

A Case of Incidental Epidermolytic Hyperkeratosis Occurring Normal Looking Skin Adjacent to Folliculitic Papules: In Veterans Who Participated in Vietnam War

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On histological examination, an epidermolytic hyperkeratosis was observed adjacent to follicular papules on the back of a 53-year-old man. It has been reported that incidental epidermolytic hyperkeratosis occur either within various lesion (epidermal neoplasm, melanocytic neoplasm, scars, and inflammatory conditions) or in the normal skin adjacent to the lesion. This patient participated in the Vietnam War for 2 years, and had had contact with defoliants. He was treated for multiple peripheral neuropathies and cerebral infarcts. In keratinocytes, 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD; Agent Orange) contained in defoliating agents is associated with altered patterns of keratinocyte differentiation. So, as a cause of incidental epidermolytic hyperkeratosis, defoliant contact could be suspected.

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Key Words : Incidental epidermolytic hyperkeratosis, 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD; Agent Orange)

Epidermolytic hyperkeratosis is a distinctive histological expression confined to the epidermis. It occurs as a major feature of bullous congenital ichthyosiform erythroderma, but has also been observed occasionally as an incidental histological finding in a variety of lesions¹. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD; agent orange), a kind of dioxin isomer, is contained in Agent Orange that was used for defoliation during the Vietnam War. TCDD elicits a disease spectrum of biological sex-, strain-, age-, and species-specific effects, including carcinogenicity, immunotoxicity, developmental toxicity, hepatotoxicity, neurotoxicity, skin diseases, and loss of body weight. We herein describe

incidental epidermolytic hyperkeratosis occurring in normal looking skin adjacent to folliculitic papules in veterans who had had contact with defoliants in the Vietnam War, and present the pathomechanism.

CASE REPORT

A 53-year-old man visited our clinic complaining of pruritus on his back for 10 years. On past history, he had had contact with defoliants when he participated in the Vietnam War for two years, and has been diagnosed and treated for multiple peripheral neuropathies and multiple cerebral infarcts. Physical examination revealed multiple small erythematous papules on his back (Fig. 1). Skin biopsies were taken from an erythematous papule and normal looking skin of the back adjacent to papule. Histopathology of the skin biopsy from the papular lesion showed the typical appearance of folliculitis, remarkable perifollicular necrosis and infiltration of lymphocytes (Fig. 2). At one margin of the normal looking skin specimen, a single rete, contiguous

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with the normal epidermis, contained the features of epidermolytic hyperkeratosis which showed compact hyperkeratosis and parakeratosis, variously sized clear spaces around nuclei in the stratum spinosum and granulosum, and a markedly thickened granular zone containing an increased number of small and large, irregularly shaped, basophilic keratohyalin-like bodies (Fig. 3).

DISCUSSION

Frost and Van Scott first introduced epidermolytic hyperkeratosis in 1966². It is characterized by variously sized clear spaces around the nuclei in the upper stratum spinosum and granulosum, a

markedly thickened granular layer containing an increased number of irregularly shaped keratohyalin granules, and compact hyperkeratosis³. This is the distinctive histopathologic change that has been described as the main feature of bullous congenital ichthyosiform erythroderma and as an incidental finding in other cutaneous disorders. Lesions in which the pathologic changes of incidental epidermolytic hyperkeratosis have been reported include dermal fibrohistiocytic lesions, epithelial neoplasms, hereditary disorders, inflammatory conditions, and melanocytic neoplasms⁴. In bullous congenital ichthyosiform erythroderma, this pathologic change is present in a wide area of the epidermis and may result in the formation of bullae. In contrast, most lesions containing incidental changes of epidermolytic hyperkeratosis do not have blisters and show this pathologic feature in a single epidermal rete ridge⁵.

Mahaisavariya et al⁴ retrospectively evaluated 21 specimens containing incidental epidermal hyperkeratosis. According to this report, epidermolytic hyperkeratosis was noted in numerous epidermal neoplasms, melanocytic neoplasms, scars, and inflammatory conditions either within the lesion or in the normal skin immediately adjacent to the lesions. Because lesions were noted on the back, head and neck, extremities, chest, flank, and breast, there was no specific site of predilection.

Recent studies confirm earlier findings that most of the toxic effects of TCDD are caused by its binding to a protein called aryl hydrocarbon receptor. The binding of TCDD to this protein triggers various

events that result in toxic sequelae⁶. Skin diseases associated with Agent Orange are chloracne, porphyria cutanea tarda, skin cancers and hyperproliferation related condition⁷. TCDD has been shown to induce differentiation in human keratinocytes. This effect is antagonized by retinoids and involve interaction between TCDD and retinoids in the regulation of epithelial differentiation⁶. Panteleyev *et al*⁸ reported TCDD affects keratin 1 and 17 gene expression and induces keratinization in hairless mice. This patient participated in the Vietnam War for two years and then suffered from multiple peripheral neuropathies and multiple cerebral infarcts which may be related to Agent Orange. He had dry skin, folliculitis and pruritus for more than 15 years. The pathogenesis of incidental epidermolytic hyperkeratosis has not been elucidated. However, Fuchs *et al*⁹ suggested that a mutation in genes that encoded the suprabasal keratin 1 and/or keratin 10 might be responsible for the abnormality in tonofilament formation found in patients with bullous congenital ichthyosiform erythroderma. And, ultrastructural evaluation also revealed tonofilament abnormal aggregation within the suprabasal epidermis corresponding to the distribution of keratin 1 and 10¹⁰. As with bullous congenital ichthyosiform erythroderma, the pathologic changes in incidental epidermolytic hyperkeratosis have also been noted in this particular distribution^{11,12}.

Further studies and more reports of similar cases are required to clarify the pathomechanism of this condition.

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