A Case of Bleomycin induced Streaky Pigmentation and Scleroderma

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Bleomycin, a tumoricidal antibiotic agent, may produce unusual cutaneous manifestations such as pigmentation scleroderma, and gangrene.

We report a case of the development of linear streaky pigmentation and cutaneous scleroderma in a patient treated with bleomycin for choriocarcinoma of undescented testis. The patient was 45-year-old male presented with linear brown and slate gray streaking over the trunk and extremities after three cycles of chemotherapy(bleomycin, etoposide, cisplatine). After the fourth cycle of the same chemotherapy, 18 weeks after initiation of bleomycin, the development of cutaneous scleroderma-like conditions was observed involving the same sites. Histopathologic examination showed increased basal pigmentation and thick collagen bundles through the entire dermis, extending to the subcutis.

Herein, we describe a case of streaky pigmentation and scleroderma in association with bleomycin anticancer chemotherapy simultaneously in a patient.

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Key Ward : Bleomycin, Hyperpigmentation, Scleroderma

Chemical agents have been known to induce thickening and hardening of the skin. These specific compounds include polyvinyl chloride, bleomycin, pentazocin, L-5 hydroxytryptophan and carbidopa.

Bleomycin is a commonly used anti-tumor antibiotics for Hodgkin's disease, lymphosarcoma, and embryonal cell carcinoma. It may produce unusual cutaneous manifestations including hyperpigmentation, scleroderma-like condition, infiltrated plaques, nodules and gangrene[1]. Although the development of scleroderma or pigmentation in association with exposure to bleomycin has been reported[2,3], but to our knowledge, the development of bleomycin induced hyperpigmentation and scleroderma dose-dependantly in a patient has not been reported in the literature.

Herein, we describe a case of streaky pigmentation and scleroderma in association with bleomycin anticancer chemotherapy. Our presented patient supports that bleomycin induced cutaneous manifestations may be dose-related and hyperpigmentation could appear before the development of scleroderma.

CASE REPORT

A 45-year-old male patient was found to have a choriocarcinoma of undescented testis with lung metastasis. There was a $7 \times 12 \times 11$cm sized mass in the lower abdominal cavity on the abdominopelvic CT scan and nodular density in both lung fields on chest X-ray. After surgical removal of the abdominal mass, he was treated with combination chemotherapy consisting of bleomycin 30mg $\times$ 2,

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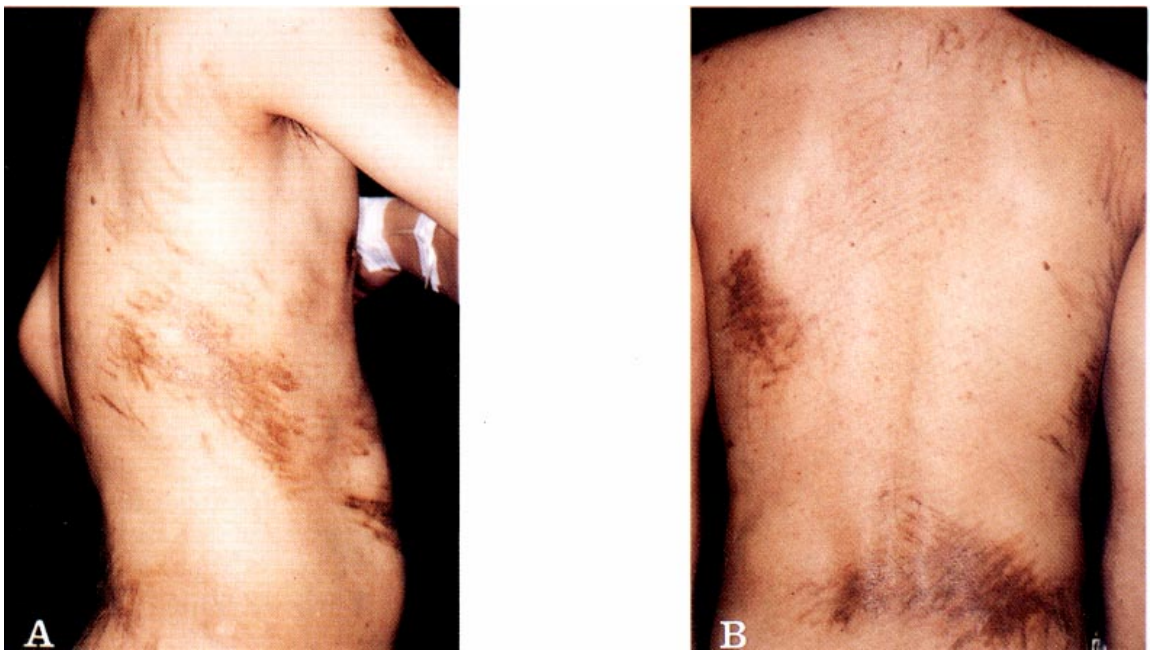
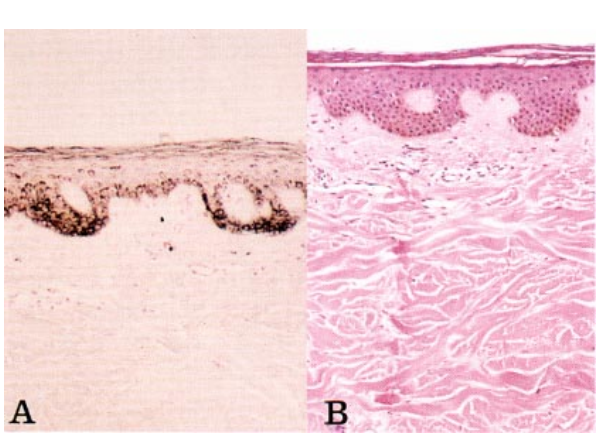


Fig. 1. (A) Brown and slate gray streaky pigmentation and scleroderma like condition on the flank. (B) Similar skin findings are observed on the back.



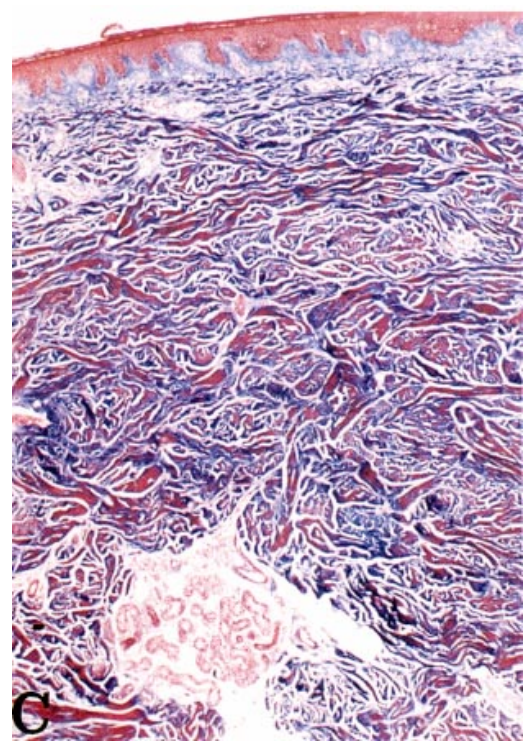


Fig. 2. (A) The basal pigmentation is markedly increased(Fontana Masson stain, ×40). (B) Hypocellular and e osinophilic dermis with densely packed thick collagen bundles through entire dermis(H-E stain, ×40). (C) Blue staining thick collagen bundles are extending deep dermis and subcutis(Masson-trichrome stain, × 40).

etoposide 80mg×4, and cisplastin 150mg×1 with a total of four cycles.

He was noticed to have linear brown and slate gray streakings over the trunk and proximal extremities after three cycles of chemotherapy(12 weeks after the initiation of chemotherapy), with 180mg of the accumulated dose of bleomycin. The streakings changed to dark brown and sclerotic during the 4th cycle(six weeks after the 3rd cycle of chemotherapy). A few weeks later, with an accu-

mulated dose of 240mg of bleomycin, his skin showed more darkening, hardening, and induration on the same sites(Fig. 1 A, B).

Laboratory tests were within normal range for complete blood count, liver function test, urinalysis, EKG, alpha-fetoprotein and testosterone but markedly elevated for ß-human chorionic gonadotrophin (82,034mIU/ml) and lactic dehydrogenase(614IU/L). The abdominal mass was surgically excised and confirmed as a choriocarcimoma originated from undescented testis. A 4 mm punch biopsy specimen was taken from the brownish scleroderma-like lesion on the abdomen. The epidermis showed mild hyperkeratosis and markedly increased basal pigmentation(Fig. 2A). The dermis was hypocellular and eosinophilic, and showed densely packed thick collagen bundles with the focal area of homogenization(Fig. 2B). On the Masson trichrome stain, blue color stained thick collagen bundles were observed through the entire dermis and extending to the subcutis(Fig. 2C).

We treated him with an application of a topical corticosteroid ointment. The pigmentation gradually improved, and the sclerosis of the skin was slightly relieved with this treatment. Up to now, there was no evidence of tumor mass, metastasis, nor recurrence.

DISCUSSION

The adverse effects of bleomycin include systemic reactions such as fever, headache, nausea and pulmonary fibrosis as well as cutaneous reactions. The cutaneous changes include alopecia, stomatitis, nail changes, indurated plaque, gangrene, and uncommon menifestations such as hyperpigmentation, and scleroderma. Sclerodermatous changes have been reported to occur in patients exposed to certain chemicals or drugs: polyvinyl chloride, carbidopa, pentazocin, L-5 hydroxytryptophan and bleomycin[1,4,5].

The pathogenesis of bleomycin induced toxicity is essentially unknown, but it is suggested that the toxicities may develop in a dose-related fashion[6]. The bleomycin induced hyperpigmentation usually occurs on the pressured areas and finger nails[7,8,9] as well as in areas of irritation or along the scratch marks[1,10,11]. Previously, the streaky hyperpigmentation, which is now recognized as a typical configuration in bleomycin induced pigmentation, was thought to be a postinflammatory hyperpigmentation because its appearance is very similar to scratch mark. And moreover the attempts to reproduce this hyperpigmentation by scratching the skin while treated with bleomycin were unsuccessful1. Recent studies have shown that bleomycin has a direct toxic effect on melanocytes, producing hyperpigmentation. Bleomycin induces cellular damage by cleaving the chromosomes in the internucleosomal regions and degrading chromatins. The damage occurs far more readily in non-proliferating or slowly proliferating cell populations, such as melanocyte. Increased melanogenesis had been demonstrated in melanocyte in the skin specimen taken from bleomycin treated patients[12]. Scleroderma and pulmonary fibrosis by bleomycin is believed by lipid peroxidation, and DNA strand breakage mediated by hydroxyl radical mechanism[13]. The development of sclerosis of the skin and pulmonary fibrosis depends upon the accumulated dosage, so the former occurring earlier at a low dose and the latter at a higher dose[13].

The course of hyperpigmentation by bleomycin has been reported to be gradually reversible when the drug was discontinued. It has also been reported that the sclerotic change cleared when therapy was completed[14]. Cohen1 et al reported that in five out of six patients, sclerodermatous changes gradually cleared when therapy was completed. As previously reported, in our case, the streaky pigmentation and the sclerotic changes gradually improved after discontinuation of bleomycin therapy. Also we experienced that the pigmentation improved earlier and then the sclerosis was slowly relieved.

In our case, he had no symptoms suggestive of any other connective tissue diseases, and no history of exposure to other chemicals or drugs before this therapy with bleomycin. He developed the streaky hyperpigmentation after the third cycle of chemotherapy on the trunk and extremities and sclerodermatous change after the fourth cycle on the same sites. The histologic examination revealed changes similar to those seen in classic scleroderma. So we concluded that the unusual skin manifestations of this patient was due to the bleomycin anticancer chemotherapy.

Our presented patient supports the hypothesis of dose-related fashion of bleomycin-induced cutaneous manifestations, that is, the streaky hyperpig-

mentation may appear before the development of scleroderma with the increase of accumulated dose. Considering the widespread use of bleomycin in combination with other chemotherapeurtic regimens, it is possible that bleomycin induced complications occur more frequently than recognized. Therefore, history of exposure to chemicals or drugs should be carefully investigated in a patient with scleroderma. Furthermore, when linear streaky hyperpigmentation occurs in a patient treated with bleomycin, one should consider the possibility of the development of scleroderma.

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