Atypical Eruption Due to Chemotherapeutic Agent

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We report a case of atypical eruption due to chemotherapeutic agent in a 60-year-old man who presented with asymptomatic, erythematous, 0.5cm in diameter, confluent, and elevated papules and plaques confined to the face. The patient was previously diagnosed with small cell carcinoma of the lung with liver metastasis. Two months after the diagnosis, a first course of chemotherapy including etoposide was started. Five days after starting the chemotherapy, the patient developed a facial eruption. Histopathologic examination demonstrated increased epidermal mitotic figures, cells in metaphase arrest, basal cell layer hyperpigmentation, prominent dyskeratosis, and squamous atypia. The most distinctive histologic feature was the presence of starburst cells, which are markedly enlarged pale staining keratinocytes containing small basophilic fragments of nuclear debris haphazardly scattered throughout the cytoplasm in a starburst pattern. (Ann Dermatol 13(4) 232~234, 2001).

Key Words : Atypical eruption, Chemotherapeutic agent, Starburst cell

The adverse skin reactions of chemotherapeutic agents occur commonly and are quite diverse in clinicopathologic presentation[1]. However, distinctive histologic changes in the skin lesion have been described with only a few chemotherapeutic agents such as etoposide and busulfan[2]. Etoposide(VP-16) is a semisynthetic derivative of podophyllotoxin, an active constituent of podophyllin. It appears to inhibit DNA synthesis by causing single- and double-strand DNA breakage, which may be related to its ability to act as an inhibitor of the topoisomerase II enzyme. And it inhibits cell division by binding to microtubular proteins at the colchicine binding site[2-5]. We report a case of a atypical eruption due to chemotherapeutic agent similar to that initially reported by Yokel, et al., which developed after etoposide therapy.

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CASE REPORT

A 60-year-old male visited our clinic with asymptomatic, erythematous, 0.5cm in diameter, confluent, and elevated papules and plaques confined to face (fig. 1). The patient was previously diagnosed with small cell carcinoma of the lung with liver metastasis. Two months after the diagnosis, a first course of chemotherapy was started. This included etoposide, 160 mg and ifsphamide, 2250mg on Days 1, 2, and 3, and cisplantin, 160mg on Day 1. Also, dexamethasone, lorazepam, dimenhydrinate, and furosemide were administered. Five days after starting the chemotherapy, the patient developed a facial eruption. There was no fever or lymphadenopathy. Although the WBC count was elevated, there was no absolute eosinophilia. CT scans, bronchoscopy, liver/spleen scan and liver biopsy all suggested small cell carcinoma of the lung with liver metastasis. Histopathologic examination of the skin demonstrated increased epidermal mitotic figures, cells in metaphase arrest, basal cell layer hyperpigmentation, prominent dyskeratosis, and squamous atypia. A perivascular lymphocytic infiltration was also noted (Fig. 2). The most distinctive histologic feature was the presence of star-

Table. 1. Various reports of chemotherapeutics that developed cutaneous eruptions with starburst cell

Cases		Chemotherapeutic agents
Yokel, et al.	Case 1	Etoposide, docorubicin, cyclophosphamide
	Case 2	Etoposide, methotrexate, hexamethylmelamine
	Case 3	Etoposide, doxorubicin, cyclophosphamide
	Case 4	Etoposide, daunomycin
Harvell, et al.	Case 1	Etoposide, cyclophosphamide, carboplatin
	Case 2	Busulfan, cyclophosphamide
Present case		Etoposide, ifosphamide, cisplantin

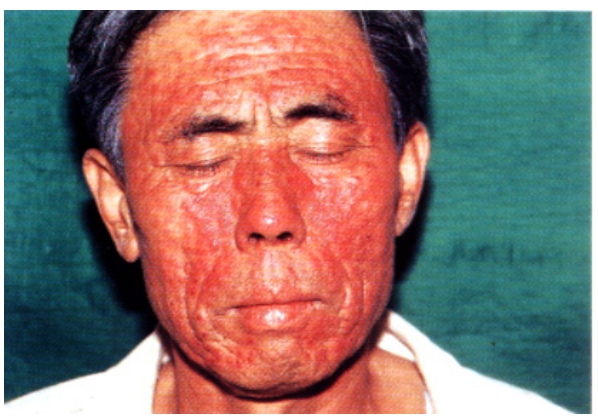

Fig. 1. Numerous, erythematous, 0.5cm sized, confluent, and elevated papules and plaques on the face.

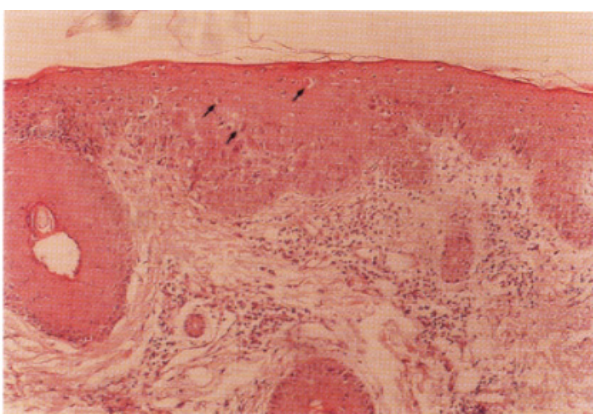

Fig. 2. A photomicrograph showing scattered necrotic keratinocytes, dyskeratotic cells (arrows) and perivascular lymphocyte infiltration (H&E , ×100).

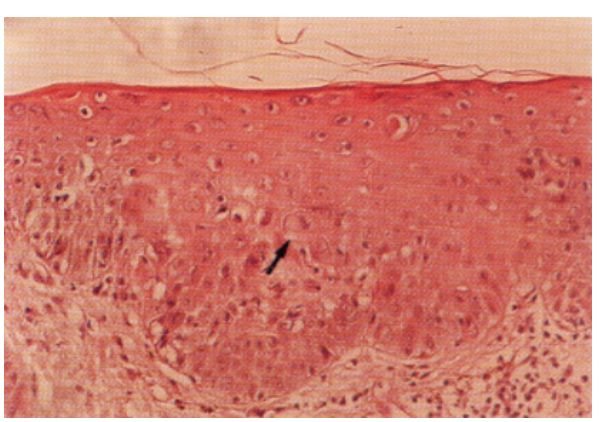

Fig. 3. In the epidermal layer, there are numerous dyskeratotic cells and a single starburst cell. Starburst cell is a large pale-staining keratinocyte, showing haphazardly arranged nuclear debris (arrow) (H&E , × 200).

burst cells, which are markedly enlarged pale staining keratinocytes containing small basophilic fragments of nuclear debris haphazardly scattered throughout the cytoplasm in a starburst pattern (Fig. 3). After two weeks of oral antihistamine administration and limited application of topical steroid ointments, the skin lesions subsided. Subsequent multi-agent therapy, including etoposide, was administered without recurrence of the cutaneous complications.

DISCUSSION

The adverse cutaneous manifestations of chemotherapeutic agents are varied and range in severity from trivial and cosmetic to generalized, dose-limiting and life-threatening[1]. A variety of histologic patterns have also been described in association with systemic administration of chemotherapeutic agents. Especially, it has been reported that cer-

tain drugs such as etoposide and busulfan presented unique histological changes[2]. In 1987, Yokel et al[3]. reported a histologically distinctive reaction that occurred in four patients who presented with different types of underlying malignancies (small cell carcinoma of the lung, acute lymphocytic leukemia, and diffuse large cell lymphoma) and received etoposide(VP-16) therapy at a dose range of 175-512.5mg/day (Table 1). The etoposide-induced eruptions appeared 5 to 11 days after starting the therapy. The primary lesions were usually erythematous papules that demonstrated variable pruritis and scale. Although there was no characteristic distribution, the most common site was the trunk. Etoposide induced drug eruption does not necessarily appear after the first administration, and in one case, skin lesions developed after the second administration of etoposide. In addition, it appears to be unrelated to dosage and contributing factors to its development, are not known. In 2 patients, there was no recurrence of the rash, even after repeated administrations. Within 3 weeks of symptomatic treatment, all rashes resolved spontaneously. Histopathologically, previously reported cases were similar to ours except that in one case there was cytologic atypia in eccrine ducts, similar to that usually seen in the epidermis. Starburst cells were observed in all four cases. The starburst cell most closely resembles the "podophyllin cell" seen within 48 hours after topical podophyllin application to condyloma[7,8]. Etoposide and podophyllin are structurally related derivatives of podophyllotoxin, and may inhibit mitosis through related mechanisms. The starburst cell, observed in etoposide induced drug eruption, can be differentiated from the podophyllin cell by the patient's clinical history and by the presence of background cytological atypia seen in chemotherapeutic reactions, in general. The busulfan cell is an abnormally large keratinocyte that is seen following busulfan therapy. These histologic abnormalities appear between 15 and 45 days after the initiation of busulfan therapy, and are not always associated with a clinically apparent rash. Histopathologically the busulfan cell is characterized as having an enlarged nuclei up to 22 microns in diameter, irregular nuclear contours, increased cytoplasm, and prominent keratohyaline granules[2,3,5,6]. In 1998, from a study of a patient who received cyclophosphamide and busulfan chemotherapy, Harvell et al[9]. suggested that the starburst cell and busulfan cell are not pathognomic changes caused by specific to single chemotherapeutic agents (Table 1). Instead, they are an expression of dysregulated mitosis, possibly induced by several classes of chemotherapeutics. Further investigation is required to confirm this. Starburst cell not only appears to etoposide, but also to other chemotherapeutic agents.

REFERENCES

1. Susser WS, Whitaker-Worth DL, Grant-Kels JM: Mucocutaneous reactions to chemotherapy. J Am Acad Dermatol 40:367-98, 1999.
2. Fitzpatrick JE: The cutaneous histopathology of chemotherapeutic reactions. J Cutan Pathol 20:1-14, 1993.
3. Yokel BK, Friedman KJ, Farmer ER, Hood AF: Cutaneous pathology following etoposide therapy. J Cutan Pathol 14:326-30, 1987.
4. Philips NC: Oral etoposide. Drug Intell Clin Pharm 22:860-3, 1988.
5. Fitzpatrick JE: New histopathologic findings in drug eruptions. Dermatol Clin 10:19-36, 1992.
6. Jerker BJ, Hood AF: Chemotherapy-induced cutaneous reactions. Semin Dermatol 8:173-81, 1989.
7. Sullivan M, King LS: Effects of resin of podophyllin on normal skin, condyloma acuminata, and verrucae vulgaris. Arch Dermatol Syphilol 56:30-45, 1947.
8. Wade TR, Ackerman AB: The effect of resin of podophyllin on condyloma acuminatum. Am J Dermatopathol 6:109-22, 1984.
9. Harvell JD, Hashem C, Williford PL, White WL: Grover's like disease in the setting of bone marrow transplantation and autologous peripheral blood stem cell infusion. Am J Dermatopathol 20:179-84, 1998.