

# Ischemic Digital Gangrene After Bleomycin: A Case Report

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## ABSTRACT

Case studies have indicated that bleomycin may cause ischemic ulceration and gangrene. A 40-year old male patient suffering from pain in his left foot for a week and his fifth toe had turned black. Three months ago, he had undergone surgery due to testicular anaplastic seminoma on his left testicle and had been given post-operative 2 cycles of bleomycin, etoposide and cisplatin chemotherapy. The fifth toe finally had to be amputated due to the progression of the gangrene. Digital ischemia can also be witnessed as a paraneoplastic syndrome in the absence of chemotherapy. We believe that the endovascular lesions on the small arterioles and capillary endothelium characteristically caused by bleomycin can cause digital ischemia finally leads to gangrene.

**Key Words:** Bleomycin, Ischemic gangrene, Seminoma, Toxicity

## ÖZET

### Bleomisin Sonrası İskemik Digital Gangren: Olgu Sunumu

Bleomisin, iskemik ülserasyon ve gangren'lere neden olabileceği literatürde vaka sunumları şeklinde bildirilmektedir. Bir haftadır devam eden sol ayakta ağrı, sol beşinci parmakta siyahlaşma şikayetleri ile hastanemize başvuran 40 yaşında erkek bir hasta sunulmaktadır. Hasta 3 ay önce sol testis testiküler anaplastik seminomu tanısı ile opere olmuş ve postoperatif 2 siklus BEP (Bleomisin, Etoposide, Cisplatin) kemoterapisi verilmişti. Gangrende, progresyon olması nedeniyle hastanın sol ayak 5. parmağı ampute edildi.

Digital iskemi, kemoterapi yokluğunda paraneoplastik sendrom olarak da görülmektedir. Bununla beraber bleomisin, küçük arteriol ve kapiller endotelial üzerinde karakteristik endovasküler lezyona yol açarak digital iskemi sonucunda gangrene yol açabilmektedir.

**Anahtar Kelimeler:** Bleomisin, İskemik Gangren, Seminoma, Toksikite

## INTRODUCTION

Bleomycin is an antineoplastic antibiotic derived from *Streptomyces verticillus*, used for the treatment of the Hodgkin Disease, testicular cancer, kaposi sarcoma, and the tumors of the head and neck. It causes single or double chain breakage and/or DNA fragmentation by attaching itself to the cellular DNA. Due to the absence of the hydrolysis enzyme, its accumulation causes toxicity in the lungs and on the skin. It has side effects such as pulmonary fibrosis in the lung, and alopecia, ischemia, hyperpigmentation, sclerosis, nail loss on the skin and rarely ischemic gangrene (1-3). It causes the Raynaud's Phenomenon through the vasospastic mechanism and ischemic gangrene through leucocytoclastic vasculitis. Bleomycin also causes digital ischemic gangrene by generating endothelial damage in the small arterioles and capillaries. Studies have shown that bleomycin causes collagen accumulation in the arteriole endothelia, alters the prostacyclin - thromboxane balance, causes hypercoagulability by effecting the coagulation mechanism, and clogs the arteries by increasing apoptosis on the vessel endothelia. (3-6). Our case report focuses on the formation of digital ischemic gangrene after the 2nd cycle BEP protocol treatment, given as adjuvant therapy, for testis anaplastic seminoma. It was treated by low molecular weight heparin, ticlopidine, calcium channel blocker, and pentoxifylline. Yet, the treatment was not successful in stopping the progression of the gangrene. This report built on the aforementioned case study analyzes ischemic gangrene related to bleomycin in conjunction with academic literature on the subject.

## CASE

A 40-year old male patient applied to our hospital for treatment. He complained to have been suffering for the last seven days from pains in his left foot. His fifth toe on the foot was turning black. Three months ago he had been diagnosed with left testicular anaplastic seminoma, been operated and given post-operative 2 cycles BEP (bleomycin 30 mg/m<sup>2</sup>, etoposide 100 mg/m<sup>2</sup>, cisplatin 20 mg/m<sup>2</sup>) chemotherapy. It was not possible during the physical examination of the left leg to take the popliteal artery, anterior and posterior tibial arteries, and dorsalis pedis artery pulses. No pathological evidence was

found in other systemic examinations. Laboratory test findings indicated his blood biochemistry, protein C, protein S, antithrombin III, and factor V Leiden values were normal. The lower extremity Doppler USG showed stenosis in the patient's proximal posterior tibial artery. It was also not possible to trace the blood flow after the 1/3 distal segment of anterior tibial artery. The patient was hospitalized and immediately given pentoxifylline and low molecular weight heparin. The gangrene on the fifth toe of his left foot progressed and his first toe also turned black (Figure 1). Histopathology of amputated fifth toe of left foot revealed as suppurative inflammation at dermis, subcutaneous tissue and erosion at epidermis (Figure 2). The patient's fifth toe was amputated by the consultation of the Orthopedics clinics. Amlodipine 5 mg/day was added to the patient's treatment. The lower left extremity Doppler USG carried out three weeks later still showed no trace of blood flow in the arteries due to stenosis. Bleomycin was taken out of the patient's protocol and the case was monitored with heparin and amlodipine treatment.

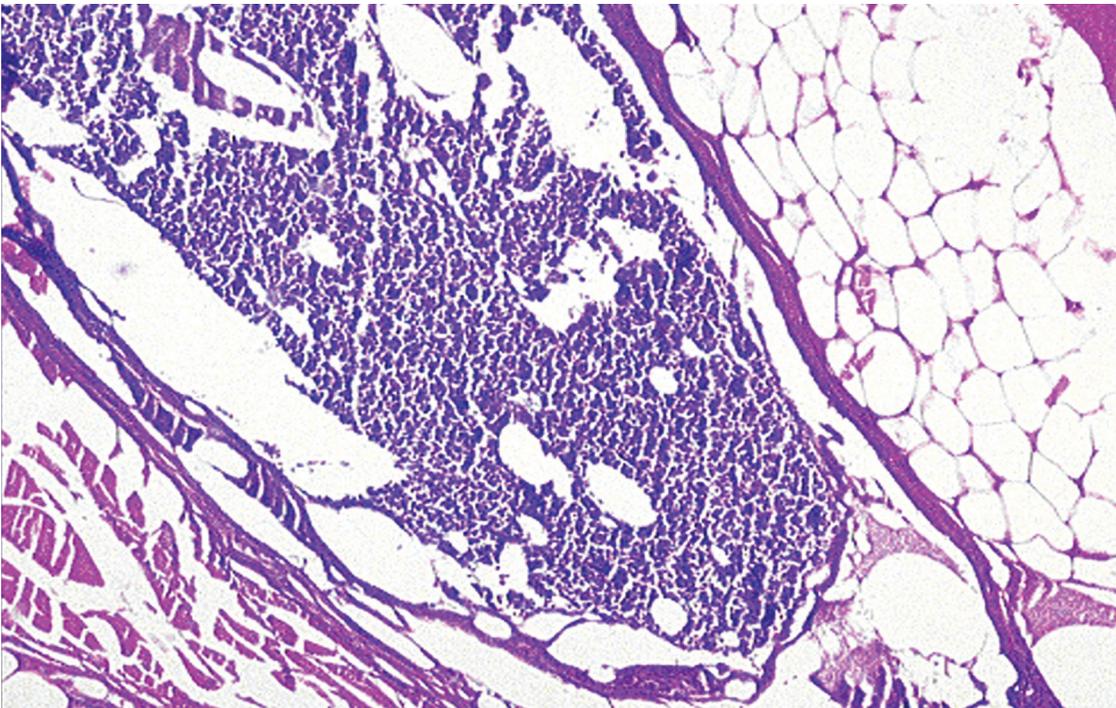
## DISCUSSION

In cancer patients, digital ischemia can also be witnessed as a paraneoplastic syndrome in the absence of chemotherapy. Nevertheless, the endovascular lesions on the small arterioles and capillary endothelial characteristically caused by bleomycin can cause digital ischemia which finally may lead to gangrene. The Reynaud phenomena (with or without ulceration), which is a side effect of Bleomycin may also lead to gangrene (1-3).

Correria et al. have claimed that the rapid skin transformations taking place on both hands of the patients after 60 mg bleomycin treatment result in gangrene. They have also hypothesized that endovascular lesions, platelet activation, disorder of the thromboxane and prostacyclin system, autonomic dysfunction, and a vasculitic event might be responsible for the formation of acral erythrocyanosis that leads to acute digital ischemia and gangrene.1 Another study has reported that the side effects of bleomycin are related to the increase in plasma TNF-alpha. 2 As widely known, TNT-alpha increases the procoagulatory effect in the blood vessels by both increasing the production of tissue factor



**Figure 1.** Gangrene on the fifth toe of patient's left foot.



**Figure 2.** Suppurative inflammation and fatty necrosis at dermis and subcutaneous tissue.

and tissue plasminogen activator inhibitor, and decreasing the activation of endothelial thrombomodulin and protein C.4 Vayssairat et al. have reported that Bleomycin treatment on a patient with HIV infection and Kaposi Sarcoma has led to the formation of gangrene of the finger after a total Bleomycin dose of 500 mg while all coagulation tests (including protein C, protein S, and antithrombin III tests) showed that the platelet and fibrinogen levels were normal. Here, Vayssairat et al.'s argument was that the ischemic digital gangrene observed with this patient had developed in connection with endothelial cell damage (5). Another study has declared bleomycin causes vasospastic changes, ischemic digital ulcer and gangrene in the small blood vessels, and emphasized the implications of long term bleomycin treatment on toxicity.6 Hansen et al. have reported that the Raynaud phenomenon formed after the Vinblastine, Bleomycin, and Cisplatin treatment of a metastatic germ cell was linked to drug-related vasospastic changes (7). Cohen et al. have shown that bleomycin is related with the narrowing down of the small blood vessels as well as the succeeding intensive collagen accumulation on the vessel walls that causes ischemic necrosis (8). Finch et al. have shown that bleomycin stimulates the production of collagen and other nonspecific types of protein on normal skin fibroblast culture (9).

Therefore, the endovascular lesions on the small arterioles and capillary endothelial characteristically caused by bleomycin can cause digital ischemia which finally leads to gangrene. Regarding a systemic disease like cancer, we must bear the fact in mind that apart from the secondary causes, the chemotherapeutics used for treatment may also cause rare but important side effects.

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