CASE REPORT

Candidal Arthritis After Complete Treatment of Systemic Candidiasis

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Over the last few decades, the incidence of invasive candidal infections in neonatal intensive care units has increased dramatically. Various complications, such as arthritis, endocarditis, meningitis, and endophthalmitis, have been reviewed. We present the case of a premature infant with systemic candidemia. Arthritis was discovered 6 months after completion of amphotericin B therapy, and was successfully treated with oral fluconazole for 6 weeks. We conclude that long-term follow-up is particularly important in patients with treated candidemia. To prevent complications, prolonged treatment with high-dose amphotericin B is suggested for systemic fungal infection, and oral fluconazole is an effective alternative for candidal arthritis. [*J Chin Med Assoc* 2005;68(4):191–194]

Key Words: arthritis, candidiasis, prematurity

Introduction

Over the last few decades, the incidence of invasive candidal infections in neonatal intensive care units has increased dramatically.[1–3] This may be due to the early use of peripherally inserted central venous catheters, prolonged use of antibiotics, hyperalimentation, gastrointestinal defects, corticosteroid use, surgery, and skin trauma. Various complications of systemic fungal infection have been reviewed, such as arthritis, endocarditis, meningitis, and endophthalmitis.[1,3] However, some reports showed that candidal arthritis may develop several months after the completion of systemic antifungal therapy.[4,5] We present the case of a premature infant with systemic candidemia and arthritis 6 months after completion of treatment with amphotericin B. The arthritis was successfully treated with oral fluconazole for 6 weeks.

Case Report

A male infant with a gestational age of 29 weeks and birth bodyweight of 1104 g was born spontaneously to a gravida 3 para 3 mother. The maternal history included gestational diabetes mellitus, and 2 doses of intramuscular dexamethasone before delivery. Apgar scores were 5 and 6 at 1 and 5 minutes, respectively. A physical examination was essentially normal, except for mild grunting and subcostal retraction at birth. After a transfer to our neonatal intensive care unit, the patient was intubated with mechanical ventilation because of respiratory distress and cyanosis. A course of bovine surfactant (beractant [Survanta®; Abbott Laboratories Inc, Columbus, OH, USA]) was given under the impression of respiratory distress syndrome, and umbilical catheters were inserted for fluid supply and laboratory monitoring.

On the day of admission, arterial blood-gas and other parameters were as follows: $PaCO_2$ 46.4 mmHg; PaO_2 122 mmHg; pH 7.29; bicarbonate 21.9 mmol/L; and base excess –4.6 mmol/L. A complete blood cell count revealed the following values: white blood cells 5900/μL (neutrophils 34%, lymphocytes 60%, monocytes 2%, and normoblasts 2%); hemoglobin 15.3 g/dL; and platelets 34,400/μL. Blood biochemistry revealed sodium 132 mmol/L, potassium 5 mmol/L, blood urea nitrogen 7 mg/dL, creatinine 0.5 mg/dL,

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C-reactive protein (CRP) 0.49 mg/dL, alanine aminotransferase 19 IU/L, and aspartate aminotransferase 78 IU/L. A central venous catheter was inserted peripherally in the right antecubital fossa for parenteral nutrition on the patient's third day of life.

At birth, septic work-up was performed, and intravenous ampicillin and gentamicin were given. Bacterial cultures were all negative. However, the patient's condition deteriorated on the seventh day of life. Cultures were repeated, and antibiotics were switched to oxacillin and ceftazidime. *Candida albicans* was isolated from a peripheral blood culture 3 days later. The peripherally inserted central line was removed, and amphotericin B was started at a dosage of 0.25 mg/kg/day after a test dose. Cerebrospinal fluid (CSF) culture was negative, but the tip of the removed central venous catheter grew *C. albicans*. The blood was clear of *C. albicans* after 2 weeks of amphotericin B, and treatment was continued for another 2 weeks; a total of 25.6 mg/kg was given. Weekly blood cultures for fungus were taken 3 times, but all proved to be negative. Further investigations for disseminated fungal disease, including renal ultrasound, ophthalmologic examination, and echocardiogram, were all negative. The patient's condition improved gradually, although complications of prematurity (intraventricular hemorrhage with post-hemorrhagic hydrocephalus, and patent ductus arteriosus) developed later. After the episode of systemic candidiasis, postnatal corticosteroids were not used, and a central venous line was not reinserted peripherally.

The patient was re-admitted at age 6 months. His vital signs were normal, and bodyweight gain was acceptable. Unfortunately, a swollen left knee joint with erythema and tenderness was discovered incidentally. There was no history of a wound or trauma. A series of bone scans and long-bone X-rays were negative. However, an inflammatory process was found over the left knee joint during a magnetic resonance imaging study (Figure 1). The peripheral leukocyte count was 16,500/μL (neutrophils 61%, lymphocytes 25%, monocytes 7%, and eosinophils 6%), hemoglobin concentration was 8.2 g/dL, platelet count was 101,000/μL, and CRP level was 2.14 mg/dL. Vancomycin (45 mg/kg/day) was given initially because coagulase-negative *Staphylococcus aureus* was isolated from the left knee joint aspirate. Signs of arthritis did not improve after 7 days of treatment, and the patient became febrile, with a temperature up to 38°C. The left knee joint was aspirated again, and 0.2 mL of whitish fluid was obtained for culture; *C. albicans* was apparent 3 days later.

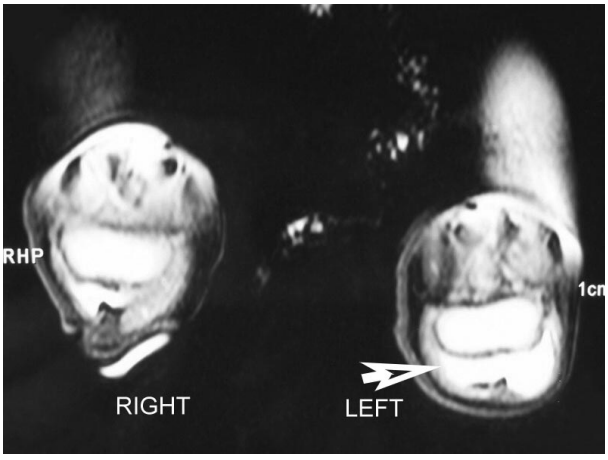

Figure 1. Cross-sectional, T2-weighted, magnetic resonance imaging scan showing fluid accumulation in the left-knee synovial cavity (arrow).

CSF and blood cultures were all sterile. Intravenous amphotericin B was administered again, but, because of difficult vascular access, treatment was switched to oral fluconazole (8 mg/kg/day) 2 days later. The fever subsided gradually, and the erythematous appearance of the left knee joint improved during the following 2 weeks. Eight days after fluconazole therapy, synovial fluid from the left knee joint was clear of *C. albicans*. The baby was discharged at that time, but the left knee joint was still mildly swollen, with some limitation of movement. Oral fluconazole therapy was continued for a total of 6 weeks. Liver function tests were normal. The baby was followed-up at age 1 year, and all the joints, including the left knee, were freely movable without any signs of inflammation.

Discussion

Fungal sepsis occurs in as many as 10% of low-birthweight infants.[6] Most cases are due to *Candida* spp., particularly *C. albicans, C. tropicalis, C. parapsilosis, C. lusitaniae* and *C. glabrata*. *C. albicans* is the leading cause of neonatal fungal sepsis, but non-albicans *Candida* spp. have become more frequent causes.[7] Risk factors for late-onset systemic candidiasis include prematurity, low birthweight, mechanical ventilation, the use of broad-spectrum antibiotics, corticosteroid therapy, central vascular catheters, parenteral hyperalimentation, intralipid infusion, prolonged endotracheal intubation, necrotizing enterocolitis, and immunologic immaturity.[8] The clinical manifestations of systemic candidiasis vary and are indistinguishable from those of systemic infections

caused by other pathogens. Nonetheless, fungal infections should be considered in patients who have been hospitalized for a prolonged period with parenteral nutrition or broad-spectrum antibiotic therapy. Intravenous amphotericin B (total dosage 25–35 mg/kg) remains the standard treatment for candidal sepsis; moreover, general consensus exists that the removal of foreign bodies, including prostheses and catheters, helps to clear candidal infection. The intravenous or oral use of fluconazole for neonatal candidemia has been suggested as an alternative to amphotericin B,[9,10] but the safety and efficacy of fluconazole in this setting requires further large-scale, multicenter trials.

Eighty-five percent of cases of pediatric fungal arthritis occur in infants aged less than 6 months, as do 70–80% of cases associated with osteomyelitis.[11] Infection originates hematogenously and seeds either into the synovium or metaphyseal vessels. About 2-thirds of patients with fungal arthritis initially have fever and tender joint(s), but mild arthritic symptoms may delay the diagnosis for months to years.[12] Blood cultures should be obtained from all infants with suspicious infection. Diagnostic aspiration of the joint should be attempted to isolate the pathogen, and bone scintigraphy remains more sensitive than plain radiography for early diagnosis.[13] Intravenous amphotericin B is the drug of choice for both candidal arthritis and systemic fungal infection, although some reports have shown that fluconazole is an effective alternative for the treatment of fungal arthritis in premature infants.[14,15]

This case is interesting because the left-knee arthritis occurred 6 months after the completion of treatment for systemic fungal infection. This highlights the previous observation that the presentation of arthritis may be delayed from several months to 1 year after the treatment of neonatal candidiasis.[4,5] However, the pathogenesis remains unclear. Swanson et al[5] suggested that *Candida* spp. might be latent or indolent in the joint or liver for a period of time by demonstrating the same DNA-based typing of organisms from the initial candidemia and subsequent arthritis. This implies that, during the initial candidiasis, there is seeding of infection into the joints that is suppressed, but not eliminated, by amphotericin B. Thus, what is the optimal duration and dosage of treatment in neonatal candidiasis? A previous study suggested that 7–14 days of amphotericin B therapy after the last positive blood culture may be adequate,[16] and that a total dose of 25 mg/kg should be sufficient.[17] However, candidal arthritis occurred in our patient, even with the above recommended duration and dosage of treatment. From this observation and previous reports,[4,5] we postulate that the current strategy for managing neonatal candidemia may be inadequate. Further research regarding more aggressive amphotericin B treatment, either alone or in combination-therapy regimens, should now be considered. Although we cannot prove that the 2 *C. albicans* specimens from blood and subsequent synovial fluid in our patient were of the same serotype, the possibility of asymptomatic candidal recolonization and transient fungemia exists; this underscores the importance of follow-up in neonates with candidemia.

In conclusion, systemic candidiasis has become more common in neonates hospitalized for prolonged periods. Although our current regimen of amphotericin B can cure most cases, care should be taken to evaluate fungal seeding to other parts of the body, especially the joints. From our experience in this case, a more aggressive duration and dosage of amphotericin B should be considered for systemic candidiasis, and fluconazole is an effective alternative for candidal arthritis.

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