CASE REPORT

CRYPTOCOCCUS NEOFORMANS SEPTICEMIA IN AN IMMUNOCOMPETENT NEONATE: FIRST CASE REPORT IN THAILAND

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Abstract. Neonatal infection due to *Cryptococcus neoformans* is extremely rare. We report a case of a 21-day-old neonate diagnosed with cryptococcal septicemia who was successfully treated with amphotericin B. He was born to a human immunodeficiency virus (HIV) seronegative mother. This report alerts general pediatricians and neonatologists to consider *Cryptococcus neoformans* infection as a possible cause of sepsis in newborn infants.

INTRODUCTION

Cryptococcus neoformans (C. neoformans) is a widespread encapsulated fungus found in soil that contain excreta from pigeons. It is predominantly an opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS) (Dromer *et al*, 1996). Although its incidence has increased rapidly in recent years, it has rarely been reported in neonates. Since the first case report in 1948, there have been only seven neonatal cases reported in the English literature (Neuhauser and Tucker, 1948; Heath, 1950; Raubitschek, 1958; Gavai *et al*, 1995; Kaur *et al*, 2002; Giusiano *et al*, 2004). We report a case of non-HIV-infected neonatal cryptococcal septicemia in Thailand, a first case report for this country.

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CASE REPORT

A 37-week-gestation male neonate who had a history of congenital diaphragmatic hernia (CDH) diagnosed in *utero* was born by elective Cesarean section to a healthy 33-year-old mother with good antenatal care. Spontaneous rupture of membranes occurred 4 hours before delivery. The birth weight was 3,360 g, and the Apgar scores were 2 and 7 at 1 and 5 minutes, respectively. The infant was intubated, and transferred to the neonatal intensive care unit (NICU). A chest roentgenogram revealed a left-side thoracic CDH. At 1 hour of age, persistent pulmonary hypertension of the newborn developed and was confirmed by echocardiography. Central line catheters were placed in the umbilical artery and vein for administration of intravenous drugs, parenteral nutrition, and to monitor arterial blood gases. The cardiovascular system was maintained using dopamine (20 µg/kg/min), dobutamine (20 µg/kg/min), and epinephrine (0.4 µg/kg/min). Prostacyclin PGI_2 (Ilioprost®) was started and titrated to a maximum dose

of 4 ng/kg/min. Inhaled nitric oxide was then begun because of persisting severe refractory hypoxemia. Ampicillin and gentamicin were started for presumed sepsis after cultures were obtained. On Day 2 of life, the infant's temperature was 37.8ºC and his cardiorespiratory status continued to deteriorate. The antibiotics were changed to meropenam and vancomycin after a second sepsis work-up. On Day 8 of life, a central venous catheter was placed in the left femoral vein to allow administration of other intravenous drugs. On Day 17 of life, another episode of septicemia and pulmonary hemorrhage were detected. Laboratory investigations revealed a hematocrit of 43%, a total white blood count of 8,450 cells/mm^3 (60% polymorphic neutrophils; 25% lymphocytes; 15% monocytes), and a platelet count of 22,000 cells/mm^3. Blood chemistry and coagulogram were within normal range. Chest roentgenograms revealed increased bilateral pulmonary infiltration, and thus cefoperazone-sulbactam and netilmicin were added for coverage of a nosocomial multidrug-resistant gram-negative infection that was epidemic in the NICU at that time. On Day 21 of life, pulmonary hemorrhage and thrombocytopenia were unchanged despite multiple platelet transfusions and broad spectrum antibiotic coverage.

A blood culture taken on Day 21 showed budding yeast and intravenous amphotericin B was started on Day 27 of life. The infant developed an unexplained generalized seizure on Day 30, which was well controlled with phenobarbital. On Day 31 of life, *C. neoformans* was identified from a blood culture. A cerebrospinal fluid examination was not performed due to unstable cardiovascular status. A repeated blood culture, after 4 days of amphotericin B, still showed budding yeast, and all central lines were removed. Following counseling, the mother and patient were tested for human immunodeficiency virus (HIV) antibodies and found to be seronegative. The patient gradually improved after central line removal. A blood culture on Day 21 of treatment was sterile for the first time. Amphotericin B treatment was continued for 5 weeks to ensure complete eradication of the fungus.

On Day 48 of life, he underwent surgery to repair the diaphragm, and was extubated 4 days later. Further chest roentgenograms at that time revealed changes suggestive of chronic lung disease, for which he was treated with furosemide. Liver function tests showed evidence of cholestatic jaundice which may have been caused by prolonged nothing-per-oral (NPO) and intravenous parenteral nutrition, and he was treated with ursodeoxycholic acid. An eye examination showed no evidence of fungal infection, and a cranial ultrasonography showed no evidence of hydrocephalus. The infant was discharged from the hospital on Day 102 of life.

DISCUSSION

Infection due to *C. neoformans* is found mainly in adult patients with AIDS, infrequently in children, and rarely in neonates (Dromer *et al*, 1996). To our knowledge, only 7 neonatal cases have been reported in the English literature since 1948 (Neuhauser and Tucker, 1948; Heath, 1950; Raubitschek, 1958; Gavai *et al*, 1995; Kaur *et al*, 2002; Giusiano *et al*, 2004). Four cases reported between 1948 and 1954 died, probably due to delayed diagnosis and lack of antifungal agents. (Neuhauser and Tucker, 1948; Heath, 1950; Raubitschek, 1958).

Disseminated cryptococcosis in neonates usually involves multiple sites, most commonly the central nervous system, leading to meningitis, encephalitis, obstructive hydrocephalus, chorioretinitis, and endopthalmitis (Neuhauser and Tucker, 1948; Heath, 1950; Raubitschek, 1958; Kaur *et al*, 2002). The clinical presentation including fever, irritability, lethargy, poor feeding, abdominal distension,

convulsion, anemia, and thrombocytopenia, are indistinguishable from bacterial sepsis (Neuhauser and Tucker, 1948; Gavai *et al*, 1995; Kaur *et al*, 2002). Other manifestations, such as hepatosplenomegaly, pneumonia, and cutaneous infections have also been reported (Neuhauser and Tucker, 1948; Raubitschek, 1958). There are other features rarely reported, such as liver disease (noncaseating granulomas, hepatitis, or cirrhosis), renal miliary abscesses, cataracts, and scattered intracranial calcifications (Neuhauser and Tucker, 1948). These features may mimic congenital infections such as toxoplasmosis, rubella, and cytomegalovirus infections.

Neonates are at increased risk for opportunistic infections due to immaturity, or problems with cellular or humoral immunity (Bellanti *et al*, 2005). Central venous catheterization, parenteral nutrition, and antibiotic usage are also documented risk factors for fungal sepsis (Makhoul *et al*, 2001; Krčmery *et al*, 2002). Our case, as well as 2 earlier reported cases, had central venous catheters in place when cryptococcosis occurred (Kaur *et al*, 2002). We hypothesize the use of broad spectrum antibiotics, central venous catheterization, and prolonged parenteral nutrition increased the risk for this infection, although the mode of *C. neoformans* acquisition is not clear.

Sirinavin *et al* (2004) and Castro *et al* (2006) reported insidious courses of disseminated cryptococcosis in infants born to HIV-infected mothers, with onset at 3 and 4 months of age, respectively. These cases suggest *C. neoformans* transmission is likely to occur during the postpartum period. *Cryptococcus neoformans* colonization in the mother's endocervix was found in one case, which suggested that transmission may have occurred during delivery (Neuhauser and Tucker, 1948).

Because of the limited number of cases, there is no validated standard treatment for *C. neoformans* in neonates. All three reported cases that survived, including our case, were successfully treated with amphotericin B with or without flucytosine (Gavai *et al*, 1995; Kaur *et al*, 2002). One infant was successfully treated with amphotericin B and fluconazole (Sirinavin *et al*, 2004). Prompt removal of the central venous catheter is an important measure for clearing fungemia and preventing complications (Dato *et al*, 1990).

In conclusion, neonatal cryptococcosis is extremely rare. The clinical features are similar to that of bacterial sepsis. In infants with clinical sepsis refractory to broad spectrum antibiotic coverage, especially in cases with central venous catheterization and parenteral nutrition, fungal infection should be considered. Specific antifungal therapy and prompt removal of the central venous catheter are important for a successful outcome.

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