Disseminated candida infection in a term infant.

Suwimol Sanpavat*


A fullterm neonate who developed systemic fungal infection, causing pulmonary infiltration, meningitis, osteoarthritis, endophthalmitis and urinary tract infection was reported. The major risk factor was prolonged use of broad spectrum antibiotics for bacterial sepsicemia. Treatment with Amphotericin B and 5 fluorocytosine was favourable. Early diagnosis and treatment are emphasized.

Key words: Candida infection, disseminated, neonate

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การทดสอบความก้าวหน้าในการรักษาโรคติดเชื้อ พบว่าการใช้ยา Amphotericin B และ 5-fluorocytosine ในการรักษา สามารถลดความรุนแรงของอาการของโรคติดเชื้อได้ดีและเข้าสู่ระดับการหายรักษา ผลการทดลองนี้ช่วยในการพัฒนาระบบการรักษาโรคติดเชื้อ
Disseminated fungal infection has been increasingly recognized in the newborns especially the very low-birth weight infants.\(^1\)\(^,\)\(^2\) It has been reported in term infants with meconium aspirated syndrome,\(^3\) malrotation,\(^4\) necrotizing enterocolitis,\(^5\) myelomeningocele and sacrococcygeal terratoma.\(^6\) Factors predisposing the infants to infection are prolong hospitalization and antibiotic administration, parenteral nutrition, indwelling catheter,\(^7\) surgery or intensive care along with invasive procedures.\(^7\) Candida albicans is the most common organism responsible for the infection. Other species include C. tropicalis, C. parapsilosis, C. lusitaniae, C. glabrata, C. guillermondii,\(^8\)\(^-\)\(^10\) and Malassezia furfur.\(^11\) We report the case of a term infant who developed disseminated candidiasis involving lungs, meninges, eyes, joints and urinary tract, and successfully treated with amphotericin B and 5 fluorocytosine.

**Case report**

A 2900 grams, fullterm female infant was born to a 22 year-old gravida 2, para 2 mother. Pregnancy was uncomplicated and delivery was via vagina without prolonged rupture of the membrane. The Apgar scores were 9 and 10 at 1 and 5 minutes respectively. Physical examination was within normal limit. Her first few days of life were uneventful. However, her mother developed fever and foul-smelling amniotic fluid shortly after delivery, and was treated with ampicillin, gentamicin and metronidazol for endometritis, although her blood, urine, and cervical swab culture yielded no organisms.

On day 5, the infant developed bile-stained vomiting, abdominal distension and mucous stool. Roentgenogram of the abdomen revealed fixed bowel loops. The complete blood count, stool examination were within normal limit, and stool culture grew no organism. The stool occult blood was negative twice, but subsequently became positive. Necrotizing enterocolitis (NEC) was suspected, and ampicillin and gentamicin were administered.

On day 10, five days after treatment for NEC, she became febrile. Complete blood count (CBC) showed leukocytosis with polymorphonuclear predominant. The cerebrospinal fluid (CSF) examination and roentgenogram of the chest were normal. Cloxacillin and amikacin instead of gentamicin were administered after blood, urine and CSF culture were obtained. The infant developed disseminated intravascular cuagulopathy 5 days later and supportive treatment was given. Amikacin was replaced with Cefazidime when Klebsiella pneumoniae and Klebsiella species were isolated from the blood and urine respectively. She was still febrile, but was active and took her feeding well. Oral and intertrigous candidiasis were discovered at the age of 24 days and was treated with mycostatin.

On day 28, despite the continuation of antibiotics, the fever persisted and swelling of the elbows was noted. Roentgenogram showed soft tissue swelling of the involved joints, and infiltration of the lungs. The CSF contained wbc 250/mm\(^3\) with 90% polymorphonuclear cells and 10% lymphocytes, protein 90 mg/dl, glucose 22 mg/dl with serum glucose 104 mg/dl. Blood and urine culture evere again taken. Urine and stool examination revealed budding yeast cells and hyphae. Blood and CSF subsequently grew C. albicans but urine culture was contaminated. Antifungal therapy with amphotericin B and 5 fluorocytosin (5 FU) was initiated. Amphotericin B was given intravenously, 0.05 mg/kg/day, over 6 hours and slowly increased to 1 mg/kg/day. 5 FU 100 mg/kg/day was given orally, Hydrocortisone 1 mg/kg/day was administered during the first several days of antifungal treatment, (Table 1).

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<th>Table 1. Course of the infant’s illness.</th>
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<td><strong>Dx</strong></td>
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<td>Necrotizing enterocolitis</td>
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<td>Antibiotics</td>
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<td>Gentamicin</td>
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<td>(total 6 wk)</td>
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Early in the course of the treatment, arthritis continued with involvement of several joints including the knees, elbows and hips (picture 1-4). The joint fluid, obtained by needle aspiration, was clear and grew no organism. Fever subsided at the age of 48 days, after 12 days of antifungal therapy. Repeated blood, urine and CSF culture 48 hours after the patient was afebrile were sterile. The CSF protein was 89 mg/dl, sugar 29 mg/dl, wbc 214/mm$^3$ and 80% of them were mononuclear cells.

**Figure 1.** Swelling of soft tissue of the knee joint. Haziness and widening of the joint space with radiolucent bands at the metaphysis of the femur and fibula, compatible with septic arthritis.

**Figure 2.** Soft tissue swelling of the elbows. Radiolucency of the metaphyseal ends of both elbows and wrists.
Figure 3. Soft tissue swelling with cortical destruction.

Her eyes appeared normal externally, however, ophthalmologic examination discovered opacity of the vitreous and multiple foci of retinitis, compatible with fungal retinitis.

Arthritis subsided after 35 days of treatment. Renal function, liver function, electrolyte and CBC were checked periodically and were within normal limit. Amphotericin B and 5 FU were given for a total of 6 weeks. Repeated ophthalmologic examination showed improvement of the retinitis. The CSF still had high protein and low glucose level but no pleocytosis. The infant was discharged in good condition at the age of 90 days.

Discussion

Candida albican is part of the normal flora of the gastrointestinal tract. It is also a common inhabitant and frequent pathogen of the female genital tract, especially during pregnancy.\(^\text{(13)}\) Congenital neonatal candidiasis has been documented.\(^\text{(14-16)}\) Infants acquired colonization of Candida during labour and delivery. Baley et al.\(^\text{(17)}\) reported the colonization rate in the very low-birth-weight infants to be 26.7%. Early colonization within the first week of life was demonstrated predominantly in the respiratory and GI tract.\(^\text{(17)}\) This may serve as a reservoir of infection. Our patient manifested mucocutaneous candidiasis after 19 days of broad spectrum antibiotics given for NEC and Klebsiella septicemia. Prolonged antibiotics administration suppressed the normal flora of the GI tract and allowed candida overgrowth, as shown by the presence of blastospores and hyphae in the urine and stool of the patient. Antibiotics and the relatively incompetent neonatal immune mechanism were the only risk factors in this patient, resulting in tissue invasion and dissemination of the fungus.

Joint involvement presents as erythema, warmth, swelling and limitation of movement.\(^\text{(3,18,19)}\) Initial roentgenography reveals only soft tissue swelling.\(^\text{(20)}\) Diagnosis was by culture of the aspirated synovial fluid. Infection may respond well to medical treatment, therefore, surgical intervention is not the rule as in the treatment of pyogenic osteoarthritis.\(^\text{(20)}\)

Baley et al reported a 50% incidence of enophthalmitis in the very low-birth weight infants with systemic candidiasis.\(^\text{(18)}\) The lesion appears as a fluffy white ball and haziness of the vitreous.\(^\text{(18,21)}\) The prognosis is good following systemic therapy,\(^\text{(21)}\) however, follow up is required since recurrence and complication have been reported.\(^\text{(22,23)}\)

Diagnosis of systemic candidiasis is obtained
by cultivation of candida from the blood, urine, CSF and other body fluid. Recognition of the disease is delayed due to the indistinguishable presentations from those of bacterial sepsis,(24) the intermittency of positive culture(1), and the tendency to dismiss the positive culture for a contamination. Tuck(25) suggested that finding budding yeast cells, particularly hyphae in the urine was to be considered an indication for antifungal therapy. Other considered endophthalmitis in an infant whose systemic cultures were negative, the diagnosis of invasive candida infection.(18) Ultrasonography and computerized axial tomography may be useful for the detection of renal, central nervous system and cardiovascular involvement.(18)

Early diagnosis and treatment yielded a favourable outcome. The drug of choice is amphotericin B, given slowly intravenously. Nephrotoxicity is the major side effect.(26) Hepatotoxicity, bone marrow suppression, fever, chills and GI disturbance have been reported.(18) It is recommended that 5 fluorocytosine (5 FU) is to be used simultaneously with amphotericin B.(26) Penetration into the central nervous system and synovial fluid are excellent.(28) Side effects are the same as those caused by amphotericin B. Careful monitoring of the renal and hepatic function is mandatory. Miconazole has been used occasionally both with success(27,28) and failure.(29) It has poor CSF penetration and a high relapse rate in adult.(18) In our patient, response to amphotericin B and 5 FU was satisfactory, and no side effect was documented.

Conclusion

Disseminated fungal infection is now frequently diagnosed in the neonatal period, and causes serious morbidity and mortality. Suspicion of the disease should be maintained in the infant with high risk factors, so that early diagnosis and treatment are ensured.

References