รายงานผู้ป่วย

Disseminated candida infection in a term infant.

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A fullterm neonate who developed systemic fungal infection, causing pulmonary infiltration, meningitis, osteroarthritis, endophthalmitis and urinary tract infection was reported. The major risk factor was prolonged use of broad spectrum antibiotics for bacterial septicemia. 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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ทารกคลอดครบกำหนดในรายงาน มีภาวะติดเชื้อราในกระแสโลหิต ซึ่งแพร่กระจายไปยังปอด เกิดอาการเยื่อหุ้มสมองอักเสบ ข้ออักเสบ ตาอักเสบ และการติดเชื้อราในทางเดินปัสสาวะ ความเสี่ยงต่อเชื้อราในทารกเกิดจากการใช้ยาปฏิชีวนะรักษาโรคติดเชื้อจากบัคเตรีเป็นเวลานาน ผู้ป่วยได้รับการรักษาด้วย Amphotericin B และ 5 fluorocytosine จนอาการดีขึ้น ถึงแม้จะเป็นโรคที่มีความรุนแรงแต่การวินิจฉัยและเริ่มรักษาตั้งแต่ระยะแรกเริ่มของการติดเชื้อ จะทำให้การพยากรณ์โรคดีขึ้น

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,[3] surgery or intensive care along with invasive procedures.[7] Candida albican is the most common organism responsible for the infection. Other species include C. tropicalis, C. parapsiolsis, C. lusitaniae, C. glabrata, C guilliermondii,[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 Ceftazidime 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 intertriginous 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. albican 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 administed during the first several days of antifungal treatment, (Table 1).

Table 1. Course of the infant's illness.

	day 5	day 10	day 15	day 24	day 28	> 1 month
Dx	Necrotizing enterocolitis	fever - Klebsiella pneumoniae in blood - Klebsiella sp. in urine	DIC	oral and intertriginous candidiasis	- osteoartheritis - pneumonia - urinary tract infection - meningitis - fungemia	fungal retinitis
antibioties	Ampicillin	← Cloxacillin →		← Mycostatin →	← Amphotericin B →	
	Gentamicin	← Amikacin →	← Ceftazidime →		← 5 FU → (total 6 wk)	

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.

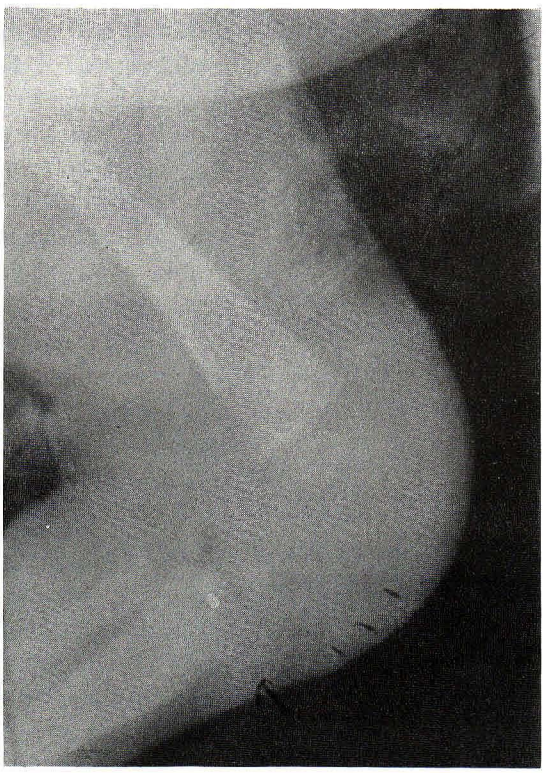

Figure 1. Swelling of soft tissue of the knee joint. Haziness and widening of the joint space with radiolucent bands at the metaphysis of the femur and fibula, compatible with septic arthritis.

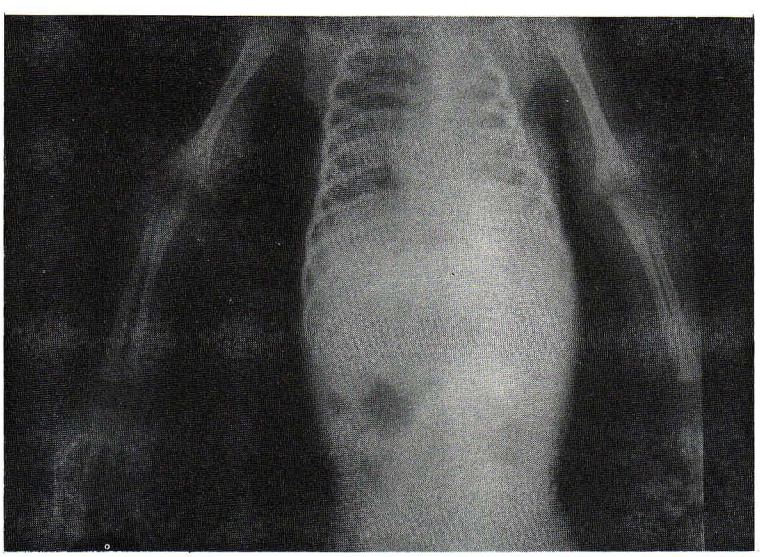

Figure 2. Soft tissue swelling of the elbows. Radiolucency of the metaphyseal ends of both elbows and wrists.

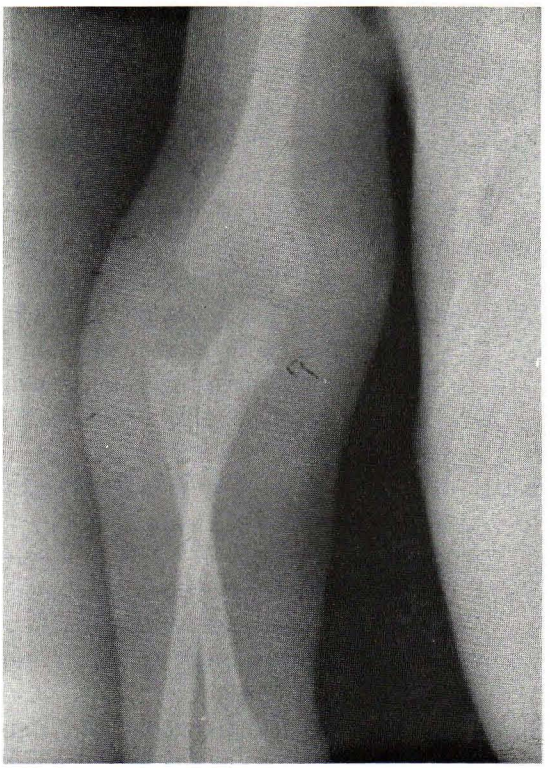

Figure 3. Soft tissue swelling with cortical destruction.

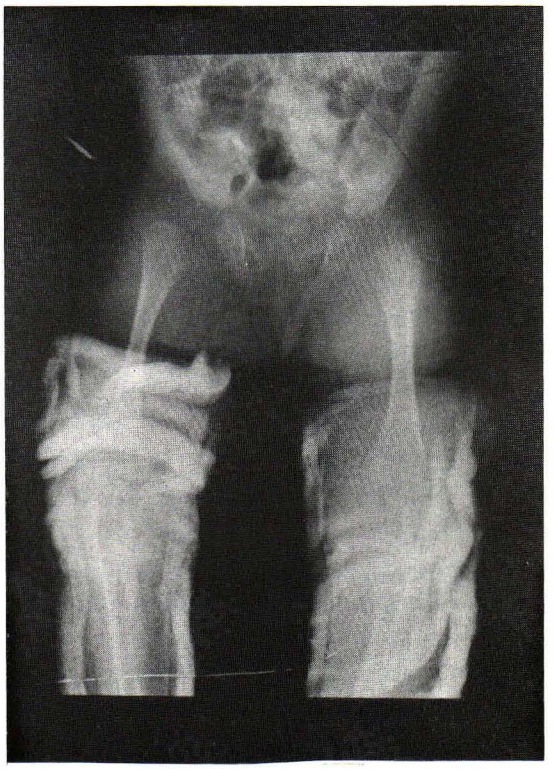

Figure 4. Septic arthritis both hips with secondary subluxation.

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.[13] Congenital neonatal candidiasis has been documented.[14-16] Infants acquired colonization of Candida during labour and delivery. Baley et al.[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.[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 mornal 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.[3,18,19] Initial roentgenography reveals only soft tissue swelling.[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 osteoartritis.[20]

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

Diagnois 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 septicemia,[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 fovourable outcome. The drug of choice is amphotericin B, given slowly intravenously. Nephrotoxicity is the major side effect.[26] Hepatoxicity, 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

1. Baley JE, Kliegman RM, Fanaroff AA. Disseminated fungal infection in very low-birth-weight infants. Clinical manifestations and epidemiology. Pediatrics 1984 Feb; 73(2): 144-52
2. Johnson DE, Thompson TR, Green TP, Ferrieri P. Systemic candidiasis in very low-birth-weight infants (< 1500 grams). Pediatrics 1984 Feb; 73(2): 138-43
3. Klein JD, Yamanchi T, Horlick SP. Neonatal candidiasis, meningitis and arthritis: observations and a review of the literature. J Pediatr 1972 Jul; 81(1): 31-4
4. Chesney PJ, Justman RA, Bogdanowicz WM. Candida meningitis in newborn infants: a review and report of combined Amphotericin B- Flucytosine therapy. John Hophins Med J 1978 May; 142(5): 155-60
5. Smith SD, Tagge EP, Miller J, Cheu H, sukarochana K, Rowe MI. The hidden mortality in surgically treated necrotizing enterocolitis: fungal sepsis. J Pediatr Surg 1990 Oct; 25(10): 1030-33
6. Khan MY. Anuria from Candida pyelonephritis and obstructing fungus balls. Urology 1983 Apr; 21(4): 421
7. Valdivieso M, Luna M, Bodey GP, Rodriguez V, Groschel D. Fungemia due to Torulopsis glabrata in the compromised host. Cancer 1976 Oct; 38(4): 1750-6
8. Baley JE, Kliegman RM, Annable WL, Dahms BB, Fanaroff AA. Torulopsis glabrata sepsis appearing as necrotizing enterocolotis and endophthalmitis. Am J Dis Child 1984 Oct; 138(4): 965-6
9. Butler KM, Baker CJ. Candis: an increasingly important pathogen in the nursery. Pediatr Clin North Am 1988 Jun; 35(3): 543
10. Dick JD, Rosengard BR, Merz WG. Fatal disseminated candidiasis due to amphotericin B resistant C. guilliermondii. Ann Intern Med 1985 Jan; 102(1): 67-8
11. Shek YH, Tucker MC, Vieiana AL, Manz HJ, Conner DH. Malassezia furfur-disseminated infection in premature infants. Am J Clin Pathol 1989 Nov; 92(5): 595-603
12. Dankner WM, Spector SA. Malassezia furfur sepsis in neonates. J Pediatr 1985 Oct; 107(4): 643-4
13. Ruiz-Valasco V, Rosas J. Prophylactic clotrimazole treatment to prevent mycosis contamination of the newborn. Int J Gynecol Obstet 1978 Jan; 10(1): 70-71
14. Dvorak AM, Gavaller B. Congenital systemic candidiasis. N Engl J Med 1966 Mar 10; 274(10): 540-3
15. Lopez E, Aterman K. Intra-uterine infection by Candida. Am J Dis Child 1968 Jun; 115(6): 663-70
16. Johnson DE, Thompson TR, Ferrieri P. Congenital candidiasis. Am J Dis Child 1981 Mar; 135(3): 273-5

17. Baley JE, Kliegman RM, Boxerbaum B, Fanaroff AA. Fungal colonization in the very low-birth-weight infant. Pediatrics 1986 Aug; 78(2): 225-32
18. Baley JE. Neonatal candidiasis: The current challenge. Clin Perinatol 1991; 18: 263-80
19. Pittard WB3d, Thullen JD, Fanaroff AA. Neonatal septic arthritis. J Pediatr 1976 Apr; 88 (4pt1): 621-4
20. Svirsky-Fein S, Langer L, Milbauer B, Khermosh HO, Rubinstein E. Neonatal osteomyelitis caused by Candida tropicalis. J Bone Joint Surg 1979 Apr; 61-A: 455-9
21. Baley JE, Annable WL, Kliegman RM. Candida endophthalmitis in the premature infant. J Pediatr 1981 Mar; 98(3): 458-61
22. Hill HR, Mitchell TS, Matsen JM, Quie PG. Recovery from disseminated candidiasis in a premature neonate. Pediatrics 1974 May; 53(5): 748-52
23. Michelson PE, Rupp R, Efthimiadis B. Endogenous Candida endophthalmitis leading to bilateral corneal perforation. Am J Ophthalmol 1975 Nov; 80(5): 800-3
24. Miller MJ. Fungal infection. In: Remington and Klein, Infecteous diseases of the fetus and newborn infant.2nd ed. Philadelphia: WB Saunders, 1986. 464-506.
25. Tuck S. Neonatal systemic candidiasis treated with miconazole. Arch Dis Child 1980 Nov; 55(11): 903-6
26. Baley JE, Kliegman M, Fanaroff A. Disseminated fungal infections in very low-birth-weight infants; therapeutic toxicity. Pediatrics 1984 Feb; 73(2): 153-7
27. Bennett JE. Flucytosine. Ann Intern Med 1977 Mar; 86(3): 319-22
28. Clarke M, Davies DP, Odds F, Mitchell C. Neonatal systemic candidiasis treated with miconazole. Br Med J 1980 Aug 2; 281(6236): 354
29. McDougall PN, Fleming PJ, Speller DCE, Daish P, Speidel BD. Neonatal systemic candidiasis: a failure to respond to intravenous miconazole in two neonates. Arch Dis Child 1982 Nov; 57(11): 884-6