Primary Cutaneous Zygomycosis due to *Absidia corymbifera* in a Child with Acute Leukemia

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A 2-year-old boy with acute lymphoblastic leukemia and neutropenia on intensive induction chemotherapy, developed a necrotizing skin lesion under an armboard used to stabilize an intravenous line. The necrotizing skin lesion was refractory to itraconazole and fluconazole therapy, and the skin biopsy and cultures grew *Absidia corymbifera* as the etiologic organism on day 26. Since the organism was highly susceptible to amphotericin B, he was treated with systemic and local amphotericin B as well as granulocyte colony-stimulating factor (G-CSF) followed by debridement of the ulcerated lesion and skin grafting. The zygomycotic lesion cleared on day 45. There was no evidence of recurrent fungal disease. Systemic and local amphotericin B and G-CSF were effective in clearing the skin lesion. We would like to emphasize that meticulous local hygiene and frequent inspection of covered areas is of great importance in preventing skin lesions by such nonvirulent environmental fungi. The use of G-CSF should also be included in the treatment regimen of primary cutaneous zygomycosis in neutropenic patients.

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INTRODUCTION

Primary cutaneous zygomycosis is an uncommon disease. Cutaneous zygomycosis is usually seen as a manifestation of disseminated diseases in immunocompromised patients. The clinical and histopathologic features of acute lymphoblastic leukemia in a child undergoing remission induction therapy, who developed primary cutaneous zygomycosis on his forearm underneath an arm board is reported in this case report.

CASE REPORT

The patient was a 2-year-old boy with acute lymphoblastic leukemia on induction chemotherapy. His treatment regimen included vincristine sulfate, pirarubicin, L-asparaginase, and dexamethasone. He was placed on oral itraconazole and sulfamethoxazole-trimethoprim for prophylaxis of opportunistic infections.

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On the sixth therapeutic day (day 6), he developed a low grade fever. Intravenous cefmetazol sodium and aztrenam therapy was administered immediately. On day 8, an enlarging tender nodule, 2 cm in diameter, with a surrounding erythematous zone was noted on the flexor aspect of the left forearm, which had been taped to an armboard to secure an intravenous catheter. The blood neutrophil count fell to 25 cells/μL. On day 10, the patient's temperature rose to 39.5°C and vesicles developed in the center of the nodule. A fungal infection was suspected and intravenous fluconazole was started (100 mg/day). Within 2 days, ulcers developed from when the vesicles ruptured and enlarged to 6 cm in diameter. Several macules and papules also spread to 6 cm in diameter. Clear fluid was oozing from the ulcers, and swab cultures of the fluid yielded a rapid growth of a floccose and whitish-gray fungi. Direct microscopic examination disclosed aseptate hyphae with an infundibuliform apophysis and sporangia pyriform. The fungus was identified as *Absidia corymbifera*. Cultures of blood, sputum, and urine were negative for fungal or bacterial pathogens. There was no clinical or roentgenographic evidence of pulmonary infection at that time.

When the induction therapy was completed, the bone marrow evaluation indicated a complete remission.

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Granulocyte colony-stimulating factor (G-CSF) was started on day 15, when debridement of the lesions was performed. There had been necrosis beneath the ulcers (Fig. 1). The histopathological examination of the skin biopsy specimens, obtained by debridement, showed aseptate hyphae that had extended within the epidermis and dermis, and penetrated through the blood vessels (Fig. 2). An intravenous infusion of amphotericin B (0.25 mg/kg/day) was started, and the dose was gradually increased to 1 mg/kg/day. In addition, a local injection of amphotericin B and amphotericin B ointment were applied to the necrotic lesions, and the surrounding erythematous zone. Systemic and local amphotericin B was successful in preventing the enlargement of the necrotic and erythematous lesions; and G-CSF raised the neutrophil count into the normal range within 1 week. Subsequently, the fever subsided and his general condition was improved. On day 31, the granulation tissue that developed in the debridement area and the lesion cultures for the fungus were negative. On day 45 he received a skin graft, and systemic amphotericin B was discontinued after a 6 week course. Since there was no evidence of recurrent fungal infection, chemotherapy was started 3 weeks after skin grafting. Details of this clinical course are shown in Fig. 3.

DISCUSSION

Zygomycetes are characterized by broad, branching, and nonseptate hyphae. The 3 genera of pathogens in this family are *Rhizopus*, *Absidia*, and *Mucor*. Of these opportunistic organisms, *Absidia* is the least associated with human infections.[1] Zygomycosis usually involves necrotic, progressive infection of rhinocerebral, cutaneous, gastrointestinal, pulmonary, and vascular areas in compromised patients. Primary cutaneous zygomycosis is very rare and usually seen in individuals with an interrupted integument, like diabetics with superficial ulcers, trauma or burn patients, or cancer patients on prolonged intravenous therapy.[2]

In this patient, primary cutaneous zygomycosis developed on the forearm, at the site of prolonged contact with an armboard. Several nosocomial outbreaks of primary cutaneous aspergillosis have been reported in leukemic children.[3,4] Investigators emphasized that contamination of armboards predisposes the patient to primary cutaneous aspergillosis.

Amphotericin B has a strong and broad-spectrum antifungal activity and is generally administered to all leukemic children on chemotherapy as prophylaxis for fungal infections. The child in this report received oral itraconazole because he failed to comply with oral amphotericin B therapy. Itraconazole is also a potent antifungal agent for *candida* and *aspergillus*, but not for *zygomycete*.

Systemic administration of amphotericin B and G-CSF is very effective in resolving cutaneous zygomycosis. Shortly after systemic amphotericin B was initiated, the lesions stabilized. Upon the return of a normal neutrophil count the lesions resolved rapidly. Before the availability of G-CSF, granulocyte transfusion was effec-

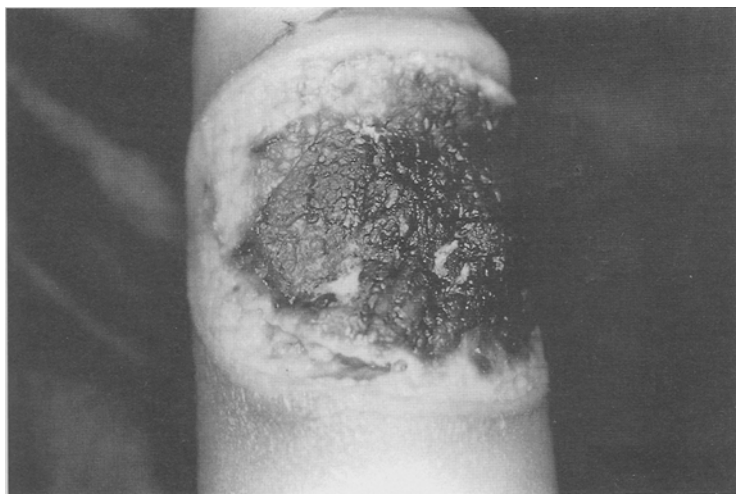

Fig. 1. Large hemorrhagic and necrotic ulcer of the flexor aspect of left forearm while taped to an armboard.

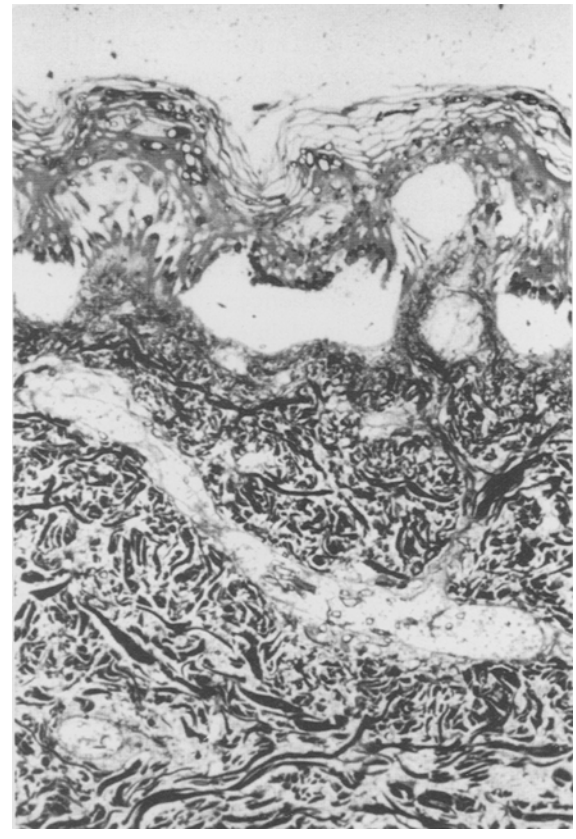

Fig. 2. Aseptate hyphae extended within the epidermis and dermis and penetrated through blood vessels. (Grocott-Gomori methenamine-silver stain).

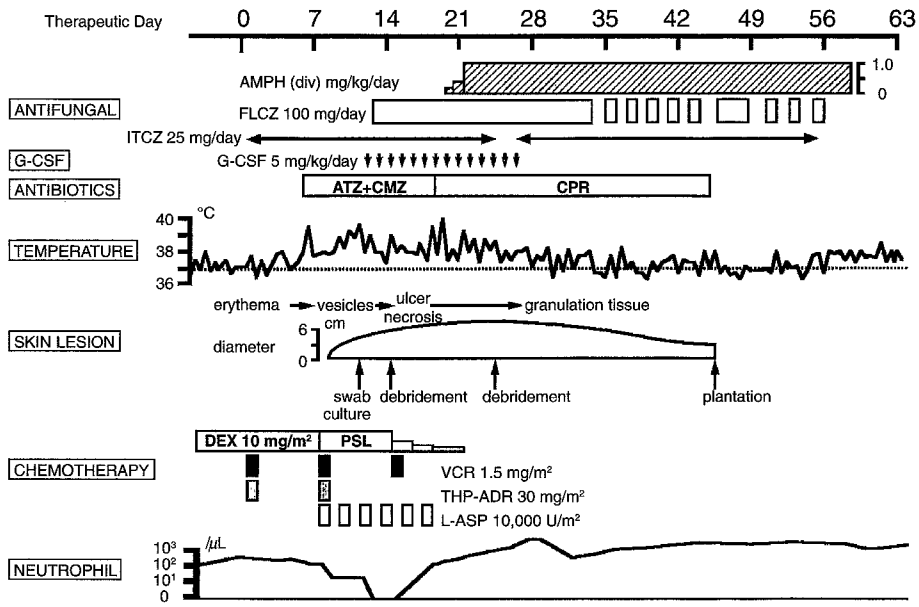

Fig. 3. Clinical course of the patient. AMPH, amphotericin B; FLCZ, fluconazole; ITCZ, itraconazole; G-CSF, granulocyte colony-stimulating factor; AZT, aztrenam; CMZ, cefmetazol sodium; CPR, cefpirome; DEX, dexamethasone; PSL, prednisolone; VCR, vincristine sulfate; THP-ADR, pirarubicine; L-ASP, L-asparaginase.

tively used for fungal infections in neutropenic patients.[5] G-CSF now replaces granulocyte transfusions, because it is more effective and safely increases the neutrophil count. Topical antifungal therapy, for example local injection and ointment application of amphotericin B, may also be indicated.[6,7] However, whether such topical therapy can be beneficial or preventive in the systemic fungal infection remains unclear.

Based on the experience with this patient, we have established a new guideline for prevention of fungal infections in neutropenic children. All intravenous administration equipment, including armboards, overlying bandages, and tapes must be sterile and changed daily. Any covered area should be inspected frequently. No further cutaneous fungal infections have been experienced.

In conclusion, frequent inspections of skin covered areas, especially under or around the armboard, should be emphasized. Administration of amophotericin B is indicated as prophylaxis for fungal infections, and prompt presumptive diagnosis is the key to immediate and appropriate therapy in neutropenic children.

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