Flagellate Hyperpigmentation in a Scratched Area after Bleomycin for Pleurodesis

A Case Report and Review of the Literature

Yi-Shan Liu1 Ya-Hui Chen1 Jyh-Seng Wang2 Tien-Yi Tzung1, 3

Bleomycin, derived from Streptomyces verticillus, is used extensively in anti-cancer, anti-viral, anti-bacterial, and anti-tumor therapy. We present herein a case of 50-year-old woman with right pleural effusion due to liver cirrhosis treated with a single intrapleural instillation of bleomycin for cavitary sclerosis. Generalized itching occurred within 24 hours. Subsequently, streak-like hyperpigmentation soon appeared in the post-scratched areas. A skin biopsy showed an obvious increase in the amount of melanin pigment throughout the epidermal layer without increased melanocytes. After topical application of corticosteroid, the pruritus and hyperpigmentation faded. We also review the literature and the various clinical and histopathological features associated with this cutaneous complication of bleomycin, discussing the possible pathogenic mechanisms. (Dermatol Sinica 24: 269-274, 2006)

Key words: Bleomycin, Flagellate hyperpigmentation, Hyperpigmentation, Pleurodesis
INTRODUCTION

Bleomycin is an antibiotic with antitumoral properties that was first isolated from soil fungus, *Streptomyces verticullis*, in 1965, by Umezawa. It is currently used in the treatment of malignancies, including lymphoma, testicular carcinoma, and squamous cell carcinoma. It inhibits the incorporation of thymidine into DNA and causes single-strand breaks, inhibiting DNA synthesis. As part of a chemotherapeutic regimen, bleomycin has been found to cause several mucocutaneous reactions, such as alopecia, stomatitis, skin hyperpigmentation, nail change, radiation recall, hypersensitivity reaction, flush, and neutrophilic eccrine hidradenitis. Flagellate hyperpigmentation occurs in 8% to 20% of patients receiving a cumulative dose of over 100 mg, but can occur at a dose as low as 14 mg. This specific pattern of pigmentation occurs de novo or follows linear erythematous plaques or urticarial-like lesions, and is sometimes accompanied by pruritus or tenderness. We report here one patient developing diffuse flagellate hyperpigmentation only on scratched areas following intrapleural instillation of bleomycin.

CASE REPORT

A 50-year-old woman was a victim of HBV-related liver cirrhosis with splenomegaly and hypoalbuminemia (2.3 g/dl) diagnosed two years prior to presentation. She suffered from cough, chest pain, and dyspnea when exercising, owing to recurrent right side transudative pleural effusion associated with hypoalbuminemia. Pleurocentesis with pigtail drainage was performed. Following radiographic confirmation of complete fluid evacuation, bleomycin (50 mg) was instilled into the pleural space as a sclerosing agent for chemical pleurodesis.

The patient had few skin complaints in the past. Generalized and intense pruritus associated with scratching throughout her whole body involuntarily was developed within 24 hours following bleomycin intrapleural instillation. Subsequently, many brownish streaks appeared on the scratched areas without any preceding significant erythematous or urticarial lesion by the next day. A dermatologist was consulted.

![Fig. 1](image1)

Generalized well-demarcated hyperpigmented patches in a striated pattern appearing over the entire body surface, with the exception of the areas beyond scratching.

![Fig. 2](image2)

Melanin pigmentation markedly increased throughout the entire layer of epidermis from the basal cells to the corneocytes, with some melanin incontinence in the upper dermis. (2A: H & E, x200, 2B: Fontana-Masson stain, x200)
and the physical examination revealed numerous well-demarcated hyperpigmented flat patches in a striated pattern over her entire body surface, with the exception of the areas beyond scratching (Fig. 1). Hyperpigmentation over the small joints of the hands, elbows and knees was not noted. There was no mucous membrane involvement, along with no clinical or radiological evidence of pulmonary complications. A skin biopsy was taken from a streak-like area of hyperpigmentation on her abdomen and was examined under both light and electron microscopy after proper processing. Light microscopy demonstrated a marked increase of melanin pigmentation throughout the entire layer of epidermis from the basal cells to the corneocytes, as well as some melanin incontinence in the upper dermis (Fig. 2A & 2B), and a sparse perivascular lymphocytic infiltrate was noted in the upper dermis. The number of melanocytes was unremarkable, as shown by S100 stain (Fig. 3). Electron microscopy disclosed the presence of increased melanosomes in the basal cells and in cells of both the spinous mous layer and the cornified layer (Fig. 4). We prescribed oral anti-histamines and topical glucocorticoid. Her hyperpigmentation gradually faded in the following months.

**DISCUSSION**

Bleomycin is a sulphur-containing antibiotic with anti-tumor properties. It has a cytostatic effect, bringing about cell damage in low concentrations by inhibiting mitosis, and in high concentrations by blocking the incorporation of thymine into DNA in the S-phase and by splitting the DNA into smaller fractions, inhibiting DNA synthesis. After administration, 50% of bleomycin is excreted in the urine unchanged, and a hydrolase enzyme inactivates the rest. The hydrolase enzyme is absent in the skin and lungs, leading to a high concentration of the drug in these organs, which in turn is thought to account for its remarkable cutaneous and pulmonary toxicity such as pulmonary fibrosis. The bone marrow toxicity of bleomycin is practically null.

The well-documented cutaneous reactions to bleomycin are alopecia, stomatitis, nail changes, flagellate hyperpigmentation and pigmentation localized to areas of pressure and palmar creases. Less frequently observed dermatologic complications include hyperkeratotic plaques on the knees and elbows, scleroderma-like process on the hands, erythema multiforme, Raynaud phenomenon, and neutrophilic eccrine hidradenitis. Gangrene has been reported in extreme scleroderma-like situations when the blood supply has become critically compromised. Fingernail loss has been reported after intralesional bleomycin administration for recal-

---

**Fig. 3**

Melanocytes with normal counts. (S100 stain, x200)

**Fig. 4**

Increased melanosomes forming dense perinuclear rings seen in the basal cells, and in cells of both the spinous layer and the cornified layer. (Electron microscopy, x20,000)
citrant periungual warts. Bleomycin has been thought to affect the nail matrix area and subsequently interface with normal nail keratinization.\

The overall incidence of skin hyperpigmentation in patients receiving bleomycin is approximately 30%. Flagellate hyperpigmentation occurs in 8% to 20% of cases, generally occurring after a cumulative dose of between 90 and 285 mg. A direct relationship with dosage was proposed by Guillet et al. Some cases have been reported with injected doses as low as 14 mg intralesionally, 15 mg intravenously and 30 mg intrapleurally.\

The course of bleomycin-induced flagellate hyperpigmentation varies. Most patients initially develop generalized pruritus several hours to several weeks after administration of bleomycin. Some patients present flagellate erythema prior to hyperpigmentation, but some do not. The time lag between administration and erythema varies from 1 hour to 8 weeks, while the time lag between administration and hyperpigmentation varies considerably from less than 24 hours to 7 months. They are most commonly seen on the proximal aspect of the extremities and trunk, although the entire body could be involved.\

A variety of pathological reaction patterns have been reported for flagellate erythematous plaques, including inflammatory oncotaxis, fixed drug eruption-type reaction, lymphocytic vasculitis, and urticarial allergic drug eruption. The exact mechanism producing this hyperpigmentation remains unclear, and diagnosis is based on the characteristic clinical presentation. A variety of theories have been proposed, including local accumulation of bleomycin in the skin due to vasodilatation caused by a dermatographic stimulus such as local trauma (rubbing or scratching) and tape stripping. Evidence of hyperpigmentation confined to newly formed striae distensae after treatment with bleomycin also presumed that increased new blood vessels in the early stage of striae distensae allows increased quantities of bleomycin to be delivered to selected skin sites. This might lead to a direct toxic effect of bleomycin on the keratinocytes. However, some authors have tried unsuccessfully to reproduce the reaction by scratching. Our patient's presentation with streaked pigmented bands developing only on scratched areas supports the idea that hyperpigmentation arises in sites subjected to scratching. It hints that there may be a significant interrelationship between scratching and this special cutaneous adverse effect.\

Different hypotheses, based on histopathologic and ultrastructural findings, have been proposed to explain the mechanism of increased melanogenesis. Obviously, a totally normal immune system is not essential for the production of this peculiar bleomycin-induced pigmentation, since it has been previously reported in a patient with acquired immune deficiency syndrome (AIDS), as well as in patients with cancer receiving immunosuppressive therapy with bleomycin alone or in combination with other agents. Dopa staining of a hyperpigmented area shows larger melanocytes with larger and more complex dendritic processes and enhanced dopa-oxidase activity than in adjacent nonpigmented skin, suggesting that this hyperpigmentation is the result of a localized increase in melanogenesis. Keratinocytes containing an increase in the number and size of melanosomes forming dense perinuclear rings in most cells have been identified. It implies that the transfer of melanin increases possibly because of decreased epidermal turnover, allowing prolonged contact between keratinocytes and melanocytes. Nevertheless, the precise transfer time has not been measured.\

Intradermal injections of bleomycin into normal human skin could cause time- and dose-dependent localized erythema and induration, leaving post-inflammatory hyperpigmentation. Histopathologic findings imply that bleomycin is either directly or indirectly cytotoxic to keratinocytes and the eccrine epithelium, and immunohistology suggests that pro-inflammatory cytokine secretion occurs. Histological features of an early erythematous eruption after bleomycin treatment reveals a superficial
perivascular inflammatory infiltration. The pigmentary changes observed after erythema are thought to be due to a post-inflammatory effect.17

Post-inflammatory changes are mentioned in many articles, although the theory has been controversial, since a history of prior skin changes has been rarely obtained. The role of local inflammation is not favored by Guillet et al, since there is no pigment incontinence in the dermis in their histological data.7 The pathology of our case did reveal some pigment incontinence in the upper dermis, although no skin erythema preceding the hyperpigmentation was noted clinically. Additional studies are required to determine the cause of the pruritus and to explain the linear pattern of pigmentation.

Some authors have found that patients receiving glucocorticoid therapy along with bleomycin very seldom develop pigmented lesions,9 and proposed prophylactic anti-pruritus agents, such as systemic glucocorticoid and antihistamines, may reduce the incidence of bleomycin-induced flagellate hyperpigmentation. However, rash develops in some patients despite the administration of systemic glucocorticoid as part of chemotherapy. It has been suggested that mild cases may respond to antihistamines and/or systemic glucocorticoid. Most cases are reversible following cessation of bleomycin therapy. However, careful consideration among alternative chemotherapeutic regimens and the advantages of continuing bleomycin treatment for the neoplasm is necessary.10 In our case, topical glucocorticoid with oral antihistamines diminished the pruritus, causing the streak-like hyperpigmentation to fade gradually.

In summary, bleomycin-induced flagellate hyperpigmentation is a unique cutaneous drug eruption, which arises in a proportion of individuals exposed to this drug. There is no clear relationship between the dose and the incidence of side effects. The mechanism and the reason for the localized hyperpigmentation of the skin reaction in a linear pattern are unknown, but the process of post-inflammatory hyperpigmentation is suggested. Therefore, further studies are required. Its presence may cause fear and psychological distress in these patients. In extensive utilization of bleomycin, dermatologists should be mindful of this specific adverse cutaneous reaction, especially in patients who are concerned about the appearance of any skin changes.

REFERENCES