Flagellate Hyperpigmentation Following Intralesional Bleomycin Treatment of Verruca Plantaris

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Background: Flagellate hyperpigmentation is a well-documented complication of systemic bleomycin sulfate therapy when using doses of 100 U or more as an antineoplastic agent. Two cases occurred after using systemic doses from 15 to 30 U injected intravenously or intrapleurally; however, it has not been described as a complication following intralesional treatment of verruca plantaris.

Observations: We report a case of flagellate hyperpigmentation after intralesional injection of 14 U of bleomycin for verrucae plantaris and review the literature associated with this cutaneous complication.

Conclusions: Flagellate hyperpigmentation from extremely low doses of intralesional bleomycin is a previously undescribed complication. Although the mechanisms of reaction are not clearly understood, the clinician should be mindful of this uncommon complication.

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REPORT OF A CASE

A 31-year-old woman was evaluated for a cutaneous eruption following treatment with bleomycin for recalcitrant verruca plantaris. During a single office visit 10 weeks earlier, she had been treated with 14 intralesional injections of bleomycin into the verrucae on the plantar surfaces of both feet. Approximately 1 U was delivered per injection in a sequential fashion. Each injection was in a different lesion. A cumulative dose of 14 U of bleomycin was delivered. The patient subsequently developed generalized pruritus and urticaria within 1 hour of the 14 injections. Thereafter, she rapidly developed erythematous streaks on her trunk, which became hyperpigmented by the following morning. The patient was treated with oral methylprednisolone for 6 days (24 mg for 2 days, 16 mg for 2 days, and 8 mg for 2 days), which temporarily relieved the urticaria and pruritus. However, the streaky hyperpigmentation progressed over the course of the next month as her pruritus returned. She was evaluated by a local dermatologist and began a 15-day tapering course of prednisone (60 mg for 5 days, 40 mg for 5 days, and 20 mg for 5 days). Simultaneously, she was referred to the Department of Dermatology at Naval Medical Center San Diego for further evaluation.

On presentation to our department, findings from her physical examination were notable for hyperpigmentation in mul-

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Multiple, well-demarcated, horizontal, linear streaks on her abdomen in all 4 quadrants (Figure 1). The streaks ranged from 5 to 15 mm in width and 2 to 10 cm in length. There was no scale, lichenification, or urticaria. Examination findings also revealed numerous lesions on the soles of her feet bilaterally consistent with verruca plantaris (Figure 2). There was no evidence of necrosis or thrombosis of the verrucae. Test results for the human immunodeficiency virus antibody were negative, and she was anergic to purified protein derivative of tuberculin, Candida, and mumps antigens. We prescribed 5% imiquimod cream under occlusion to selected verrucae and considered dinitrochlorobenzene sensitization.

**COMMENT**

Bleomycin is an antibiotic derived from Streptomyces verticillus. In low doses, the antineoplastic properties are achieved by inhibition of mitosis. At higher concentrations, bleomycin is cytostatic by blocking DNA uptake of thymidine in the S-phase of the cell cycle. Intralesional bleomycin has been reported in multiple studies as being highly effective in the treatment of recalcitrant verruca vulgaris. Most studies report overall cure rates of more than 85%, but some range as high as 95%. It is thought that the drug's efficacy in the treatment of verrucae is due to its effects on cellular DNA, which impede viral survivability by limiting turnover of host cells, but induction of tumor necrosis factor has also been reported as a possible mechanism. It has been shown that expression and up-regulation of activation antigens (human leukocyte antigen class II) and cell adhesion molecules (intercellular adhesion molecule-1, endothelial leukocyte adhesion molecule-1, and vascular cell adhesion molecule-1) occur after the injection of bleomycin into human skin. Given its toxic nature as a chemotherapeutic agent and the increased incidence of adverse effects, treatment of common warts with bleomycin has been limited to cases that do not respond to conventional therapies. Some authors have raised the possibility of using bleomycin as a first-line agent because of the relatively simple procedure and increased patient satisfaction when compared with destructive modalities such as cryotherapy or electrocautery. The efficacy of bleomycin therapy may be related to location of the verrucae. Plantar warts were cured only 60% of the time, whereas periungual and other extremity locations have shown cure rates of 94% and 95%, respectively.

Commercially available bleomycin is usually prepared at a concentration of 1 U/mL, where 1 U is equal to 1 mg. Most studies describe techniques in which a cumulative dose of 0.1 to 2.0 U is injected into an affected area, with single lesions receiving approximately 0.2 U. Bleomycin injected into normal human skin clinically produces inflammatory responses at concentrations as low as 0.01 U/mL and a plateau of clinical response at doses greater than 0.1 U/mL. Incremental histopathologic responses, however, are shown at concentrations of up to 1 U/mL. The optimal dosage for treatment of verrucae with bleomycin has not been established, but safe and effective ranges between 0.1 U and 2.0 U per treatment have been identified.

Cutaneous reactions to bleomycin are well documented. Alopecia, stomatitis, and hyperpigmentation are commonly seen after systemic chemotherapy using bleomycin. Flagellate hyperpigmentation is classically associated with systemic bleomycin, but pigmentation can also be localized to areas of pressure and palmar creases. Hyperpigmentation limited to striae distensae following antineoplastic therapy with 204 U of bleomycin was described in one report. Less frequently observed dermatologic complications include hyperkeratotic plaques on knees and elbows; scleroderma-like collagen deposits in the hands, which can compromise blood flow and induce digital gangrene; blisters; painful inflammatory nodules on fingers; infiltrated violaceous plaques; and erythema multiforme. Raynaud phenomenon following intralesional injection has been reported as well as linear papules and erythematous macular lesions forming within 24 hours of bleomycin treatment. Nail changes...
such as Beau’s lines, growth retardation, shedding, onychodystrophy, and onycholysis have been reported.\textsuperscript{11} Neutrophilic eccrine hidradenitis has also been described as a superimposed complication accompanying the typical bleomycin-induced flagellate hyperpigmentation.\textsuperscript{12}

When used in its approved applications as a systemic chemotherapeutic agent for squamous cell carcinoma, lymphoma, testicular carcinoma, and malignant pleural effusion, bleomycin causes adverse cutaneous reactions in 50% of treated patients and pulmonary complications in 10% of patients.\textsuperscript{17} In comparison to other bodily tissues, the skin and lungs demonstrate decreased activity of hydrolases required for the inactivation of bleomycin.\textsuperscript{1,5} This may explain the increased concentration of the drug in these tissues and the corresponding prevalence of dermatologic and pulmonary complications after systemic treatment.\textsuperscript{10,19}

The course of bleomycin-induced flagellate hyperpigmentation is varied. Most patients initially develop generalized intense pruritus several hours to several weeks after administration of bleomycin.\textsuperscript{1,13,14,22} Erythematous linear streaks eventually progress to the typical flagellate hyperpigmentation.

Several hypotheses regarding the cause of hyperpigmentation have been proposed. Some believe the linear lesions are induced by rubbing or scratching the skin, which causes the drug to leak out of blood vessels.\textsuperscript{13} Histopathologically, the lesions show a localized increase in melanogenesis from hyperactive and enlarged melanocytes,\textsuperscript{21} postinflammatory pigmentation secondary to pigmentary incontinence,\textsuperscript{22} and increased number and size of melanosomes in the keratinocytes of the basal layer.\textsuperscript{12,14,23} There is slower epidermal turnover with prolonged contact between melanocytes and keratinocytes\textsuperscript{4} and altered pigment maturation resulting in melanin distribution to the upper horny layers.\textsuperscript{24} Others believe accumulation of bleomycin in the skin causes a subsequent fixed drug eruption due to the direct effects of bleomycin on the keratinocytes.\textsuperscript{25}

Most cases are reversible following cessation of therapy; however, persistence of hyperpigmented streaks for up to 1 year after treatment has been reported.\textsuperscript{4,13,14} An additional report\textsuperscript{26} describes flagellate hyperpigmentation following bleomycin therapy in a patient with acquired immunodeficiency syndrome that persisted for more than 6 months after cessation of bleomycin.

Diverse cutaneous reactions to bleomycin therapy are fairly common in the literature and are reported as having an incidence of 8% to 20% in patients receiving cumulative doses greater than 100 U.\textsuperscript{11,13,14} The 2 lowest reported doses with systemic dermatologic complications are 15 U given intravenously as part of an anti–Hodgkin lymphoma regimen and 15 U given intravenously as a diagnostic test for lung cancer.\textsuperscript{13,27,28} These patients presented with widespread pruritus and numerous truncal erythematous plaques and papules that developed into flagellate hyperpigmentation.\textsuperscript{13} The only other report\textsuperscript{26} to our knowledge of low-dose bleomycin causing flagellate hyperpigmentation involves the intrapleural administration of 30 U of bleomycin for treatment of mesothelioma. Linear streaks of flagellate hyperpigmentation subsequently developed on the patient’s arms and back.

Flagellate hyperpigmentation has been reported to occur following administration of 15 U intravenously and 30 U intrapleurally; our patient received less than 15 U intracutaneously. Flagellate hyperpigmentation is one of many cutaneous reactions complicating bleomycin therapy. Its exact mechanism of reaction is not clearly understood, although most theories involve increased levels of melanin due to various intercellular interactions as well as toxic effects of the drug itself. Physicians should be aware that flagellate hyperpigmentation is a common cutaneous complication after bleomycin therapy, potentially even after small intracutaneous doses.

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