Cutaneous Lesions as the First Sign of Disseminated Mucormycosis

Sir,

Fungal infections are a frequent cause of death among immunocompromised patients, accounting for 21% of the fatal infections in leukemic patients (1). Mucormycosis organisms are common opportunistic pathogens (2) that infect patients with diabetic ketoacidosis, leukemia or lymphoma, therapeutic immunosupression or neutropenia (1, 2). Six clinical forms are recognized: rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated and miscellaneous (central nervous system, bone, kidney, heart,...) (3). While primary cutaneous mucormycosis is an uncommon but well-known disease, cutaneous lesions in disseminated mucormycosis are an infrequent event (4, 5). We present a leukemic patient with cutaneous lesions as the first sign of disseminated mucormycosis.

CASE REPORT

A 54-year-old non-diabetic woman was diagnosed in August 1992 of acute myelogenous leukemia, M5 FAB subtype, without extramedullar disease. Complete remission was achieved with one cycle of daunorubicin-cytarabine-etoposide, and two cycles of consolidation chemotherapy were given. In October 1992, as a complication of the last cycle, an acute pericarditis developed which was treated with corticosteroids for 19 days. In February 1993, a bone marrow harvest was made, followed by a cycle of daunorubicin-cytarabine. A few days later, the patient developed a cutaneous relapse with four well-defined, erythematous nodules, 1–2 cm in diameter, on the trunk, confirmed by histological examination. A bone marrow aspirate showed a 70% infiltration of blast cells. One week later, she was admitted for reinduction chemotherapy with idarrubicin-cytarabine. An extrapleural mass in the apex of the left lung, and a severe pancytopenia with 760 leukocytes/mm^3 (14% neutrophils, 70% lymphocytes, 15% blasts), 17,000 platelets/mm^3 and a hemoglobin level of 8.9 g/dl were found. An enterococcal septicemia, developed on day 0 (the day of the beginning of reinduction chemotherapy), was treated successfully with antibiotics. On day 8, the patient was afebrile and both the cutaneous lesions and the apex mass, on chest radiography and computerized tomography, had disappeared, suggesting that the latter was also a leukemic infiltration. On day 11, scattered 0.5 to 3 cm erythematous plaques that quickly became purpuric and necrotic in the center, overlying ill-defined nodules, appeared. The patient presented several lesions on the right thigh, one 3 cm in diameter on the right abdominal flank, and others on the left palm, fourth left finger (Fig. 1), and left side of the nose. Her clinical status deteriorated rapidly with hypoxemia and neurologic deficit, although she remained afebrile. On day 12, a cutaneous biopsy was taken and empirical treatment with amphotericin B was begun. A chest radiography showed an infiltrate in the upper lobule of the left lung. The patient died of brain stem compression due to intracerebral hemorrhage, 36 h after the first cutaneous lesion appeared.

Microscopic examination of the cutaneous biopsy showed hemorrhage with necrobiotic collagen in the dermis, hydropic degeneration of the basal layer and signs of ischemic cell necrosis in the epidermis. The medium-sized vessels of the dermis and subcutaneous tissue were filled with multiple tubular structures. Periodic acid-Schiff and Grocott-Gomori's methenamine silver stains confirmed the presence of broad, right-angle branching, non-septate hyphae that occluded the lumen of the vessels, some of them crossing to the dermis and subcutaneous tissue through apparently intact vessel walls (Fig. 2). There was very little inflammatory response. The autopsy disclosed generalized vascular invasion due to right-angle branching, non-septate hyphae and widespread hemorrhagic infarcts on brain, lungs, liver, myocardium, stomach, large and small intestine and kidneys. On Sabouraud's agar media, a *Mucoral* grew, which could not be typified due to later contamination of the culture.

DISCUSSION

Disseminated mucormycosis is infrequent. Around 40% of cases have been described in patients with hematological malignancies (3), and it is the third leading cause of fungal infection in this kind of patient, after disseminated candidiasis and aspergillosis (6). Infection usually arises from inhalation of spores followed by local infection and subsequent hematogenous dissemination (3). Cutaneous involvement in disseminated mucor-

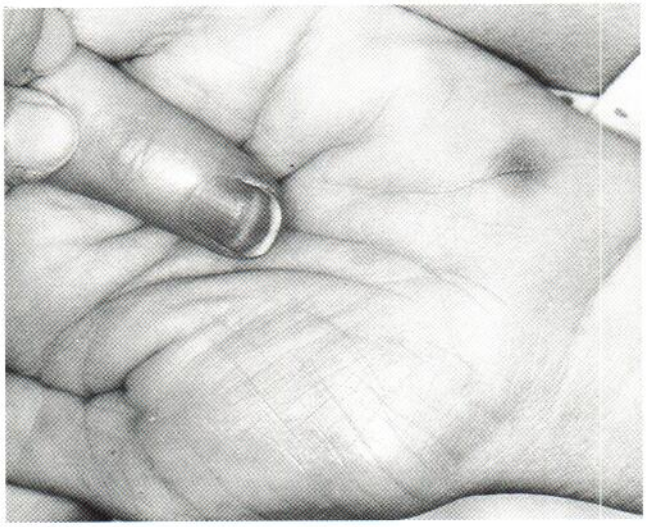

Fig. 1. Two well-defined, purpuric lesions on the left palm and the distal phalanx of the fourth finger.

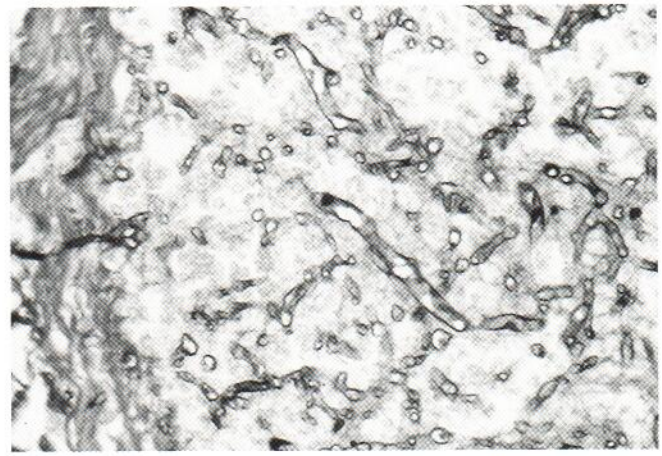

Fig. 2. A medium-sized vessel of the subcutaneous tissue occluded by broad, non-septate hyphae, with right-angle branching. One of the hyphae crosses the vessel wall. (Grocott-Gomori's methenamine silver ×200).

mycosis is a rare manifestation (5, 7). Although it has been described in 15% of cases (3), most of them were burnt patients. We have found only five reports of disseminated mucormycosis with cutaneous involvement in patients with hematological malignancies (3, 4, 8–10). Skin lesions have been described as painful, indurated nodules with ecchymotic centers (9), or solitary, erythematous plaques with a dark, purple center (4, 10) sometimes evolving to ecthyma gangrenosum-like lesions (8).

The diagnosis depends on obtaining tissue for histopathological examination and culture (3), and, sometimes, it can also be made from potassium hydroxide preparation of tissue smears (2). The histological hallmarks are invasion of blood vessel walls by hyphae, thrombus formation, and infarction of surrounding tissue (1). The irregularly shaped, broad 10–20 μm in diameter), non-septate hyphae, with right-angle branching, are pathognomonic of mucormycosis (6). Mucormycosis is the most acutely fulminant fungal disease of man (2). Ingram et al. (3) found only 17 of 185 cases correctly diagnosed while the patients were alive. Mortality is very high, near 90% despite systemic administration of amphotericin B, surgical debridement, control of acidosis and reduction of immunosuppression (3, 6).

In our case, skin lesions were the first of the disease. Our review of the literature has revealed that cutaneous involvement is described as a prominent feature (4, 5), but not as the first manifestation of the disease. Although a biopsy was performed rapidly, the fast, fatal evolution, despite empirical treatment with amphotericin B, did not allows us to perform an ante mortem diagnosis. We have not found any clear portal of entry. The scar of the previous cutaneous biopsy, indwelling catheter areas and other surfaces of the body were free of lesions. We do not have enough data to consider the lungs as the portal of entry, although this cannot be ruled out. As early recognition of the disease and visualization of the hyphae constitute the cornerstone of therapy (3), we suggest that early biopsy and direct examination of any suspicious skin lesion should be performed in immunocompromised patients.

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