CASE REPORT

Bleomycin-induced skin toxicity: is it always flagellate erythema?

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SUMMARY

Bleomycin-induced skin toxicity is a rare and unique complication. We report a 35-year-old man with nodular lymphocytic predominant Hodgkin's lymphoma, stage IVB, who was started on adriamycin, bleomycin, vinblastin and dacarbazine (ABVD) chemotherapy. He developed pruritic hyperpigmented, patchy skin lesions on the neck, back, chest and thighs after IA cycle of ABVD chemotherapy. Lesions were not typical flagellate rash but hyperpigmented, patchy and mildly pruritic lesions over the trunk and proximal extremities. Lesions increased with continuation of bleomycin and improved gradually after removing the drug from chemotherapy schedule. The patient was in complete remission after VI cycles of chemotherapy (AVD Regimen) and skin lesions healed with minimal residual hyperpigmentation.

BACKGROUND

Two major toxicities of the drug bleomycin are pulmonary and skin toxicity. Bleomycin is rapidly inactivated by an enzyme in most of the tissues except the lung and skin where this enzyme is present in lower concentration. Lung toxicities are relatively common while typical skin toxicities are very uncommon.

The classical cutaneous toxicity of bleomycin is flagellate erythematous hyperpigmentation which is well described in the literature. Other skin toxicities include infiltrated violaceous plaques, sclerodermoid lesions, erythema multiforme and warty hyperkeratotic lesions on knees and elbows. Changes in nails, alopecia and stomatitis are other rare manifestations. Awareness of this toxicity is important because mild non-progressive lesions can be managed with wait and watch policy with continuation of chemotherapy while severe and progressive lesions need discontinuation of bleomycin. No difference in treatment outcome has been noted in such patients. This classical skin toxicity is easily appreciated in fair skin patients but may be difficult to appreciate in the dark skin patients.

CASE PRESENTATION

This 35-year-old man presented to the haematology outpatient department of JIPMER, a tertiary care centre in south India, with symptoms of fever, weight loss and multiple swellings in body of 3 months duration. Weight loss was about 7 kg and he had history of night sweats. He did not have any other significant comorbidity and used to take alcohol occasionally. On examination he had mild pallor, icterus and generalised lymphadenopathy

(multiple level cervical 3×2 cm, bilateral axillary 3×2 cm and bilateral inguinal 4×3 cm lymph nodes) without any tenderness, matting or discharging sinuses. Systemic examination revealed moderate hepatomegaly (6 cm below right costal margin) and mild splenomegaly (3 cm below left costal margin). Examination of other systems showed that they were within normal limits. Lower cervical lymph node biopsy was performed which confirmed the diagnosis of Nodular lymphocytic predominant Hodgkin's lymphoma (NLPHL). Contrast-enhanced CT scan of thorax, abdomen and pelvis revealed generalised abdominal lymphadenopathy, hepatomegaly with focal lesions in liver and irregular liver surface along with mild splenomegaly. Bone marrow was not involved. Serum lactate dehydrogenase and alkaline phosphatase values were 570 IU/L and 750 IU/L, respectively. The patient was diagnosed with stage IV Hodgkin's lymphoma—NLPHL type.

He was started on ABVD chemotherapy (doxorubicin 25 mg/m², bleomycin 10 mg/m², vinblastine 6 mg/m², and dacarbazine 325 mg/m²; all of which were administered intravenously on days 1 and 15) with plan for IV cycles of chemotherapy followed by response evaluation. The patient developed erythematous skin lesions on the neck, chest and abdomen, back and thighs after 10 days of day 1 chemotherapy although his B symptoms had improved. These patchy lesions were associated with mild itching and looked like superficial abrasion of skin. We started on topical corticosteroids with skin consultation and in view of few and small lesions decided to continue with day15 chemotherapy. Skin lesions increased remarkably in number and size and looked alarming (figures 1–3). Considering that bleomycin-induced progressive skin toxicity the drug was withdrawn from further chemotherapy and AVD chemotherapy was continued.

TREATMENT

Topical steroids were applied on lesions after skin consultation, which showed some improvement.

OUTCOME AND FOLLOW-UP

Skin lesions regressed in size slowly and only small hyperpigmented areas were left at the end of IV cycles of chemotherapy. Post VI cycles of AVD the patient achieved complete response (CR). Currently the patient is in once-in-3-month follow-up with the haematology outpatient department and the skin lesions have completely subsided.

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Figure 1 Hyperpigmented, patchy, mildly elevated skin lesions of various shapes and sizes situated at the back of the patient.

Figure 2 Skin lesions as described in [figure 1](#), present in lower axilla and upper chest.

DISCUSSION

Bleomycin is an antitumour antibiotic that was isolated from a strain of *Streptomyces verticillus* in 1966.¹ It has been used to treat a variety of malignancies, including Hodgkin's lymphoma, germ cell tumour, squamous cell carcinoma of the head and neck, cervix, and oesophagus and sclerotherapy for recurrent pleural effusion. Two major toxicities of bleomycin are pulmonary and skin toxicity. Bleomycin is rapidly inactivated by enzyme hydrolase in most of the tissues except lung and skin where this enzyme is in lower concentration.²⁻³ Lung toxicities are relatively common while typical skin toxicities are very uncommon.

The cutaneous toxicities of bleomycin include changes in nails, alopecia and stomatitis. More characteristic lesions of skin

Figure 3 Skin lesions as described in [figure 1](#), present at upper back on left side.

toxicity are variety of hyperpigmented changes, infiltrated violaceous plaques, sclerodermoid lesions, erythema multiforme and warty hyperkeratotic lesions on the knees and elbows. Hyperpigmented lesions associated with bleomycin may be diffuse, patchy or linear. Linear type lesion is characterised by flagellate cutaneous hyperpigmentation on the trunk and extremities.⁴ Fyfe and McKay have reviewed and published an article 'Toxicities associated with bleomycin' where they mentioned skin toxicity and bleomycin-induced pneumonitis are complications associated with bleomycin. Lung toxicities are more commonly recognised and may be fatal. Skin toxicity is very rare in even in large volume centres for lymphoma management.⁵ Appaji *et al*⁶ has reported 15-year-old boy with Intracranial germ cell tumour who underwent surgery, cranial radiotherapy and later treatment with bleomycin, etoposide and cisplatin regimen.

Biswas *et al* has reported a 22-year-old case of mixed cellularity Hodgkin's lymphoma, stage IIIBX who developed bleomycin-induced flagellate skin rash 4 days after administration of first cycle of ABVD chemotherapy. These lesions did not respond to antihistaminics and calamine lotion. Rapid response was noted following the discontinuation of bleomycin from the next cycle.⁷ Chen *et al* reported a 25-year-old man with Hodgkin's lymphoma Nodular sclerosis type stage IIIBX who was started on ABVD chemotherapy. On day 7 of the first cycle the patient presented with skin lesions presumed to be folliculitis but did not respond with antibiotics. The patient had progressive nodular itchy skin lesions which was biopsied later and was suggestive of flagellate erythema. Bleomycin was removed from chemotherapy regimen without any effect on outcome.⁸

Flagellate erythema usually occurs after a cumulative dose of 90–285 mg. It can appear within 24 hours to 2 months of

administration of bleomycin and usually resolves after discontinuation of bleomycin from chemotherapy. Corticosteroids have not been found to be effective.⁹

Our patient had skin lesions which were not typical of flagellate erythema or flagellate hyperpigmentation. Skin lesions were hyperpigmented, patchy, mildly elevated lesions of varied size which appeared after 1 week of bleomycin administration, progressed on drug continuation and improved after discontinuation.

Learning points

- ▶ Bleomycin-induced skin toxicity is a rare complication.
- ▶ Usually it is a classical linear flagellate erythematous lesion.
- ▶ Patchy lesions can also be seen as in our patient.
- ▶ Awareness and early recognition of this entity is important to modify chemotherapy and avoid further toxicity.

Contributors SPV had performed full clinical evaluation of the patient and AS has helped him in work up along with review of the literature. VKV and TKD helped in planning and management of this patients and follow-up.

Competing interests None declared.

Patient consent Obtained.

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