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Localized Muscular Mucormycosis in a Child with Acute Leukemia

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Mucormycosis is a rare fungal infection of childhood, occuring mainly in patients with chronic illnesses such as diabetes and malignancies. The fungus seldom grows in culture and confirmation of the diagnosis depends on histologic examination of infected tissues. To date, the reported natural history of the disease has been rapid progression and a fatal outcome. Therefore, the importance of early diagnosis by tissue biopsy and early treatment with surgical debridement and systemic antifungal therapy cannot be overemphasized. The pulmonary system is the most common site for mucormycosis in patients with leukemia. We report what we believe to be the first successfully treated case of isolated muscular mucormycosis occurring in a child with biphenotypic acute leukemia. The diagnosis was made promptly by tissue examination at the time of surgical debridement. The patient was also given systemic amphotericin-B therapy.

Key words: mucormycosis – muscle – leukemia – childhood

INTRODUCTION

Mucormycosis is a rare suppurative mycotic infection caused by certain genera of the class Zygomycetes, order Mucorales. Mucorales are usually not pathogenic in the normal host, but cause opportunistic infection in patients with diabetes, leukemia, lymphoma and other malignancies. Patients with burns, organ transplantation or prolonged immunosuppressive therapy are also susceptible. Intravenous drug users are also at risk of acquiring the disease.

Mucormycosis is characterized by vascular invasion and intravascular thromboses accompanied by intense suppuration and the production of black necrotic pus. Untreated cases progress rapidly and often end in death. We describe a child with acute leukemia who developed mucormycosis limited to the muscle of the lower extremity and was treated successfully with early debridement and systemic administration of amphotericin-B.

CASE REPORT

A 9-year-old Korean boy was diagnosed as having biphenotypic acute leukemia at Dong San Medical Center, Keimyung University, Taegu, Korea. The patient had a history of intermittent fever and proptosis for 3 weeks prior to admission. On admission he had shown generalized weakness, bilateral proptosis, mild hepatosplenomegaly and cervical lymphadenopathy on physical examination. The total white cell count was 63 900/μl with 4% neutrophils, 4% lymphocytes, 4% monocytes, 6% myelocytes and 82% blast forms and the hemoglobin level was 8.4 gm/dl with 100×10^3/μl platelets. A bone marrow aspiration specimen contained 90.4% undifferentiated blasts, representing two separate populations of neoplastic cells with different lineage expression and showing positive periodic acid-Schiff (PAS) and peroxidase (POD) staining. The immunophenotype was B-lymphoid with myeloid lineage-positive cells. The patient was given cytosine arabinoside and idarubicin as an induction regimen, according to the Korean Society of Pediatric Hematology/Oncology protocol. Ten days after initiation of chemotherapy he developed a fever of 39–40°C. The following day, he complained of pain in his left thigh just above the knee, when the total white cell count was 400/μl. The lesion was tender, but no swelling was seen.

The regional lymph nodes were not enlarged. There was no history of intramuscular or subcutaneous injection in this region and there were no symptoms or signs referable to respiratory or sinus infections.

Ultrasonography of the affected region of the extremity revealed an ill-defined echogenic mass involving the left vastus intermedius muscle with a low echogenic focus at the center, suggestive of myositis (Fig. 1). Magnetic resonance imaging also showed an ill-defined enhanced mass on the T1-weighted image and a round high-signal-intensity area on the T2-weighted image, suggesting a hemorrhagic lesion in the vastus intermedius (Fig. 2). An excisional biopsy was carried out, which revealed thickened muscle and periosteum containing inflamed and necrotic tissue (Fig. 3). The gross specimen consisted of multiple pieces of pale gray soft tissue in aggregates, and a section of this specimen showed a round cystic space with an inner wall covered

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Abbreviations: PAS, periodic acid-Schiff; POD, peroxidase.

Figure 1. Longitudinal ultrasonogram of the left thigh reveals an ill-defined, echogenic mass involving the vastus intermedius muscle with a central low-echogenic focus (arrow).

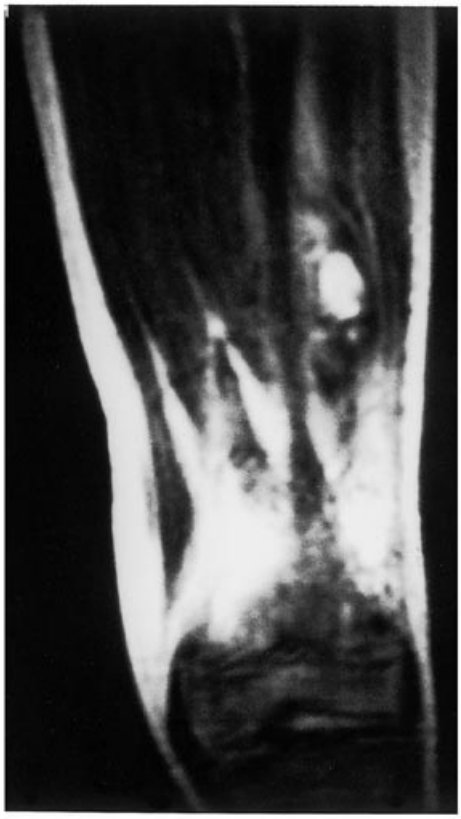

Figure 2. T2-weighted magnetic resonance image reveals a round, high-signal-intensity mass, appearing as a high-signal-intensity area on the T1-weighted image, representing a hemorrhagic lesion in the vastus intermedius muscle.

with yellowish-brown necrotic debris and a brownish ovoid ball measuring 1.0 × 0.8 × 0.5 cm in the cystic space (Fig. 4). Microscopically, the brownish ovoid ball contained many irregularly branching non-septate hyphae intermixed with necrotic muscle fibers and neutrophil infiltrates (Fig. 5). A histologic diagnosis of mucormycosis was made, but fungal cultures of the biopsy material, blood and urine were all negative. The lesion was debrided and the patient was started on amphotericin-B postoperatively, to a total dose of 1.02 over 6 weeks.

On completion of this therapy, the lesion was clear and the patient's leg remained free of infection 6 months after discharge. He went into remission successfully following completion of the induction and consolidation therapy.

DISCUSSION

The class Zygomycetes consists of two orders, the Mucorales and Entomophthorales. The hyphae of mucorales are characteristically large, and often twisted or ribbon-like, and are unique among pathogenic fungi in having no septa. Mucormycosis may be subdivided into several distinct clinical forms depending on the site of involvement: rhinocerebral, pulmonary, gastrointestinal, cutaneous, disseminated and other rare forms (1). In Korea, rhinocerebral, cutaneous, pulmonary, renal and endocardial as well as disseminated forms of mucormycosis have been reported. Among these, cases of the rhinocerebral form are most common, as in other countries (2,3). Involvement of muscle in cases of disseminated mucormycosis has been reported (4) but cases in which muscle is the initial or only site of infection are extremely rare. No cases of muscular mucormycosis in large series of more than 75 cases (5–7) have been reported. In patients with leukemia or lymphoma, the most frequent site of involvement is the respiratory tract (5,8). However, in the present case there were no respiratory symptoms, and both sinus and chest X-rays showed a normal appearance. Our patient is the first child with leukemia reported to have developed mucormycosis as an isolated muscular lesion during the course of remission-induction therapy.

Mucormycosis is usually acquired by humans after inhalation of spores, and occasionally may result from cutaneous inoculation of spores at the site of trauma, burn or invasive procedures in immunocompromised hosts (1,9,10). In our patient, the route of infection was unknown; he had no history of injections or trauma in the affected region.

Antemortem diagnosis of mucormycosis is difficult based on culture alone. Antemortem culture from blood, the respiratory tract and spinal fluid were all negative in 26 patients with either leukemia or lymphoma who died of mucormycosis (5). Therefore, the diagnosis of mucormycosis usually depends on biopsy

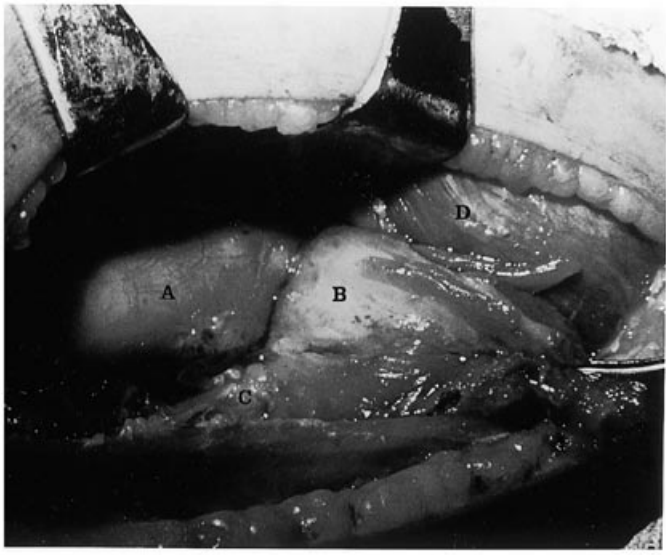

Figure 3. The lesion shows a hyperemic and thickened periosteum from the lateral aspect (A), the vastus intermedius muscle, inner aspect, detached from the femur and thickened with an indurated fascia (B), part of the biceps, necrotized and degenerated (C), and the retracted vastus lateralis (D).

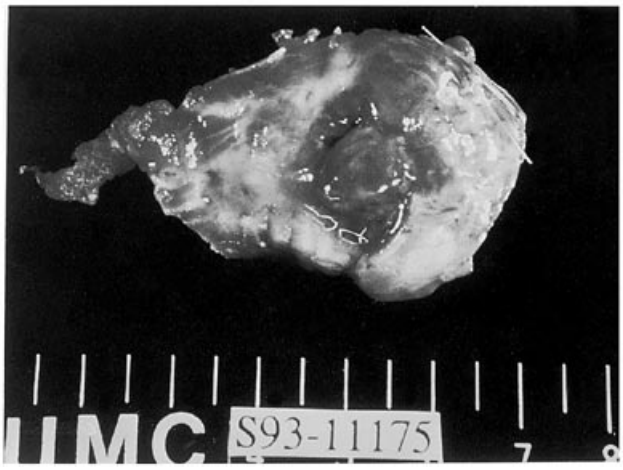

Figure 4. A brownish ovoid fungal ball, measuring 1.0 × 0.8 × 0.5 cm, is noted within a round irregular cystic space.

of the lesion and detection of non-septate hyphae. Enzyme-linked immunosorbent assay for the diagnosis of zygomycosis has been developed (1,11), but its efficacy has not been confirmed. In our patient, diagnosis of mucormycosis was made by muscle biopsy, which demonstrated the presence of non-septate hyphae in the necrotic lesion. In this case, there was also a cystic space containing a fungus ball in the lesion, which has previously been reported to be an unusual manifestation (5,8,12).

The mainstay of treatment for mucormycosis is surgical debridement followed by systemic amphotericin-B therapy. The standard medical therapy is amphotericin-B given at a maximum dose of 1.0 to 1.5 mg/kg (1). The optimal duration of therapy and the total dose of amphotericin-B are uncertain, but most patients require a total dose of 15–30 mg/kg (1,13) and many investigators have reported successful results with at least 10 days to 1 month of systemic antifungal therapy (14,15). Our patient had localized disease and received 30mg/kg amphotericin-B for 6 weeks, and this led to complete recovery. In some instances, rifampicin or flucytosine has also been used in combination with amphotericin-B (13,16,17).

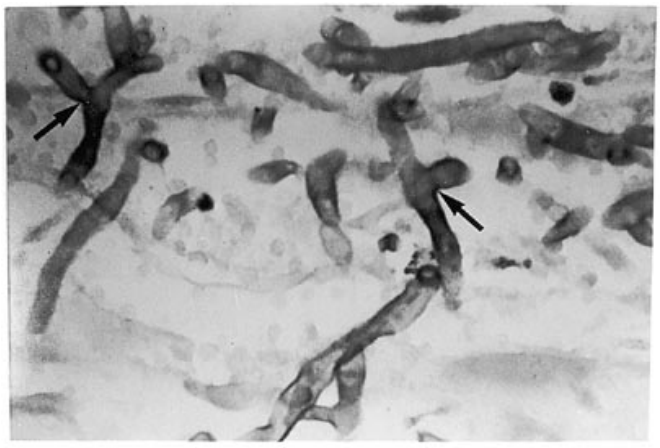

Figure 5. Light microscopic findings show abundant fungus with non-septate, broad hyphae and right-angle branching (arrow) (PAS stain).

The prognosis of mucormycosis is generally poor; only one of 15 children with histologically confirmed mucormycosis reported by Kline (6) survived. In the series of 26 cases of phycomycosis reported by Meyer *et al*. (5), only three patients received treatment, and all died. The outlook may depend on the clinical manifestation of the disease and the underlying conditions of the patients. Early diagnosis and aggressive treatment, as done in our case, are essential for a favorable outcome. In the series of 33 cases of mucormycosis reported by Parfrey *et al*. (7), survival was 73% among patients treated after 1970, as compared with only 6% in those treated before 1970. The authors attributed this dramatic improvement in prognosis to more frequent premortem diagnosis, allowing early treatment by surgical debridement and amphotericin-B therapy. In the present case, diagnosis was made early by tissue biopsy, and the patient was treated very aggressively, resulting in a successful outcome. Prompt biopsy of suspected fungal lesions in patients undergoing chemotherapy for leukemia is therefore recommended.

Acknowledgments

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