Bleomycin- induced flagellate dermatitis[*]
Dermatite flagelada induzida pela bleomicina[*]

Júlio César Gomes Silveira[1] Beatriz Moreira da Cunha[2] Rogério Ribeiro Estrella[3]

Abstract: Bleomycin is an antineoplastic drug used in the treatment of different tumors. It has several side effects, including a cutaneous hyperpigmentation with a flagellate aspect, which is considered specific to Bleomycin. We report two cases of Bleomycin-induced flagellate dermatitis and discuss the clinical and etiopathogenic aspects in a brief blibliographic revision.
Keywords: Bleomycin; Chemotherapy; Hodgkin's disease

***Resumo**: A bleomicina é agente quimioterápico usado no tratamento de diferentes neoplasias. Apresenta vários efeitos colaterais, sendo um deles a hiperpigmentação cutânea de aspecto flagelado, considerada específica dessa droga. Relatam-se dois casos de dermatite flagelada induzida pela bleomicina. Discutem-se os aspectos clínicos e etiopatogênicos em breve revisão bibliográfica.*
Palavras-chave: Bleomicina; Doença de Hodgkin; Quimioterapia

Bleomycin is an antibiotic with an antineoplastic citotoxic property. It has been used in the treatment of a variety of tumors, including Hodgkin's lymphoma, testes carcinoma and head and neck squamous cell carcinoma. Several non-specific reactions associated with the use of bleomycin have been described and they include stomatitis, alopecia, lung fibrosis, Raynaud1s phenomenon, ungueal deformities, palmplantar ulcers, bullous lesions, scleroderma, hyperkeratosic verrucous plaques and inflammatory nodules.[1,2] However, a linear skin hyperpigmentation occurs during bleomycin use. It has been described for the first time by Moulin et al.[1] in 1971, it is named flagellate dermatitis, and it is considered specific to this drug.

This paper describes two cases of bleomycin-induced flagellate dermatitis in Hodgkin's lymphoma patients, reviews the literature and discusses clinical features and the possible pathogenic mechanisms involved.

Case 1

Male patient, 18, white, complaining of pruritus and brownish lesions in the trunk, arms and neck, beginning three months before and appearing in frictioned areas due to scratching. The patient was under treatment for Hodgkin's lymphoma, in the fourth cycle of doxorubicin, bleomycin, vinblastin and dacarbazin. The dermatological exam showed hyperchromic maculae in linear disposition, with a flagellate appearance, distributed throught the trunk, neck and upper limbs (Figure 1). Hydroxizin was prescribed, resulting in the disappearance of the pruritus. No further lesions appeared in spite of continued use of bleomycin.

Case 2

Male patient, 49, brown, came to the office due to a condition of alopecia areata. At the exam, the patient presented hyperchromic maculae disposed linearly, with a flagellate appearance on the

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[1] Dermatology specialization at the Universidade Federal Fluminense - UFF - Niterói (RJ), Brazil.
[2] Resident in Dermatology, Universidade Federal Fluminense - UFF - Niterói (RJ), Brazil.
[3] Associate Professor of Dermatology, Universidade Federal Fluminense - UFF - Niterói (RJ), Brazil.

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Figure 1: Patient 1 – Linear hyperchromic maculae with a flagellate appearance on the trunk and right upper limb

shoulders, upper part of the dorsum and back (Figure 2). The lesions appeared during chemotherapy carried out eight years before the patient's visit to treat Hodgkin's lymphoma (cycles of doxorubicin, bleomycin, vinblastin and prednisone), with total remission of the disease.

Bleomycin is a polypeptide derived from *Streptomyces verticillus*, discovered in Japan by Umezawa[1-3] in 1965. It has been used as an antineoplasic chemotherapy agent for different types of tumors because it inhibits the incorporation of tymin into the DNA causing DNA fragmentation into smaller fractions.[1,2] Bleomycin spreads throughout the whole body and it is inactived by a hydrolase enzyme able to cut an ammonia group of its molecule.[1,4] This enzyme does not exist in the lungs and in the skin, therefore bleomycin is not inactivated in those organs. In this manner, there is an increased concentration of the drug in the skin and lungs, thus explaining the cutaneous and pulmonary toxicity that can be observed in the use of this drug.[4]



Figure 2: Patient 2 – Linear flagellate hyperchromic maculae covering the patient's back

Bleomycin-induced flagellate dermatitis, also called flagellate erythema, occurs mainly in the upper portion of the trunk and upper limbs. It is generally pruriginous and it may have the likeness of post-inflammatory hyperpigmentation from the beginning or start as erythematous urticaria-like lesions which progress to residual hyperpigmentation.[2-5] Its occurrence is variable, as it is described in a percent range from 8% to 66% of cases in different studies. Individual susceptibility seems to exist.[6] The lesions, which appear from very few hours up to nine weeks after exposure to the drug, occur with variable doses in the reported cases, ranging between 15 mg and 285mg.[2] Normally, flagellate dermatitis is triggered by intravenous administration and, less commonly, intramuscularly. Its occurrence is also reported after intrapleural administration of bleomycin in doses of 30 mg and 60 mg.[4,7]

The pathogenic mechanisms involved in lesion formation are controversial. Several theories have been proposed, including the increase of melanocyte stimulation by adrenocorticotropic hormone secretion and inflammatory oncotaxis.[2,7,8] However, the most widely discussed mechanism would be lesion induction by pruritus. Linear lesions are believed to be caused by the act of scratching.[2,4,6,9] A dermographic response to the pressure of the act of scratching would result in a local accumulation of the drug due to the leaking of bleomycin through dilated vessels. Reports and evidence corroborating such a theory can be found in the literature,[10] but other authors have failed in their attempts to reproduce the lesions by means of such a mechanism.[4,6]

There are several histopathological changes described in flagellate dermatitis: hyperkeratosis, parakeratosis, acantosis, spongyosis, basal layer degeneration, lymphohistiocytic inflammatory infiltrate in the dermis, melanophages in the papillary dermis and lymphocytic vasculities without epidermal alteration.[3-5] There is a normal count of melanocytes, but electronic microscopy reveals an increased number of melanosomes in keratinocytes, forming dense perinuclear rings.[2,7]

Pigmentation may persist for a long time,[3,4] as seen in case number 2. No treatment modality was described in the literature reviewed. ❑

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MAILING ADDRESS:
Júlio César Gomes Silveira
Rua Otávio Carneiro, 8 / 702 - Icaraí
24230-191 - Niterói - RJ
Telefone: (21) 2610-5664