of pre-existing seborrheic keratoses (Fig. 1). The patient claimed that the seborrheic keratoses had been noted for more than 10 years and there was no history of eruptive appearance of new seborrheic keratoses. The injection sites of docetaxel therapy were on the left, rather than right, forearm. There was no extravasation event during the docetaxel treatment. A skin biopsy was not undertaken, owing to leukopenia. The patient's skin condition was treated as eczema, with betamethasone valerate cream. The second cycle of docetaxel infusion was still administered, with the dosage reduced to 36 mg/m^2 because of the leukopenia. The inflammation of seborrheic keratoses ameliorated one week later, but the patient complained of a tingling and burning sensation over the area. One month after the onset of the lesions, an erythematous, palm-sized plaque with sensory change was noted on the right forearm, partly localized to the keratoses. Fixed erythrodysesthesia plaque (FEP) due to docetaxel was diagnosed (3). One month later, the skin lesions resolved, but the pre-existing seborrheic keratoses remained. The same skin reaction did not recur even though the patient received a further 3 cycles of docetaxel therapy.

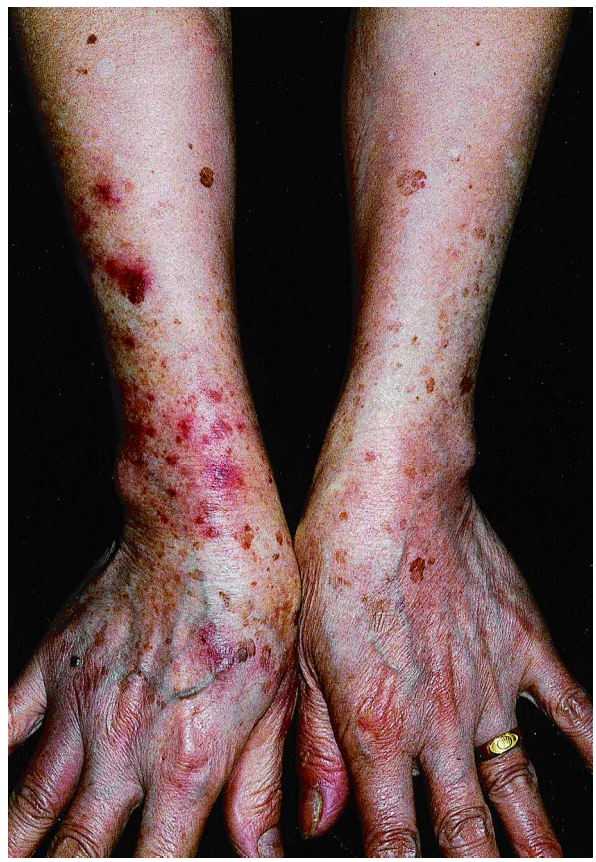

Fig. 1. Some pea- to bean-sized, itching, erythematous macules and patches with scales were noted on the right forearm and dorsum of the right hand. All of these lesions corresponded to the sites of pre-existing seborrheic keratoses.

DISCUSSION

Inflammation of seborrheic keratoses is a rarely described cutaneous reaction to chemotherapy (2) and there are only 2 previous reports mentioning this unique skin reaction (4, 5). Both of these reports describe a patient with acute myelogenous leukemia who had a rapidly increasing number of seborrheic keratoses, compatible with Leser-Trélat sign. Following chemotherapy, the seborrheic keratoses of Leser-Trélat became inflamed in both patients; with discontinuation of cytarabine therapy, the inflammatory reaction in the keratoses subsided in one of the patients (5). All the seborrheic keratoses of our patient had been present for more than 10 years, which made Leser-Trélat sign unlikely. Besides, only a few seborrheic keratoses on the right arm became inflamed, while those on the other body sites were not involved. The above features are different from those of the previous reports.

The mechanism of this reaction is unknown (2). Susser et al. (2) reviewed the mucocutaneous reactions to chemotherapy and mentioned inflammation of keratoses. This syndrome may or may not recur with the re-administration of the same chemotherapeutic agent(s). Discontinuation of chemotherapy

is not indicated by the dermatological findings alone, because the reaction is self-limited (2).

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Increased Serum Level of Vascular Endothelial Growth Factor in Crow-Fukase Syndrome

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Sir,

Crow-Fukase syndrome (POEMS syndrome) is characterized by polyneuropathy, organomegaly, endocrinopathy, M-protein in serum, and skin lesions (1–3), but its pathogenesis is still unknown. Cutaneous manifestations include hyperpigmentation, hypertrichosis, skin sclerosis, and multiple angiomas. Since multiple hemangiomas occur, systemic factors are thought to be involved.

Vascular endothelial growth factor (VEGF) is a selective mitogen for vascular endothelial cells via two types of VEGF receptors (4). VEGF is usually generated by non-endothelial cellular types. In this report, we show an increased serum level of VEGF in 2 cases of Crow-Fukase syndrome.

Serum was obtained from 2 patients with Crow-Fukase syndrome (a 57-year-old female and a 48-year-old female). Both patients visited our department with primary complaints of an increased number of angiomas on the trunk (Fig. 1). Further investigations including ultrasound and CT scans resulted in the observations listed in Table I. Based on these findings a clinical diagnosis was made of Crow-Fukase syndrome.

Serum concentrations of VEGF were assessed by enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN). As a control, serum was obtained from 2 patients with solitary pyogenic granuloma and 9 age- and sex-matched normal volunteers. The results showed that serum concentrations of VEGF were markedly elevated in patients with Crow-Fukase syndrome (175 pg/ml in Case 1 and 200 pg/ml in Case 2), as compared with normal controls (61.6 ± 24.6 pg/ml). Results in patients with solitary pyogenic granuloma showed 80 pg/ml and 100 pg/ml.

Recent studies report overproduction of VEGF in patients with Crow-Fukase syndrome (5, 6). They detect a 15–30 times increase in serum VEGF levels in patients with Crow-Fukase syndrome, as compared with control subjects (5). Conversely, our patients showed relatively low levels of VEGF compared with their results. We speculate that our patients were in an early stage of Crow-Fukase syndrome, since they were diagnosed from the cutaneous manifestations. Interleukin-6 (IL-6) is suggested to be implicated in the pathogenesis of Crow-Fukase syndrome (7, 8) as IL-6 can stimulate VEGF production (9).

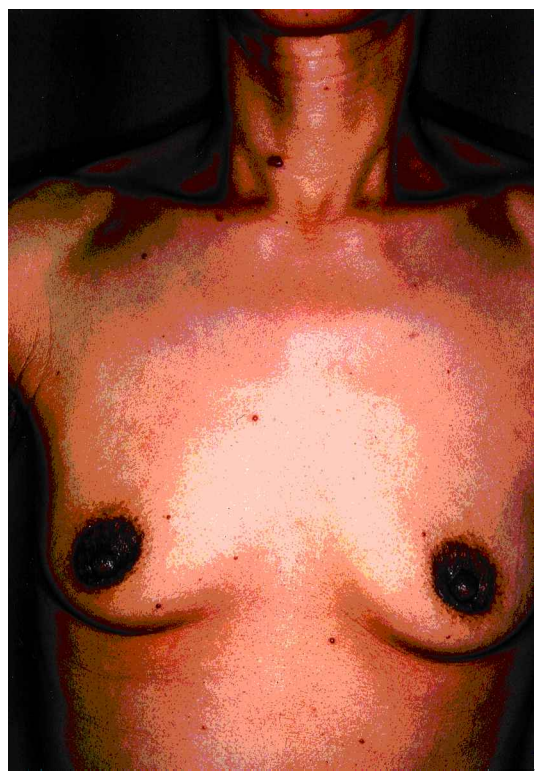

Fig. 1. A number of angiomas on the trunk of Case 2.

Chan et al. (10) classified angiomas associated with POEMS syndrome into two groups; cherry-type capillary and glomeruloid hemangiomas. They suggested that these two types of hemangioma merely represent different stages in the development of the same lesions and show different degrees of endothelial proliferation in response to angiogenic stimuli. Recent findings demonstrate increased expression of VEGF in pyogenic granulomas (11). They showed that VEGF is produced by a source outside the vascular wall and acts on target endothelial cells, raising the possibility that endothelial cell precursors might be the VEGF source in pyogenic granulomas.

Mast cells are suggested to play a role in angiogenesis by