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Letter to the Editor

Mitoxantrone-induced Discoloration of the Nails

W. SCHEITHAUER,* H. LUDWIG,* R. KOTZ† and D. DEPISCH‡

**Department of Internal Medicine II and †Department of Orthopedics, University of Vienna, Department of Surgery, Wr. Neustadt Hospital, Austria*

MITOXANTRONE is an anthracenedione cytotoxic agent that has shown substantial antitumor activity in the treatment of acute leukemia, malignant lymphomas, breast cancer, and several other malignancies. The major dose-limiting toxicity of mitoxantrone is myelosuppression. Other systemic toxicities may occur, but their overall incidence is considerably lower than with the structurally related anthracyclines [1]. Whereas alopecia still represents a common side-effect, other alterations of the integumentary system such as onycholysis are extremely rare [2]. We report on two cases with a different form of onychopathy that developed in patients receiving single agent chemotherapy with mitoxantrone for advanced breast cancer and malignant fibrous histiocytoma, respectively.

Case 1

A 66-year-old woman presented with diffuse skeletal pain 36 months after modified radical mastectomy due to adenocarcinoma of the breast. Radiography and bone scan revealed the presence of multiple osseous metastases, but chest X-ray and abdominal sonography were normal. She was started on a course of tamoxifen, 40 mg daily. After a favorable initial response that lasted 16 months, relapse with appearance of new osteolytic lesions and a malignant pleural effusion occurred. Medroxyprogesterone acetate, 1000 mg daily, was substituted for tamoxifen. Neither this nor three subsequent courses of CMF chemotherapy resulted in any improvement, and liver metastases became manifest. Treatment was changed to mitoxantrone monotherapy given as a 20 mg (14 mg/m^2) dose i.v., every 3 weeks. After three courses of treatment, painless blue discoloration of both fingernails and toenails developed (Fig. 1). Since stabilization of the disease with improvement of performance status occurred, the patient decided to stop therapy. The discoloration resolved spontaneously 4 months thereafter; the patient is still alive, and is currently being treated with a third line combination protocol consisting of 5-fluorouracil, cyclophosphamide, mitomycin C, dacarbazine, and the nitrosurea BCNU.

Case 2

A 48-year-old female patient presented with an asymptomatic 6.5 cm soft tissue lump in the proximal left lower extremity. Incisional biopsy revealed a moderately differentiated (grade 2) malignant fibrous histiocytoma. There was no evidence of distant metastases as judged by chest X-ray, liver ultrasound, bone and CT scan. Since curative tumor resection would have implicated the necessity of mutilating surgery, the patient agreed to enter a phase II study of systemic preoperative induction chemotherapy with mitoxantrone that has recently been initiated at our clinic. After two courses of mitoxantrone, 35 mg (20 mg/m^2) i.v. every 4 weeks, the patient noted the start of a blue discoloration at the bottom of her finger- and toenails. Again this finding was painless without associated dermopathy or onycholysis. Since a >50% reduction of the initial tumor size was achieved at that time, and resectability without disarticulation was deemed feasible, the patient underwent surgery. Total eradication of the tumor was confirmed histologically. Postoperative adjuvant chemotherapy has not been performed, and the patient's nail discoloration resolved within 2 months. For more than 14 months there has been no sign of local or distant recurrence in this patient.

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Correspondence should be addressed to W. Scheithauer, M.D., University of Vienna, Department of Internal Medicine II, Garnisongasse 13, A-1090 Vienna, Austria.

Both doxorubicin and mitoxantrone cause alopecia in a significant number of patients. Despite the developmental similarity beween hair and nails, it is somewhat surprising that there are only exceptional reports on anthracycline-associated onychopathies [2, 3]. In agreement with the few other, unpublished reports the manufacturers of mitoxantrone are aware of, the time of manifestation of nail changes in our patients, including reversibility after discontinuation of chemotherapy, clearly suggests a causal relationship with mitoxantrone. Its occurrence did not seem to correlate with cumulative dose, treatment efficacy, and incidence or severity of other mitoxantrone-related side-effects. Whereas the exact nature of this phenomenon has not been clarified in our patients due to ethical reasons, prolonged persistence of the drug in human tissues with marked inter-individual variations with regard to location [4] is likely to account for this finding. Spontaneous hemorrhage of the nailbed due to mitoxantrone-induced thrombocytopenia that was considered for differential diagnosis, could be excluded by continued monitoring of hematologic parameters. Though apparently harmless and rather uncommon, the painless blue discoloration of nails may be added to the list of possible side-effects associated with mitoxantrone therapy.

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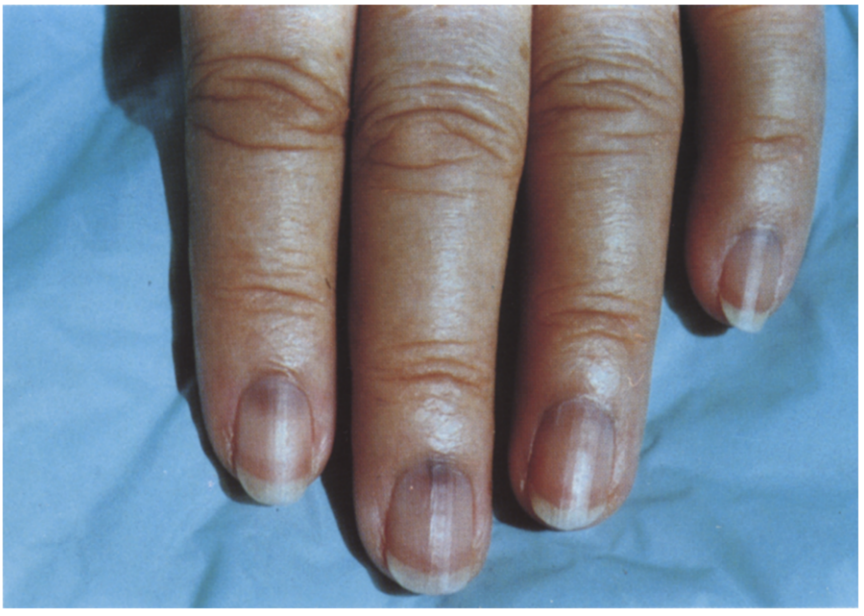

Fig. 1. Blue discoloration of finger- and toenails after three courses of mitoxantrone therapy in a patient with metastatic breast cancer.