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Letter to the editors

Nail toxicity due to the combination Adriamycin-mitoxantrone

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Sir,

Chemotherapeutic drugs often produce a variety of mucocutaneous reactions including alopecia, stomatitis, hyperpigmentation, hypersensitivity reactions, photosensitivity and, rarely, onycholysis [1, 2]. Nail changes have been described in association with a variety of cytotoxic agents, most frequently with Adriamycin, cyclophosphamide or bleomycin [2, 3]. Two cases of painful onycholysis have recently been reported by Speechly-Dick and Owen [4]. We conducted a phase I study combining three weekly mitoxantrone doses and weekly low-dose Adriamycin. A total of 32 patients were treated with increasing doses of both drugs; 4 of them developed nail toxicity.

Case reports

Case 1. A 57-year-old woman presented with a metastatic breast carcinoma, with involvement of the liver and the pleurae. Histology confirmed an invasive lobular carcinoma, and chemotherapy with cyclophosphamide, methotrexate and fluorouracil (CMF) was started. Progressive disease was noted after two cycles and the patient was treated with 10 mg/m^2 mitoxantrone three times weekly and 10 mg/m^2 Adriamycin weekly. After four cycles (total doses: mitoxantrone, 64 mg = 40 mg/m^2; Adriamycin, 160 mg = 100 mg/m^2), she developed white, painful fingernails; her toenails were normal at that time. Treatment was continued because of the disappearance of pleural involvement and a partial remission of the liver metastasis. After seven cycles, the fingernails were clearly red-brown and still painful and a minor form of onycholysis was noted; cytotoxic therapy was stopped and replaced by 40 mg tamoxifen daily. The nail toxicity resolved 3 months later. The patient showed no alopecia and had only one episode of oral mucositis during the mitoxantrone-Adriamycin treatment. She died 4 months later due to brain metastasis.

Case 2. A 53-year-old woman presented with extensive bone metastasis due to an adenocarcinoma of the breast. She started a chemotherapy (type CMF) and showed a partial remission. After seven cycles, progressive disease was observed and the patient was treated with 8 mg/m^2 mitoxantrone three times weekly and 10 mg/m^2 Adriamycin weekly. After ten cycles (total doses: mitoxantrone, 150 mg = 80 mg/m^2; Adriamycin 536 mg = 300 mg/m^2), she developed white finger- and toenails very sensitive to pressure. At that time the patient was in a complete clinical remission but died 3 weeks later due to a pulmonary embolism. She showed no loss of hair and a slight mucositis on two occasions.

Case 3. A 62-year-old woman presented with lymph node metastasis of an adenocarcinoma of the breast 2 years after mastectomy. The receptor status of the primary tumor was negative. Chemotherapy was started with 12 mg/m^2 mitoxantrone three weekly and 15 mg/m^2 Adriamycin weekly. After two cycles the patient presented with white finger- and toenails. After three cycles (total doses: mitoxantrone, 60 mg; Adriamycin, 125 mg), her nails were red-brown and she had developed hemorrhagic blisters on the soles of her feet; onycholysis of the toenails had also begun. The original treatment was stopped, but mitoxantrone was continued at the same dose. The nail toxicity disappeared, but pressing the nails still caused pain. During her treatment, the patient had grade III alopecia and one episode of severe mucositis. She died 1 year later due to extensive liver metastasis.

Case 4. A 57-year-old man presented with metastatic involvement of the lymph nodes and skin 7 years after primary resection of a scalp melanoma. Chemotherapy with dacarbazin (dimethyl triazeno imidazole carboxamide) (DTIC) was started, but rapid progressive disease was noted after one cycle. Combination chemotherapy with 12 mg/m^2 mitoxantrone three times weekly and 15 mg/m^2 Adriamycin weekly was started, to which the patient showed a minimal response. After four cycles (total doses: mitoxantrone, 176 mg; Adriamycin, 547 mg), he complained of white, painful finger- and toenails; after six cycles, they were red-brown and onycholysis occurred in several nails. Between the nail bed and the nail itself were blisters that were sometimes hemorrhagic; a biopsy of the nail-bed matrix and nail plate was carried out. On light microscopic examination, no sign of lymphocytic infiltration, arteritis, or specific alteration could be detected. Iron was absent, as was melanin. On the electron microscopic level, the epithelial cells of the nail bed showed a slightly enlarged intercellular space with the formation of interdigitations; the desmosomes were normal. No specific ab-

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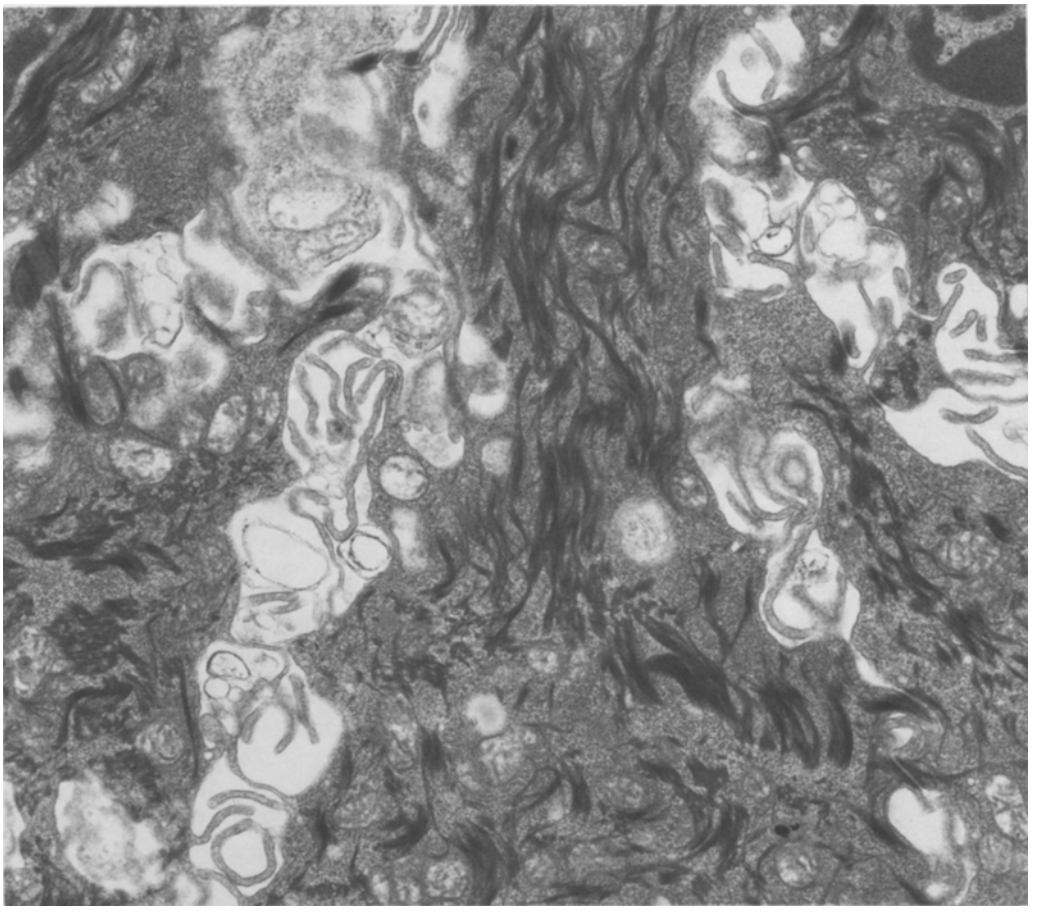

Fig. 1. Electron microscopic view (× 20,000) of a biopsy of the nailbed of a patient with nail toxicity, showing a slightly enlarged intercellular space with the formation of interdigitations

normalities could be found in the nail matrix (Fig. 1). The treatment was stopped after seven cycles due to brain metastasis, and a slow amelioration of the nailtoxicity occurred. The patient died 3 months later. During his therapy he had grade II alopecia and two periods of mild mucositis.

Discussion

As the frequency of this side effect seemed unexpectedly high, we reviewed all hospital records of patients treated since 1983 with Adriamycin or mitoxantrone in monotherapy or in combination with other cytotoxic agents. Some form of nail toxicity was noticed in 2 of 319 patients treated with Adriamycin (both times in combination with cisplatin and cyclophosphamide) and in 1 of 139 treated with mitoxantrone alone. The difference between these frequencies and the 4 of 32 in our study is highly significant (chi-square test; $P < 0.001$), suggesting a synergistic action on the nail bed. Another interesting observation was the amelioration of nail toxicity when Adriamycin was withdrawn and mitoxantrone was continued. The appearance of blisters on the soles of the feet and under the nails could indicate a kind of epidermolysis, for which some arguments can be found in the electron microscopic slides. On the other hand, the frequency of hair loss was not increased, which could mean that this nail toxicity is independent of alopecia and may offer an explanation as to why onycholysis is rare in comparison with the very common occurrence of alopecia during chemotherapy with these cytotoxic agents.

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