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CASE REPORT

# Bleomycin-induced flagellate dermatitis

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## ABSTRACT

Bleomycin is a glycopeptide antitumor antibiotic used in chemotherapy for Hodgkin's lymphoma, germ cell tumors, and squamous cell cancer. Flagellate dermatitis is a rare, but specific adverse reaction induced by bleomycin. We report a case of a 26-year-old Indian female who presented with this typical whip-like rash following the first dose of chemotherapy with bleomycin, etoposide, cisplatin regime for dysgerminoma ovary. She was treated with antihistamines and corticosteroids which relieved the symptoms, but hyperpigmentation is persisting. We report this case to make the prescribers aware of this reaction.

**KEY WORDS:** Bleomycin; Adverse Cutaneous Reaction; Flagellate Dermatitis

## INTRODUCTION

Bleomycin is a glycopeptide antitumor antibiotic isolated from *Streptomyces verticillus*. It was first developed in Japan by Umezawa, in 1966. The cytotoxic effects result from free radical-induced damage to deoxyribose backbone of DNA causing single- and double-stranded DNA break and cell death. Bleomycin is used in chemotherapy for Hodgkin's lymphoma, germ cell tumors of testis and ovary, and squamous cell carcinoma. Bleomycin is also used to induce chemical pleurodesis in recurrent malignant pleural effusions.[1]

Bleomycin is inactivated in most tissues by an enzyme bleomycin hydrolase, which cleaves the ammonia group from it. Bleomycin-induced toxicities are more in lungs and skin due to low concentration of this metabolizing enzyme in these tissues.[2] The spectrum of dermatological toxicities includes hyperpigmentation, hyperkeratosis, erythema, ulceration, Raynaud's phenomenon, nail bed changes, palmoplantar desquamation, and digital gangrene. Flagellate dermatitis is a less common but unique toxicity of bleomycin with a reported incidence of 8–20%.[3] However, with the declining use of bleomycin, this reaction has become infrequent in common clinical practice. It is important for the physician to be aware of this reaction, to recognize the nature and severity and to decide whether to continue or stop the drug.[4,5]

We report a case of a 26-year-old female diagnosed with dysgerminoma ovary, who developed flagellate dermatitis during treatment with bleomycin, etoposide, and cisplatin (BEP) regime.

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## CASE REPORT

A 26-year-old parous female on evaluation for abdominal pain was found to have a large heterogeneously hypoechoic mass lesion measuring 10 cm × 15 cm in retroperitoneum. She underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy and histopathology of surgical specimen confirmed it to be dysgerminoma of the right ovary. She was started on chemotherapy with bleomycin

30 mg on day 1, 8 and 15 along with etoposide 100 mg/m$^2$, and cisplatin 20 mg/m$^2$ on days 1–5.

About 10 days after the first dose of chemotherapy, she developed multiple linear erythematous lesions on trunk and extremities with associated burning sensation. In the next 2 days, the linear lesions became hyperpigmented. At the time of presentation, she had multiple curvilinear hyperpigmented macules of size varying from 2 cm × 0.3 cm to 10 cm ×0.5 cm in a whiplash pattern distributed on lower back and front of trunk, sides of neck, and left thigh [Figure 1].

She was treated with topical corticosteroids and antihistamines. Since she had only mild symptoms, she was continued on same chemotherapy regimen. At the time of reporting, she has completed three cycles of chemotherapy. She developed no new lesions, but hyperpigmentation of the previous lesions was persisting.

## DISCUSSION

Flagellate dermatitis was first reported as an adverse effect of bleomycin use in 1970.[6] It is considered to be a reaction specific to bleomycin and is independent of dose and route of administration. Onset of lesions can occur from day 1 to 9 weeks after bleomycin administration. Typical skin lesions are multiple erythematous linear or curvilinear lesions which later become hyperpigmented. The term "flagellate" is derived from the Latin word *flagellum*, referring to the whip-like appearance of the lesions. There may be associated with pruritus or burning sensation. There is no characteristic distribution, but reports have shown the involvement of face, trunk, and extremities.[3,6,7]

Several mechanisms for this typical whiplash-like rash have been postulated. The most probable explanation is the accumulation of bleomycin in the skin due to low concentration of metabolizing enzyme hydrolase.The linear pattern of pigmentation may be caused by scratching which induces local vasodilation by dermatographic mechanism, leading to excessive local accumulation of bleomycin. Histopathologically, the lesions have shown a spectrum of morphological findings such as urticarial hypersensitivity reaction, epidermal or spongiotic dermatitis, dermal edema, increased melanogenesis, lymphocytic vasculitis, and fixed drug eruption like reaction.[3,8]

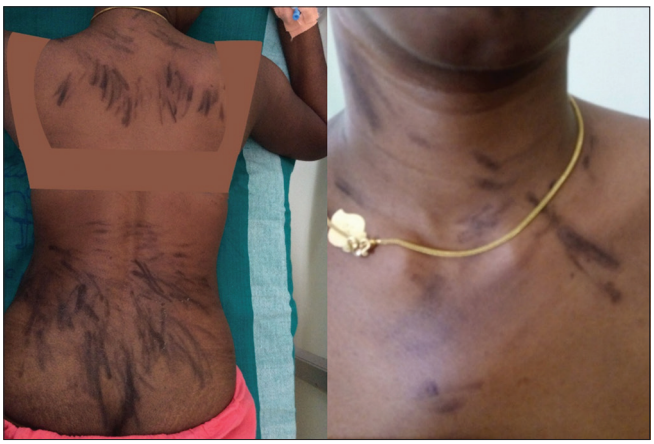

**Figure 1:** Multiple curvilinear hyperpigmented macules of different sizes in a whiplash pattern distributed on lower back and sides of neck

Flagellate dermatitis has been reported with other chemotherapeutic drugs such as peplomycin, docetaxel, and bendamustine. Other causes include dermatomyositis, adult-onset Still's disease, hypereosinophilic syndrome, chikungunya fever induced flagellate pigmentation, and consumption of shiitake mushroom.[1,8]

There is no specific treatment for flagellate dermatitis. It usually has a self-limiting course and clears within 6–8 months. They can recur or worsen on further exposure to bleomycin. Permanent hyperpigmentation in the affected areas may occur. Treatment with antihistamines and topical and oral corticosteroids has been beneficial. Severe rash requires discontinuation of bleomycin.[1,3]

From the literature, it was found that most of the cases of bleomycin-induced flagellate dermatitis were reported in patients on adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) regime for Hodgkin's lymphoma[1] and BEP regime for germ cell tumors. In a case report from Delhi, a 22-year-old male with Hodgkin's lymphoma developed flagellate dermatitis following the first cycle of chemotherapy with ABVD regime. He developed erythematous, pruritic, and popular lesions all over the body. The symptomatic treatment with topical antihistamines and corticosteroids had no effect. He was given oral corticosteroids and bleomycin was omitted from the next cycle. There was marked improvement within a week and lesions decreased in severity.[1]

A case similar to the present scenario was reported from Kashmir in a 10-year-old girl with germ cell tumor ovary. The rash appeared 3 days after the first cycle of chemotherapy with BEP regime. As the rash was not severe, bleomycin was continued. There was mild worsening of rash in the second cycle. The symptoms relieved on treatment with antihistamines and local and oral corticosteroids. The third cycle was given without any exacerbations.[9]

In another case reported from Bihar, a 7-year-old girl treated with BEP regimen for germ cell tumor developed whiplash-like hyperpigmented rash and pruritus. The rash appeared after two cycles of chemotherapy, i.e., after 90 units of cumulative dose of bleomycin. It was distributed over the scalp, arms, chest, back, abdomen, thighs, and legs. Symptomatic treatment with topical emollients, corticosteroids, and antihistamines was given. The chemotherapy was stopped following surgery. On follow-up, the patient had symptomatic relief, but hyperpigmentation persisted.[7]

Similar reaction was reported from Arkansas, the USA, in a 31-year-old male on the BEP regime for testicular cancer. The patient developed painless, non-pruritic linear hyperpigmentation on the trunk after three cycles of chemotherapy. The hyperpigmentation persisted on follow-up, but the patient was asymptomatic and did not require any other treatment.[10]

We hereby report a case of a 26-year-old female who developed typical whiplash-like erythematous lesions 10 days after the first dose of chemotherapy with BEP regime. According to the causality assessment by Naranjo algorithm, the reaction is "probable" due to bleomycin. As per the Modified Hartwig and Siegel severity scale, the reaction is of "moderate" severity and according to the Modified Schumock and Thornton preventability scale, the reaction is "probably preventable."

### Limitations

We came across only one case of bleomycin-induced flagellate dermatitis. The patient was followed up after three cycles of chemotherapy and hyperpigmentation persisted. Further, the follow-up was not done.

## CONCLUSION

We report a case of flagellate dermatitis following bleomycin administration from a tertiary hospital in Kerala. Only few cases of bleomycin-induced flagellate dermatitis are reported from India. This adverse reaction may be frightening and discomforting to the patient. As per the literature, the reaction resolves spontaneously within 5–6 months after bleomycin is stopped, although hyperpigmentation may persist. We report this case to make the prescribers vigilant about this reaction while starting bleomycin containing regimes and inform the patients regarding the same.

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