

Bleomycin Dermatologic Toxicity in a Patient with HIV-Associated Sarcoma

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INTRODUCTION

Pharmacists are often approached to evaluate potential drug related skin eruptions. With the expanding HIV population, in whom the incidence of dermatological side effects secondary to medications is a common occurrence,¹ there is an increasing demand for the pharmacist to become familiar with these types of adverse reactions.

Sulfonamide related allergic skin reactions in HIV positive patients are frequent with an incidence of up to 69%.¹ These range from generalized erythema to exfoliative dermatitis to Stevens-Johnson syndrome.² In addition, due to their many concomitant conditions, HIV patients tend to receive a number of other medications concurrently which also may cause adverse dermatological reactions. This often presents a challenge in trying to identify the causative agent. Below is a description of bleomycin induced flagellate hyperpigmentation which is characteristic of this drug and which has not been reported with other agents, including sulfonamides. The purpose of this report is to increase the pharmacist's awareness of this readily identifiable bleomycin drug related problem (DRP) to prevent unnecessary interruption of drug therapies.

Bleomycin is an antineoplastic antibiotic used to treat AIDS related Kaposi's sarcoma (KS). Lung and skin toxicities are known side effects of bleomycin.³ The occurrence of these toxicities may be related to the tendency of bleomycin to concentrate in pulmonary and cutaneous tissues, both of which are deficient in a hydrolase enzyme necessary for the inactivation of this chemotherapeutic agent. Bleomycin related dermatologic side effects include hyperpigmentation of the skin, hyperkeratosis of the hands and nails, Raynaud's phenomenon and pseudoscleroderma.¹ Skin reactions secondary to bleomycin have also been reported in AIDS patients.¹ The type of cutaneous reactions in this patient population are qualitatively similar to those reported in other patient populations.

Case

A 31 year-old female presented for treatment of disseminated KS, which involved her respiratory tract, gastrointestinal tract, and skin.

Six months before presentation to our cancer centre, she underwent investigations for a one-year history of retrosternal burning relieved only temporarily by food or antacids. An oesophageal-gastro-duodenoscopy (OGD) revealed gastritis, duodenitis, *H. pylori* colonization, and raised nodular erythematous mucosal patches in the stomach and duodenum. A colonoscopy confirmed similar lesions in the sigmoid, descending, transverse and ascending colons. Biopsies of these lesions were highly suspicious for KS. She was also found to be HIV seropositive with a CD4 count of $0.012 \times 10^9/L$. Four years earlier her HIV status was negative. The patient reported no drug allergies.

Two months before, the patient complained of shortness of breath and retrosternal burning. She denied any cough, hemoptysis, or sore throat. Investigations for opportunistic infections including *Pneumocystis carinii* pneumonia (PCP), mycobacterial infections, *Cryptococcus*, *Toxoplasma* and Hepatitis B were negative. Her CD4 count had dropped to $0.008 \times 10^9/L$ with a CD4/CD8 ratio of less than 0.115. A chest x-ray showed a bilateral reticulonodular pattern compatible with KS. The patient had multiple KS lesions on her face, upper palate, lower and upper extremities, abdomen, and trunk. She had no constitutional symptoms of fever, chills, night sweats, or lymphadenopathy. Her gastrointestinal (GI) symptoms were treated with amoxicillin 1g po bid for 14 days, omeprazole 40mg po bid for 14 days followed by 20mg po daily for six weeks with a significant symptomatic improvement. Five days later, she began cotrimoxazole-DS, one tablet po daily for PCP prophylaxis. Due to an increased risk of hematologic toxicity, anti-retroviral therapy was withheld at this point in anticipation of chemotherapy treatment for KS.

Given the widespread visceral KS involvement, it was elected to start her on adriamycin, bleomycin,

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vincristine (ABV) chemotherapy regimen. On November 10, 1994 she was given her first cycle of adriamycin 15mg IV push, bleomycin 15mg IV push, and vincristine 1mg IV push with dexamethasone 10mg IV push, and prochlorperazine 10mg po as premedication. She continued to take co-trimoxazole-DS. One to two days after the chemotherapy administration, the patient experienced pruritis and a peculiar skin eruption in the areas she had been scratching. Over the period of the next two weeks, these discoloured "scratch marks" did not fade and became indurated. The skin on her fingers also became noticeably thickened and she complained of an uncomfortable swelling of the fingers of her right hand.

When she presented two weeks later for her next chemotherapy cycle, the skin eruption, while evident all over her body, was marked over her trunk primarily in areas she had been scratching. This eruption consisted of linear, well demarcated, hyperpigmented streaks. In view of this reaction, chemotherapy was delayed and co-trimoxazole-DS was held. She was referred to the Adverse Reaction Clinic where the dermatologist confirmed that the linear pigmentation was secondary to bleomycin. At this time, it was thought that the pigmentation would probably not fade easily, but that there was no contraindication to continuing bleomycin use. However, after her appointment with the dermatologist, the patient did not return to the oncology clinic and decided against continuing with the chemotherapy treatment.

DISCUSSION

Flagellate linear hyperpigmentation is recognized as a cutaneous toxicity seen exclusively with bleomycin.⁴ Its unique appearance is easily discernable by the form of hyperpigmented, linear streaks, or flagellate post-inflammatory hyperpigmentation. Although older studies⁵ suggested that this reaction is dose related, newer reports have refuted this theory.⁶ There have been two published papers where this reaction was in fact reported after a single dose of bleomycin, similar to this patient. Mowad et al⁶ described a 36 year-old female who developed pruritic linear streaks four days after a single 15mg dose of bleomycin. In an open prospective study of 50 AIDS patients with KS, 16% of whom developed flagellate hyperpigmentation secondary to bleomycin, one patient presented with an acute onset one day after first treatment.¹ The reaction may also appear after cumulative bleomycin doses as large as 285mg. It does not appear to be related to the route of administration of bleomycin, with the intramuscular and intravenous routes being most common. However, one report of this cutaneous reaction after an intrapleural application of 30mg of bleomycin was also described.⁶ Symptoms may appear abruptly and may occur from within a few hours up to nine weeks post administration of bleomycin.⁶ The

flagellate lesions may persist for up to six months.⁷ Depending on the study, the prevalence of this specific reaction ranges from 8 to 66%.⁸ Although the exact mechanism of bleomycin induced flagellate hyperpigmentation has not been fully elucidated, one report of a biopsy of these lesions has shown increased melanogenesis.⁹

The usual management of this eruption consists of topical steroid therapy, for example with fluocinolone 0.025%. This treatment typically alleviates pruritis and erythema while the residual post-inflammatory hyperpigmentation resolves more slowly. Cutaneous hyperpigmentation is eventually reversible however, once the drug is withdrawn. Upon rechallenge with bleomycin, the reaction typically returns.⁶ Before a recommendation of bleomycin withdrawal is made, the pharmacist should conduct a thorough discussion with the oncologist and the patient during which the benefits of continuing bleomycin treatment, the severity of the dermatological reaction and other chemotherapy alternatives are closely considered.

The diagnosis of cutaneous eruptions in AIDS patients is challenging due to the many concomitant diseases and their respective treatments. This case clearly illustrates a unique adverse effect of bleomycin which is characterized by linear, hyperpigmented streaks. These may appear after a single dose but are also seen after higher cumulative doses of bleomycin. This cutaneous toxicity is reversible upon withdrawal of the offending agent, but does recur with drug rechallenge. An occurrence of flagellate hyperpigmentation in a patient with AIDS should prompt the pharmacist to consider the possibility that it is a unique adverse effect of bleomycin. ☒

REFERENCES

1. Caumes E, Katlama C, Guernonprez G, et al. Cutaneous side-effects of bleomycin in AIDS patients with Kaposi's sarcoma. *Lancet* 1990;336: 1593.
2. Zyma C, Edwards S, Hahn J, et al. Sulfonamide allergy and cross-allergenicity - answers to common questions. *New Drugs - Drug News* 1996; 14: 1-3.
3. Dorr RT, Von Hoff DD, ed. *Cancer Chemotherapy Handbook*. 2nd ed. Norwalk: Appleton & Lange. 1994. 232.
4. DeSpain JD. Dermatologic Toxicity. In: Perry MC, ed. *The Chemotherapy Sourcebook*. Baltimore, MA: Williams & Wilkins; 1992:531-47.
5. Jagoda A, Mukherji B, Young C, et al. Bleomycin, an antitumor antibiotic. Clinic experience in 274 patients. *Ann Intern Med* 1972;77:861-70.
6. Mowad CM, Nguyen TV, Elenitsas R, et al. Bleomycin-induced flagellate dermatitis: a clinical and histopathological review. *British Journal of Dermatology* 1994; 131: 700-2.
7. Lazar A, Lazar P. Streaky pigmentation in a patient with acquired immune deficiency syndrome (AIDS). *Cutis* 1988;42:397-8.
8. Guillet G, Guillet MH, de Meaux H, et al. Cutaneous pigmented stripes and bleomycin treatment. *Arch Dermatol* 1986;122:381-2.
9. Cohen IS, Mosher MB, O'Keefe EJ, et al. Cutaneous toxicity of bleomycin therapy. *Arch Dermatol* 1973;107:553-5.