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Flagellate Dermatitis: Complication of Bleomycin Therapy: A Case Report

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Abstract:
Chemotherapy-induced skin rashes are common toxicities, which require careful assessment and evaluation. Bleomycin is an anticancer antibiotic derived from Streptomyces verticillus and has been commonly used in the treatment of hodgkin disease, germ cell tumors and for pleurodesis. Flagellate dermatitis caused by bleomycin is a rare side effect with a distinctive pattern of whip-like, linear streaks. We present a case of 27 year old male, diagnosed with seminoma of right testis, post right high inguinal orchiectomy, managed with 3 cycles of adjuvant bleomycin, etoposide, and cisplatin (BEP), later developed a widespread rash indicative of classic flagellate dermatitis.

Keywords: Bleomycin, Flagellar Dermatitis, Chemotherapy Side Effects.

Introduction:

Bleomycin is an antibiotic antitumor agent first developed in Japan by Umezawa in 1966.(1) It is derived from Streptomyces verticillus. Cytotoxic effect results from generation of activated oxygen-free radicals, which cause single and double-stranded DNA break and eventual cell death. Bleomycin is commonly used in Hodgkin's lymphoma, germ cell tumor, squamous cell carcinoma of head and neck, gynaecological system and skin, as a sclerosing agent for pleurodesis in recurrent malignant pleural effusion.

Bleomycin induced toxicities are more pronounced in lungs and skin due to low concentration of the metabolising enzyme-bleomycin hydrolase in these organs.(2) The spectrum of bleomycin induced dermatological toxicity includes Raynaud's phenomenon, hyperkeratosis, nail bed changes, peeling of skin on palmar and planter surface, digital gangrene and pigmentary alterations.(3,4)

Flagellate erythema is a less common but unique toxicity of bleomycin with a reported incidence of 8-20% in available literature.(3,4) Flagellate erythema was first reported as an adverse effect of bleomycin in 1970 by Moulin et al.(5)

However, with the declining use of bleomycin, this unique reaction has become infrequent in common clinical practice.(3) Hereby, we present a case of a 27 year old male patient who presented with flagellar dermatitis after receiving third cycle of chemotherapy with BEP regime.

Case History:

A 27 year old male with complains of right testicular swelling 7 months ago, associated with pain since 3 months, underwent right high inguinal orchiectomy at an outside hospital on 18.7.2023, and presented to us on 16.8.2023. On local examination, a healthy scar was seen over right groin region of approx. 5cm.

No significant lymphadenopathy was found. Left testes was palpable along with its cord, whereas right scrotal sac was empty.
USG whole abdomen (12.6.2023) was suggestive of a mass in right testis of around 6 x 4 cm, with normal left testis.
Baseline serum markers (13.6.2023) were: S. LDH: 1534 U/L, S. AFP: 3.5 ng/ml, S. BHCG: 12.4mIU/mL.
CECT whole abdomen (11.7.2023) was showing a mass of 4.6 x 3.7 x 3.7 cm in inter-aortocaval region abutting duodenum, with indistinct fat planes posteriorly. Another mass of size 6.1 x 5.5 x 4.4 cm was present in right scrotal sac, right testis not seen separately. Horse shoe kidney was an incidental finding.
Post op specimen sent for histopathological analysis (18.7.2023) was suggestive of seminoma of right testis, invading rete testis, with increased mitotic activity and necrosis. Lymphovascular and perineurial invasion were negative. Margins were negative. No nodes were dissected. Epidermis was free of tumor, making it pT2Nx.
PET-CT whole body (19.8.2023) revealed a lymph nodal mass of 4.4 x 4.9 cm with SUV: 7.8. Post op orchiectomy changes. No other significant lesion elsewhere in the body.
Post operative serum markers (21.8.2023) were S. LDH: 874 U/L, S. AFP: 3.65 ng/ml, S. BHCG: 4.11 mIU/mL.
The patient was thus diagnosed as: Seminoma right testis, pT_2, $cN_2M_0S_2$, good risk, as per AJCC 8th ed.
Patient was planned for 3 cycles of adjuvant chemotherapy with BEP regime. He received C_3D_{16} on 14.11.2023 post which he developed progressive, linear hyperpigmented streaks involving the upper back (Figure 1) associated with itching. He was prescribed topical emollient cream for local application and oral tablet levocetirizine daily for a week for the pruritis. The lesions have started to resolve partially with no active pruritus.(Figure 2). PET-CT whole body (2.12.2023) was suggestive of near complete metabolic response. Patient is currently on follow up with no fresh complains.
His serum markers (3.12.2023) are: S. LDH: 242 U/L, S. AFP: 34.2 ng/ml, S. BHCG: 2.39 mIU/mL. He has been advised to review again after one month with serum markers.

Discussion:
Flagellate dermatitis is the occurrence of multiple whipped out lesions over multiple body areas. The term “Flagellate” is derived from latin word “flagellum” referring to characteristic whip like the appearance of the eruption.[10]
It has been reported previously in association with a wide variety of factors including autoimmune disorders such as dermatomyositis and adult-onset Still's disease, infection with human immunodeficiency virus, toxins-like in case of consumption of shiitake mushroom, and some chemotherapeutic agents such as bleomycin, peplomycin, and docetaxel.[9]
Bleomycin is an antineoplastic agent belonging to glycopeptides group and is inactivated by enzyme bleomycin hydrolase which is deficient in the skin and considerably less in concentration in the lungs leading to an increased cutaneous concentration of bleomycin in these tissues. The common mucocutaneous lesions described as a side effect of bleomycin therapy are pigmentation (~50%), alopecia (~50%), and flagellate dermatitis (8%–66%).[9]
Flagellate erythema as a cutaneous manifestation of bleomycin therapy was first described in 1970.[10]
The exact pathogenesis of bleomycin-induced flagellate dermatitis is still unknown and different other theories have been proposed for the same like micro-trauma, inflammatory oncotaxis, increased melanogenesis, heat recall, and reduced epidermal turnover allowing prolonged melanocytes –

keratinocyte contact.[9] It is usually dose dependent and a reaction as a result of bleomycin irrespective of the route of administration or malignancy being treated and usually occurs after a cumulative dose of 90–285 mg, but some cases have been reported with doses as low as 15 mg given parenterally.[9,10] It follows the administration of bleomycin by a duration ranging from day 1 to 9 weeks and may persist for up to 6 months.[10] Previous reports have also described its occurrence even with a single dose of intralesional bleomycin used for sclerotherapy.[11] The course of bleomycin induced flagellate erythema is varied. The patient can be asymptomatic or may present with a prodrome of generalized pruritus within hours to weeks of bleomycin administration and the subsequent appearance of erythematous linear streaks which progress to typical flagellate hyperpigmentation.[9] Lesions lacks specific distribution and can occur anywhere over face, neck and trunk.

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Acknowledgement:
Tables, Legends & Illustrations

Table-1: Previous reports related to bleomycin induced flagellate dermatitis.

Author, place and year	Primary diagnosis	Timing of development of flagellate rash after bleomycin therapy	Management
Pavithran *et al*., Delhi, India, 2004[8]	Ovarian granulosa cell tumor	After two cycles of BEP chemotherapy	Withdrawal of bleomycin from further treatment cycles
Chen *et al*., Boston, United states, 2007[2]	Stage IIBX Hodgkin's lymphoma	After 7 days of first cycle ABVD chemotherapy	Withdrawal of bleomycin from further treatment cycles
Ibrahimi and Anderson Boston, US, 2010[9]	Vascular malformation of posterior tongue	Within 1 week of treatment with intralesional sclerotherapy with single dose of bleomycin	Observation only with wait and watch strategy for spontaneous cessation of rash
Biswas *et al*., Delhi, India, 2013[10]	Stage IIBEX Hodgkin's lymphoma	After 4 days of first dose of ABVD chemotherapy	Omission of bleomycin from treatment regime with oral and topical steroids
Mota *et al*., Brazil, 2014[3]	Stage IVB Hodgkin's lymphoma	On day fourteen of first cycle ABVD chemotherapy	Omission of bleomycin from treatment regime with oral prednisolone
Sutradhar *et al*., Sewagram, India, 2014[11]	Ovarian dysgerminoma	After first cycle of BEP chemotherapy	Treatment details not available
Lu *et al*., Taiwan, 2014[12]	Mixed germ cell tumor of mediastinum	On day seven of first cycle of BEP chemotherapy	Omission of bleomycin from treatment regime with application of topical and systemic corticosteroids
Lee *et al*., Korea, 2014[7]	Stage IIIB nonseminomatous germ cell tumor of testes	On day ten of first cycle BEP chemotherapy	Withdrawal of bleomycin from further treatment cycles
Changal *et al*., Srinagar, India, 2014[13]	Stage IIIB nonseminomatous germ cell tumour of ovary	3 days after first cycle of BEP chemotherapy	Bleomycin was continued in next 2 cycles. Cooling before chemotherapy was used to prevent heat-recall mechanism
Boussios, UK, 2015[6]	Ovarian yolk sac tumour	4 months after third cycle of bleomycin therapy	No treatment given, spontaneous resolution within two months of onset
Basu *et al*., Kolkata, India, 2016[14]	Stage IIA Hodgkin's lymphoma	After two cycles of ABVD chemotherapy	Withdrawal of bleomycin from further cycles and topical steroids with antihistaminics
Biswas *et al*., Delhi, India, 2016[15]	Thalamic mixed germ cell tumor	After two cycles of BEP chemotherapy	Withdrawal of bleomycin from further cycles and topical steroids with oral antihistaminics

BEP – Bleomycin etoposide cisplatin; ABVD – Adriamycin bleomycin vinblastine dacarbazine

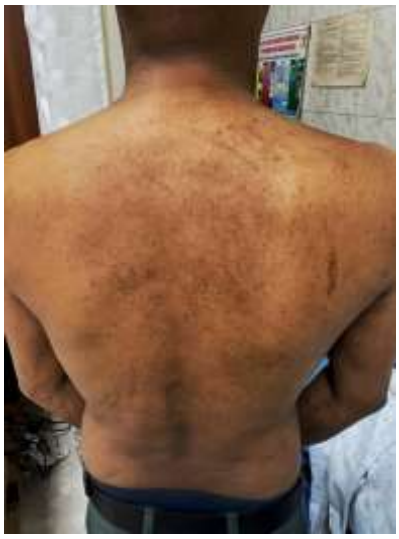

Fig. 1 showing flagellar dermatitis involving the upper back

Fig. 2 showing partial resolved flagellar dermatitis involving the upper back post 1 month of completion of bleomycin.