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### Bleomycin induced skin rashes- a case report

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#### ABSTRACT

Bleomycin is a cytotoxic glycopeptide derived from *Streptomyces verticillus* and is used in ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) chemotherapy regimen. Bleomycin is effective against several human cancers particularly lymphomas, testicular and ovarian germ cell tumors and squamous cell carcinoma. Pulmonary toxicity and skin toxicity are the major toxicities of bleomycin. The various dermatological adverse effects of bleomycin include flagellate dermatitis, erythema, hyperpigmentation, hyperkeratosis, palmoplantar desquamation, Raynaud's phenomenon. The development of rash is independent of dose and route of administration. This is a case of 68 years male patient diagnosed with Hodgkin's lymphoma who developed rashes after receiving bleomycin based chemotherapy. The patient responded well to the anti-histamines, aloe Vera-calamine lotion and bleomycin was withheld from the subsequent chemotherapy cycles.

**Keywords:** Bleomycin; Skin toxicity; Hodgkin's lymphoma.

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#### INTRODUCTION

Hodgkin's disease is a B-cell lymphoid malignancy. It was first described by Hodgkin in 1832<sup>[1]</sup>. It is estimated to account for about 10% of cases of newly diagnosed lymphomas. It is most commonly diagnosed in the 20-34 years age group, accounting for 31% of new cases but can be seen across the age spectrum from adolescents to the elderly<sup>[2]</sup>. Treatment options have evolved over time ranging from radiation, cytotoxic chemotherapies, cellular therapies and most recently targeted therapies. ABVD [Adriamycin, Bleomycin, Vinblastine, and Dacarbazine] chemotherapy

is the standard chemotherapeutic regimen for Hodgkin's lymphoma<sup>[3]</sup>.

Bleomycin is a sulphur containing antimicrobial derived from *Streptomyces verticillus* and is used as standard chemotherapy for Hodgkin's lymphoma, germ cell tumors, Kaposi sarcoma and pleurodesis for malignant pleural effusions<sup>[4]</sup>. Its potential as an anti tumor drug was described by Umezawa in 1965<sup>[5]</sup>. Bleomycin exerts its cytotoxic effects by the generation of oxygen free radicals causing single and double stranded DNA breaks and eventual cell death<sup>[6]</sup>. The adverse effects of bleomycin are gastrointestinal (mucositis, anorexia, weight loss), respiratory (tachypnea, pneumonitis, pulmonary fibrosis), dermatological (erythema, cutaneous rash, vesicles, palmar and plantar scaling, hyperpigmentation, alopecia and flagellate dermatitis) as well as general symptoms such as fever and malaise<sup>[7]</sup>.

Two major toxicities of bleomycin are pulmonary and skin toxicity. Lung toxicities are relatively common while skin toxicities are very uncommon<sup>[8]</sup>. Bleomycin is inactivated in most tissues by an enzyme, Bleomycin hydrolase which cleaves the ammonia group from bleomycin. This enzyme is active in all tissues except skin and lungs which account for these being the most common sites of toxicity. Skin reactions are the most common effects and are relatively late manifestation usually developing after several cycles of chemotherapy has been administered and when the cumulative dose has reached 150-200U, although it can occur with any dose of bleomycin<sup>[6]</sup>. Flagellate er-

ythema was first reported as an adverse effect of bleomycin use in 1970 by Moulin et al. The rash may appear following administration of bleomycin by any route: intravenous, intramuscular and topical. Males and females were found to be equally affected<sup>[9]</sup>. Flagellate erythema and other skin toxicities may be unpleasant or unsightly and are not associated with increased morbidity or mortality and usually resolves on the withdrawal of the drug. Treatment includes topical or systemic corticosteroids or oral antihistamines<sup>[9]</sup>.

### CASE STUDY

A male patient of age 68 years was diagnosed with Hodgkin's lymphoma. There was no previous history of dermatological disorders or allergy. He had the past medical history of hypertension for which he was prescribed with Furosemide 40 mg. The patient was reformed smoker. He admitted for the 6<sup>th</sup> cycle of chemotherapy with ABVD (Adriamycin, Bleomycin, Vinblastine, and Dacarbazine) chemotherapy regimen. After receiving the 5 cycles of ABVD chemo regimen, the patient developed rashes all over the body. Similar rashes appeared previously but were improved spontaneously with Cetirizine tablet. Now new rashes developed again so the patient was promptly referred to the dermatologist.

On examination it was found that the patient had a erythematous, skin coloured papules and infiltrated plaques over face, upper limbs and lower limbs suggesting a drug induced reaction. There was no mucosal involvement or systemic upset. With the characteristic appearance of the rash coinciding with the use of bleomycin, a clinical diagnosis of bleomycin induced rash was made. Routine laboratory investigations including liver function tests and renal function tests were normal. Bleomycin was withheld from the subsequent chemotherapy cycles and the patient was prescribed with Cetirizine tablet and calamine-aloe vera lotion.

### DISCUSSION

Diverse cutaneous reactions to bleomycin therapy are common in the literature and are reported as having an incidence of 8 to 20% in patients receiving cumulative doses > 100 units<sup>[10]</sup>. There is a declining use of bleomycin in current practice due to its toxicity concerns; however, it is still widely used in Hodgkin's disease, germ cell tumors and for pleurodesis. Bleomycin is inactivated by a cytosolic cysteine proteinase enzyme bleomycin hydrolase which is widely distributed in normal tissues with the exception of skin and lungs, both targets of bleomycin toxicity<sup>[6]</sup>. Lindae et al observed histological similarity to the findings in fixed drug eruption and thus suggested that the absence of hydrolase leads to an accumulation of bleomycin<sup>[5]</sup>.

Various dermatological adverse effects of bleomycin reported in the literature include skin peeling, hyperkeratosis, nail bed changes, Raynaud's phenomenon

and palmoplantar desquamation. Flagellate rash has also been reported to occur in 10% of patients treated with bleomycin<sup>[6]</sup>.

Flagellate erythema is an unusual rash typically presents with itching. It was first reported in association with bleomycin administration in 1970. The development of the rash appears to be dose independent and can appear following first administration.<sup>[3]</sup> Onset of characteristic lesions can occur anywhere from day 1 to 9 weeks after bleomycin administration. The majority of patients initially develop generalized pruritis several hours to several weeks following the administration of bleomycin<sup>[10]</sup>. There is some evidence that bleomycin can be omitted from combination chemotherapy in the treatment of Hodgkin's lymphoma without loss of efficacy.

In most cases the rash resolves spontaneously. Addressing the symptom of itch is the main treatment measure. Treatment with antihistamines, topical and oral corticosteroids may be required. Severe rash requires the cessation of drug but in mild cases the drug can be continued with regular monitoring and precautions. Lack of detoxifying enzymes for bleomycin in the skin makes it a vulnerable site for the adverse effects<sup>[9]</sup>. So the early recognition of bleomycin induced rash is important to prevent further exacerbations.

### CONCLUSION

Bleomycin induced toxicity is a rare complication. Physicians must be aware of adverse effects induced by bleomycin. In mild non-progressive rash the drug can be continued with regular monitoring while severe progressive rash requires discontinuation of bleomycin. Early recognition of adverse effects is important to modify chemotherapy and to avoid further toxicity.

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