Chronic Hydroxyurea-induced Dermatomyositis-like Eruption Showing Epidermal Dysmaturation

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Hydroxyurea is an effective treatment for a variety of myeloproliferative disodrers. A distinct cutaneous reaction to long-term administration of hydroxyurea has been characterized and designated hydroxyurea dermopathy. Epidermal dysmaturation refers to histologic changes that may be observed in the epidermis after any significant cytoreductive therapy.

We report a patient with hydroxyurea-induced dermatomyositis-like eruption showing epidermal dysmaturation who developed an erythematous scaly patches on the dorsal aspects of the hands while on long-term administration of hydroxyurea for chronic myelogenous leukemia. (Ann Dermatol 14(1) 28-30, 2002).

Key Words : Hydroxyurea, Epidermal dysmaturation, Dermatomyositis

Hydroxyurea is an effective treatment for a variety of myeloproliferative disorders. It inactivates the enzyme ribonucleotide reductase, causing inhibition of cell DNA synthesis and cell death in S phase1. Epidermal dysmaturation is a histologic term referring to changes in the epidermis such as disruption of keratinocyte maturation, loss of polarity, widened intercellular spaces, irregular large nuclei, midepidermal mitotic figures, and apoptosis, occurring after cytoreductive therapy2.

We report a case of a 34-year-old chronic myelogenous leukemia patient showing dermatomyositis-like eruption showing epidermal dysmaturation after receiving hydroxyurea.

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CASE REPORT

A 34-year-old man was referred to us for evaluation of skin lesions on his hands that had been present for more than 2 years. His clinical history included chronic myelogenous leukemia diagnosed in July 1990, since then treated with hydroxyurea (0.5-1.5g/day) and allopurinol (300mg/day). Cutaneous examination disclosed an erythematous scaly Gottron's papule-like eruption of dermatomyositis on the dorsal aspects of the hands. These lesions were most marked over the metacarpophalangeal and interphalangeal joints (Fig. 1). A biopsy specimen from the erythematous lesion on the dorsum of the right hand showed slight atrophy of the epidermis, hyperkeratosis, disruption of the normal pattern of keratinocyte maturation with many cells showing apoptosis, prominent chromatin clumping, and irregular large or multiple nuclei, within the dermis, telangiectasia thickening of vessel walls and endothelial cell swelling were observed, but there was no vasculitis (Fig 2.A, B). Results of direct immunofluorescence testing were negative. Routine laboratory tests, including serum levels of muscle enzyme and antinu-

clear antibodies, were all normal or negative.

Based on the clinical and histopathological findings, hydroxyurea-induced dermatomyositis -like eruption showing epidermal dysmaturation was diagnosed. After discontinuing hydroxyurea, the hand eruption improved within 4 weeks.

DISCUSSION

Hydroxyurea is a cytostatic agent which is used to treat CML and sometimes other myeloproliferative syndrome3,4. Its mechanism of action is not fully understood, but it appears to affect DNA synthesis and genetic control of cell replication by inhibiting the conversion of ribonucleotides in deoxyribonucleotides4. It is considered the drug of choice in the usually well tolerated and the most frequent site-effects observed are leukopenia or thrombocytopenia5. Cutaneous adverse reactions are also frequently described. Most of them (xerosis, hyperpigmentation) are also observed with other chemotherapeutic agents, but a dermatomyositis-like eruption has only been reported in patients receiving hydroxyurea6. The clinical features are typical, and consist of an erythema on the dorsa of the interphalangeal and metacarpophalangeal joints, associated with atrophic or telangiectatic changes. Skin histopathology shows vacuolar degeneration of the basal cell layer and a moderate dermal mononuclear perivascular inflammatory infiltrate. These cutaneous lesions are very similar to those seen in dermatomyositis, but clinical signs of muscle involvement have never been described. The mechanism responsible for the cutaneous changes caused by long-term hydroxyurea therapy is still unknown, but may be related to a toxic effect of hydroxyurea due to inhibition of DNA synthesis and inhibition of DNA repair. As a result of its side effect on DNA synthesizing cells, hydroxyurea may be responsible for vacuolar degeneration of the basal cells and colloid bodies, epidermal atrophy, and granular layer thickening7. The

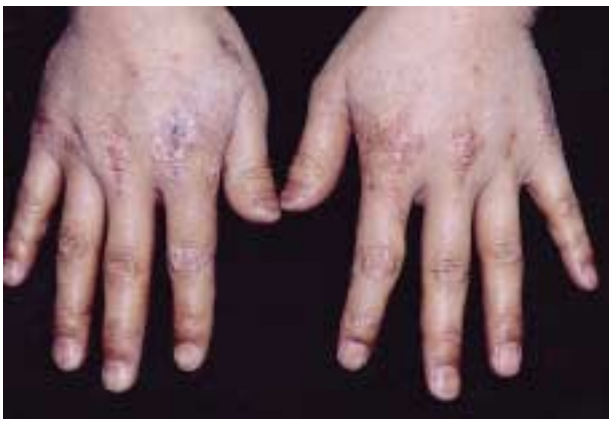

Fig. 1. Erythematous scaly patches are seen over the dorsal aspects of the hands.

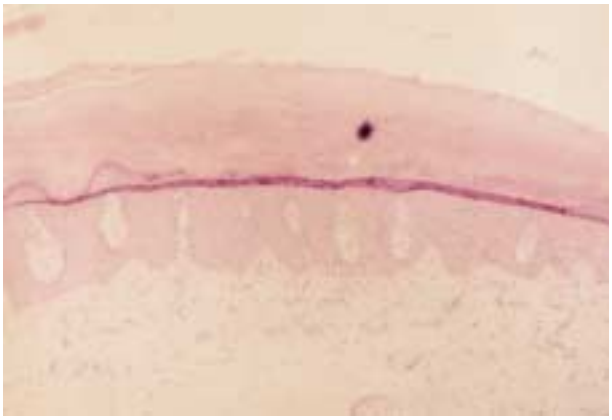

Fig. 2. A. Prominent hyperkeratosis of epidermis, a moderate dermal mononuclear perivascular inflammatory infiltrate, telangiectasia with thickening of the vessel walls (H & E stain; original magnification ×40).

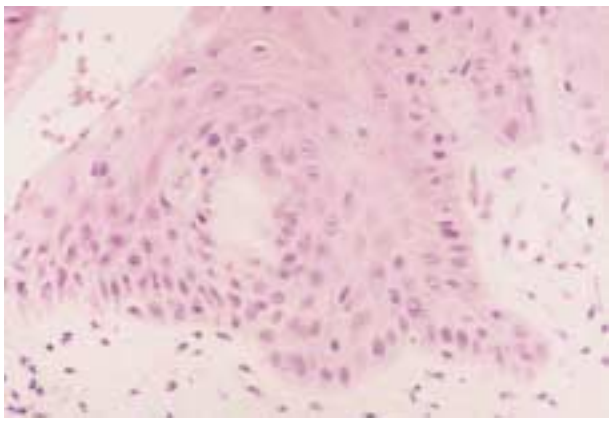

Fig. 2. B. Epidermal dysmaturation showing disruption of keratinocyte maturation, irregular large nuclei (H & E stain; original magnification ×200).

course is benign and usually lesions gradually fade in a few months after withdrawal.

Epidermal dysmaturation refers to changes in the epidermis such as disruption of keratinocyte maturations, loss of polarity, widened intercellular spaces, irregular large nuclei, midepidermal mitotic figures, and apoptosis occurring after cytoreductive therapy2,8. These changes can be observed in the epidermis after any significant chemotherapy regimen and are sometimes associated with clinical lesions and could also be attributed to prominent follicular hyperkeratosis. Keratinocyte damage is one of the most common pathologic alterations seen in chemotherapy-induced reactions. Chemotherapeutic agents that produce clinically significant generalized toxic epidermal reactions include busulfan, cytarabine, bleomycin, hydroxyurea, etopside, and methotrexate9,10. Finally, the present case shows that hydroxyurea dermopathy is a sign to change the hydroxyurea regimen to another form of chemotherapy, and we believe that hydoxyurea contributed to epidermal dysmaturation in our patient.

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