Gangrene of the Fingertips After Bleomycin and Methotrexate

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The increased use of cytostatic drugs, which are sometimes used in combination chemotherapy, may result in new and unusual cutaneous side effects. We describe a 57-year-old man with acral erythrocyanosis progressing to acute digital ischemia and gangrene that developed after combined chemotherapy (bleomycin and methotrexate) used to treat a metastatic squamous cell carcinoma of the hypopharynx. A leukocytoclastic vasculitis was found in both the acute phase and in the amputated fingertips. This supports the well-reported potential of bleomycin to trigger acral vascular toxicity.

Bleomycin is an antibiotic with antiviral, antibacterial, and antitumor activity isolated from *Streptomyces verticillus*. It has often been used to treat squamous cell carcinoma of the head and neck, either alone or in combination, usually with methotrexate.[1,2] Bleomycin is useful in combination chemotherapy because it rarely is myelosuppressive and its most significant side effects are lung fibrosis and skin changes. Cutaneous side effects include stomatitis; alopecia; erythema; hyperpigmentation; vascular toxicity, including Raynaud's phenomenon with and without ischemic ulcerations; and sclerosis-like changes that may progress to gangrene.[2,3] Methotrexate is an inhibitor of dihydrofolate reductase and can induce adverse reactions in the skin, such as alopecia, mucositis, macular erythema, epidermal necrosis, and acral erythema. Bone marrow suppression, interstitial pneumonitis unrelated to cumulative dosage, and hepatitis with long-term administration are serious systemic side effects.[4,5]

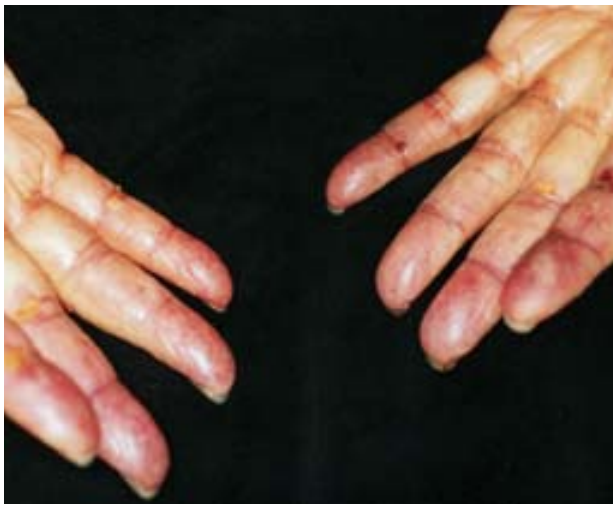

FIGURE 1. Acral erythrocyanosis with ischemic ulcerations of the fingertips.

We report an unusual case of erythrocyanosis progressing to acute ischemia and gangrene after combination chemotherapy with bleomycin and methotrexate.

Case Report

A 57-year-old man who was a heavy smoker was found to have metastatic squamous cell carcinoma of the hypopharynx in September 1997. He was submitted to surgery, where he was given 2 units of blood and staged as T4N3M0. Two months later, axillary metastasis appeared and chemotherapy was proposed. At that time, hemolytic anemia, with direct Coombs

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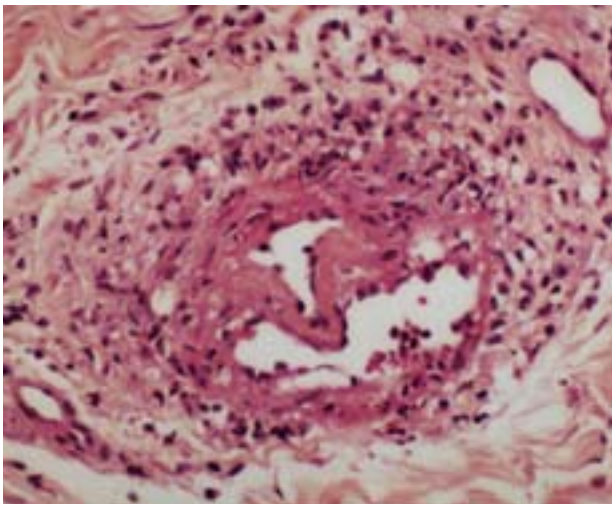

FIGURE 2. Leukocytoclastic vasculitis in the dermis.

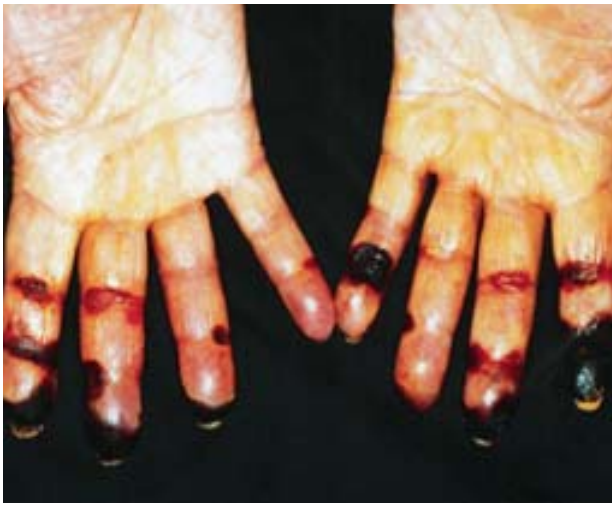

FIGURE 3. Acral erythrocyanosis with ischemic necrosis and gangrene.

test positive for IgG, IgM, and CD_3; spherocytosis; and reticulocytosis were discovered. The patient was treated daily with 60 mg of methylprednisolone and showed improvement. Soon after, he began weekly combination chemotherapy, with 30 mg of bleomycin and 45 mg of methotrexate preceded by metoclopramide. After a second cycle, the patient developed acral erythrocyanosis with ischemic ulcerations of the fingertips (Figure 1). Histologic examination around the inflamed ulcerations showed subcorneal pustules with focal necrosis of the keratinocytes. In the dermis, there were lesions of leukocytoclastic vasculitis; however, the eccrine glands showed no sign of necrosis (Figure 2). The patient did not undergo a third cycle of chemotherapy because some of the fingertips developed signs of ischemia and gangrene (Figure 3). At that time, direct Coombs, antinuclear, and antibody tests were negative, and platelet number was normal. Although treated with ticlopidine and low molecular weight heparin (Fraxiparine®), irreversible gangrene emerged in 7 fingertips, 4 on the left hand and 3 on the right, and amputation was necessary. A histologic examination showed extensive lesions of leukocytoclastic vasculitis with necrosis of the vessel walls and the surrounding tissue. Two months later, the patient died with multiple metastases.

Discussion

An increasing number of patients with malignant diseases are now cured by combination chemotherapy. However, when side effects occur, drug imputability is usually difficult to establish.

Bleomycin toxicity seems to have equally high concentrations in both the skin and lungs. Although skin toxicity is more frequent with doses higher than 100 to 200 mg, it has been known to occur with doses as low as 30 mg.[2,6] Dose-related skin toxicities include alopecia, erythema, hyperpigmentation, sclerosis, gangrene, and nail changes (eg, nail loss). Erythema and hyperpigmentation can be diffuse or patchy, may "flagellate," can be found covering recent scratch marks or pressure areas, and may occur in 30% of patients. Trauma from scratching could induce localized vasodilatation with increased concentration of bleomycin in the skin. Raynaud's phenomenon with and without ischemic ulcerations and sclerosislike changes that may progress to gangrene have also been reported.[2,3] In our patient, skin toxicity appeared after the second cycle of chemotherapy (ie, after 60 mg of bleomycin) and rapidly progressed to irreversible gangrene, which contrasts what has been reported in the literature.[2]

Capillary nail microscopy has been proposed to study bleomycin acral vascular toxicity[7] because there is a relationship between the total dosage of bleomycin and the presence of capillary abnormalities. The pathogenesis of the toxic effect of bleomycin is not fully established, but several hypotheses have been suggested, including endovascular lesion, alteration of the coagulation, platelet activation, upset of the thromboxane-prostacyclin system, autonomic dysfunction, and a vasculitic process.[7] Recently, acute side effects of bleomycin were related to tumor necrosis factor-α,[8] a cytokine that induces a procoagulant effect in blood vessels by increasing tissue-factor and tissue plasminogen–activator inhibitor production and by decreasing endothelial thrombomodulin and protein C activation.[9] In our patient, a histologic examination

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showed lesions of leukocytoclastic vasculitis in the acute phase and in the amputated fingertips, suggesting that vasculitis was strong enough to result in ischemic necrosis.

Methotrexate skin toxicity includes alopecia, mucositis, macular erythema, and epidermal necrosis.[4] An acral erythema related to a toxic rather than an allergic reaction was found after high dose methotrexate.[5]

Digital ischemia can occur as a paraneoplastic syndrome in the absence of any chemotherapy, and a synergistic drug toxicity of bleomycin and methotrexate cannot be excluded. However, the frequent and characteristic lesions on the endothelia of the capillaries and small arterioles induced by bleomycin[7] suggest to us that it could have been the main trigger of the digital ischemia and gangrene fingertips seen in this case.

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