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A Case of Bleomycin-induced Scleroderma

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The association of exposure to bleomycin with the development of scleroderma-like cutaneous abnormalities has been reported. We experienced a case of scleroderma involving the hands, feet, and forearms after bleomycin chemotherapy. The present report supports the possible causal relation of bleomycin with scleroderma. Regarding the widespread use of bleomycin, this complication is thought to be under appreciated.

Key Words : *Bleomycin, Scleroderma*

INTRODUCTION

Numerous cutaneous abnormalities have been described in association with the use of the bleomycin, including hyperpigmentation, infiltrated plaques and nodules(Cohen et al.,1973). The development of a scleroderma-like syndrome has also been reported in foreign(Finch et al.,1980 ; Kerr and Spiera,1992) and in domestic literature(Eom et al.,1993), suggesting that bleomycin should be added to the growing list of exogenous agents like tryptophan, pentazocin, vinyl chloride, hydrocarbons, or trichloroethylene, which are capable of inducing scleroderma-like changes(Rush et al., 1984 ; Haustein and Ziegler,1985 ; Owens and Medsger, 1988 ; Connolly et al.,1990). We report herein a case of scleroderma associated with bleomycin chemotherapy.

CASE REPORT

A 58-year old man was referred to our clinic with sclerotic swollen patches on both hands, feet, and forearms. One year ago, he was suffering from non-Hodgkin's lymphoma(diffuse large cell, immunoblastic type, stage IIIa). He was treated over a period of six months with combination chemotherapy consisting of bleomycin 35mg, cyclophosphamide 650mg, vincristine 3.6mg, prednisolone 60mg, adriamycin 65mg, and procarbazine 625mg with a total of eight cycles.

Two months after beginning bleomycin chemotherapy, he complained of tingling sensations in his hands and feet. Within six months of the completion of chemotherapy(280mg of bleomycin, total), he developed sclerotic swollen patches on both hands, feet, and forearms(Fig. 1). The patient had no history of Raynaud's phenomenon, sicca symptoms, dysphagia, dyspnea, muscle weakness or fever. He had had diabetes mellitus for eight years and had been treated with NPH 30~40 units for one year prior to his visit. The family history was noncontributory. Physical examinations revealed sclerodermatous skin changes as well as sclerodactyly involving the hands, feet, and forearms, but neither telangiectasia, calcinosis, digital ulcerations, nor periungual erythema was observed. Laboratory test showed within normal ranges for CBC, LFT, urinalysis, EKG, chest PA, VDRL, RA factor, cryoglobulins, and cold agglutinin, but a weakly positive reaction for antinuclear antibodies(ANA). A 4-mm punch biopsy specimen was taken from the scleroderma-like lesion on the right hand. The epidermis was normal except for increased pigmentation. The dermis showed rather dense collagen with focal areas of homogenization and periadnexal inflammatory infiltration. Atrophic sweat glands and ducts, instead of being located at the junction of

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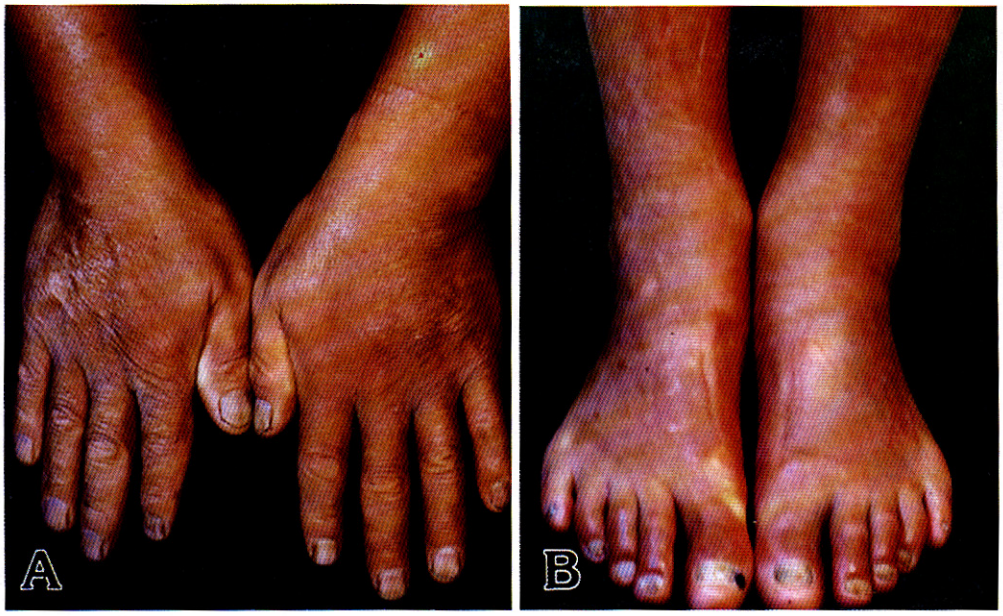

Fig. 1. Erythematous sclerotic swollen patches on the forearms, hands(A), and feet(B).

the dermis and subcutis, were found in the midportion of the thickened dermis. The subcutaneous fat was quantitatively reduced(Fig. 2).

The diagnosis of scleroderma was established for this patient through clinical, histopathological, and laboratory work-ups. He was treated with nifedipine, nicotinamide, and aspirin daily for one month. The result was a gradual resolution of the sclerodermatous lesion and swelling, although skin tightness over the distal phalanges persisted.

DISCUSSION

Sclerodermatous changes have been reported to occur in patients exposed to certain chemicals or drugs such as vinyl chloride, intramuscular pentazocine, oral ingestion of L-tryptophan, and bleomycin(Haustein and Ziegler, 1985 ; Owens and Medsger, 1988 ; Kerr and Spiera, 1992). There are some clinical differences according to the chemicals used. For example, exposure to vinyl chloride causes acro-osteolysis, Raynaud's phenomenon, pulmonary fibrosis, and distal skin thickening with nodularity(Black et al., 1986). Intramuscular pentazocine is reported to induce nodular sclerosis at the injection site(Rush et al., 1984), and oral ingestion of L-tryptophan has been suspected to be an etiologic agent of eosinophilia-myalgia syndrome(Connolly et al., 1990).

Bleomycin, which is commonly used in the treatment of certain neoplasms, is also able to induce acro-sclerosis. The incidences of bleomycin-induced scleroderma is unclear, but it seems not to be so rare. The etiology and pathogenesis of bleomycin-induced toxicity is essentially unknown. Bleomycin is believed to cause lung injury and cutaneous toxicity by lipid peroxidation, DNA strand breakage ; mediation by a hydroxyl radical mechanism has been proposed(Doelman and Bast, 1990 ; Dédée and Murrell, 1993). The development of pulmonary toxicity and sclerodermatous skin changes depends upon the dose ; the former occurring at a high dose and the latter occurring at a low dose(Kerr and Spiera, 1992). In the present case, only low dose bleomycin was administered and acro-sclerosis occurred without systemic involvement.

The present case shares some common unique features with the cases of Kerr and Spiera's(1992) : the absence of other connective tissue disease and the absence of exposure to other chemicals. Before beginning bleomycin therapy, our patient did not display symptoms suggestive of any underlying connective tissue disease. There was also no history of exposure to other drugs. He developed sclerodermatous changes

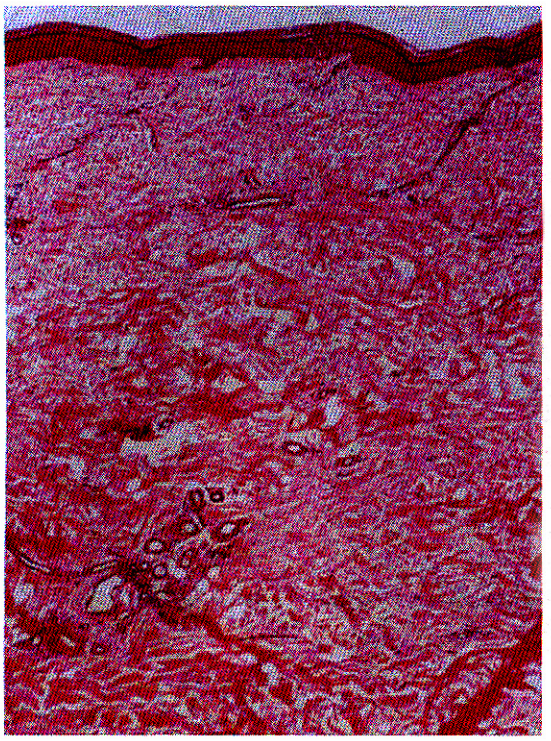

Fig. 2. Dermis shows thickened collagen bundle and moderately inflammatory infiltration and sweat glands appear atrophic and are bound down by newly formed collagen(H-E stain, ×40).

within six months of the completion of chemotherapy. Sclerodermatous skin changes were confined to the distal portions of the upper and the lower extremities, sparing the trunk and face. The stigma of the CREST variant and pulmonary changes were absent. There was a paucity of serologic abnormalities. A gradual clinical improvement was observed coincident with cessation of the administration of bleomycin, although the resolution of scleroderma was not complete and the patient was left with minimal persistent scleroderma of the distal phalanges.

Histologic changes were similar to those of classic scleroderma, but typical collagen thickening was not observed in the present case. These findings may reflect the initial edematous phase of scleroderma which may last several weeks or longer.

Considering the widespread use of bleomycin in combination with other chemotherapeutic regimens, it's possible that this type of bleomycin complication occurs more frequently than recognized. Therefore history of exposure to chemicals or drugs should be investigated in patient with scleroderma.

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