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A Newborn Baby with Cyanosis and Persistent Lung Infiltration (SNUCH CPC-37)

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This female newborn baby was transferred from a private OB/GY Clinic to SOWHA Children's Hospital NICU on her second day of life, because of low birth weight and cyanosis. She was born via vaginal route at the gestational age of 29 weeks to a 28-year-old primigradiva on Nov. 21, 1987.

On physical examination, the body weight was 1,900gm, height 46cm, head circumference 30cm and chest circumference 28cm. The estimated gestational age was 30-32 weeks by Ballard scoring system. The body temperature was 36.8C, pulse rate 140/min and respiratory rate 64/min. The baby cried weakly. Peripheral cyanosis was noticed. The anterior fontanel was open and flat. The neck was supple. Chest wall retraction was prominent. Breathing sounds were coarse. Heart beats were regular, and no murmur was audible. The abdomen was soft without distension. The liver and the spleen were not palpable. General activity, Moro and sucking reflexes were poor.

Laboratory data: CBC revealed Hb 15.5gm%, Hct 47% and WBC count 11,200 /mm3(stab;7, seg;58, lym;30, mono;5). The blood glucose was 50mg%. Serum Ca and P were 8.0mg% and 6.9mg%, respectively. Serum VDRL was non-reactive. The blood gas analysis(BGA) revealed pH 7.109, PCO2 76.1 mmHg, PO2 39.4mmHg, HCO3 23.4mmol/l, BE -7.2 and O2 sat. 52.3%. The chest X-ray showed diffuse streaky densities on both lung fields (Fig 1).

On admission, because of cyanosis and dyspnea, CPAP with 5cm H_2O and FiO_2 0.9 was applied after endotracheal intubation. Three hours later, BGA revealed pH 7.267, PCO_2 38.7mmHg, PO_2 44.6mmHg, HCO_3 17.2 mmol/l, BE -8.2 and O2 sat. 71.6%.

On the second day, BGA revealed pH 7.295, PCO_2 35.5mmHg, PO_2 70.3mmHg, HCO_3 16.7mmol/l, BE -8.4 and O_2 sat. 91.0%. FiO_2 was reduced to 0.7. Chest X-ray showed newly developed right lung infiltration.

On the third day, the serum total bilirubin increased to 15.7mg%. Phototherapy was done. Two volume exchange transfusion was done twice with O^+ fresh blood (mother; O^+, baby; A^+) until the fourth hospital day. The BGC revealed pH 7.321, PCO_2 33.7mmHg, PO_2 65.4mmHg, HCO_3 16.8mmol/l, BE -7.5 and O_2 sat. 86.2% with FiO_2 0.4. CPAP was stopped and he was placed in oxygen hood with FiO_2 0.6.

On the fourth day, the chest X-ray showed right side tension pneumothorax. BGA revealed pH 7.184, PCO_2 65.1mmHg, PO_2 50.9mmHg, HCO_3 23.7mmOl/l, BE -5.5 and O_2 sat. 86.2%. Chest tube was inserted and right sided pneumothorax improved on the subsequent chest X-ray. The brain sonography revealed both side germinal matrix·hemorrhage and hydrocephalus (Fig. 2).

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On the sixth day, the serum total bilirubin was 9.4mg%. The phototherapy was discontinued. The chest tube was removed. BGA revealed pH 7.355, PCO_2 42.7mmHg, PO_2 54.4mmHg, HCO_3 23.1mmol/l, BE -1.7 and O_2 sat. 86.0%. But chest wall retraction and irregular respiration persisted. On the seventh and the eighth day, the right side pneumothorax reappeared but improved after needle aspiration.

On the tenth day, the chest X-ray showed aggravated right lung pneumonia. The baby was lethargic. CBC revealed Hb 12.8gm%, Hct 39% and WBC count 30,100/mm^3 (stab;4, seg;67, lym;27, mono;2). The culture of endotracheal secretion revealed *Enterobacter cloacae*. The CSF examination revealed WBC 145/mm^3 (poly;30, lym;70), sugar 70mg%, protein 1,100 mg%, Cl 100mEq/L and RBC 34,600/mm^3. Cultures of blood, urine and CSF were negative. Antibiotics, Mefoxin and Gentamicin were switched to Rocephin and Amikin. The brain sonography revealed grade III intraventricular hemorrhage with hydrocephalus. Until the 15th day, her general condition became progressively worse, and she expired on Dec 7, 1987, on the 16th hospital day.

DISCUSSION

In summary, the baby was born premature at 29^{+4} weeks. Birth weight was appropriate for gestational age. On the day of admission, at 1 day of age, respiratory distress and bilateral diffuse streaky infiltrate on the chest roentgenogram were noted. She was treated with CPAP. On the 2nd day of admission, blood gases improved, but the chest P-A showed newly developed right lung infiltration. On the 3rd day, blood gases were stable and CPAP was stopped. On the 4th day, she developed right side tension pneumothorax, which was improved with the chest tube insertion. Brain sonography revealed both side germinal matrix hemorrhage. On the 6th day, the chest roentgenogram showed improvement of the right lung pneumonia, but the chest wall retraction

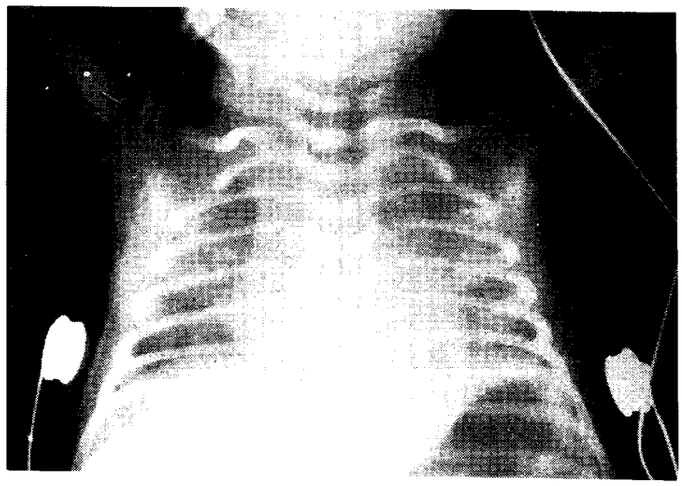

Fig. 1

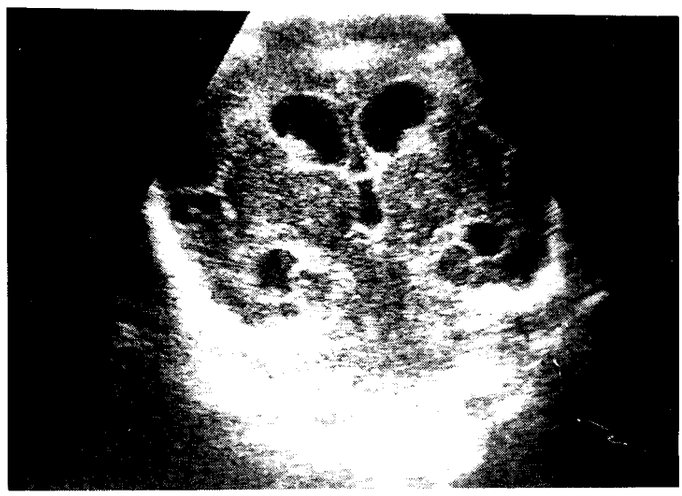

Fig. 2

and irregular respiration persisted, and the blood gas was hypoxic. On the tenth day, the patient was lethargic. There were aggravation of the right lung pneumonia, peripheral blood leukocytosis up to 30,000/mm^3. CSF examination revealed RBC 34,600/mm^3, WBC 145 /mm^3, sugar 70mg% and protein 1,100mg%. Brain sonography revealed intraventricular hemorrhage with hydrocephalus(Fig. 1). The culture of endobronchial secretion grew E. cloacae, but blood, urine and CSF grew nothing. Mefoxin and gentamicin were switched to Rocepin and amikin. Until the 15th day, her general condition got worse and she expired on the 16th hospital day with widespread patch infiltrate on the chest roentgenogram. Her illness

was dominated by initial respiratory distress soon after birth accompanied by bilateral diffuse streaky infiltrate on the chest roentgenogram, followed by apparent improvement on the next day, and, then, subsequent slow respiratory deterioration with leukocytosis and fluctuating pneumonia. Associated findings include intraventricular hemorrhage and CSF abnormalities of unknown significance.

Pneumonia and meningitis in the newborn period share with sepsis in many features of microbiology, pathogenesis and epidemiology, and diagnostic approach to pneumonia and meningitis may be similar to sepsis.

Clinical symptoms or signs of serious infections in the newborn period are very subtle, and antibiotics are usually administered at the least suspicion of sepsis because of difficulty of clinical diagnosis and high mortality. A survey of patterns of use of antibiotics in two newborn nurseries in Boston found that 4.4-10.5% of all infants were being treated for suspected sepsis, but the ratio of infant treated with antibiotics to those from whose blood bacteria were isolated was 15;1 to 28;1 (Hammerschlag *et al.* 1977). Many of suspected sepsis with negative bacterial culture results are caused by a variety of viruses. Dagan *et al.* (1989) could isolate viruses such as enterovirus, respiratory syncytial virus, influenza, parainfluenza, cytomegalovirus, etc, in 55% of 233 previously healthy infants under 3 months of age with suspected sepsis. On the other hand, significant bacterial infection may be present without bacteremia, or bacteremia may be present before but not at the time blood for culture is obtained. Squire and colleagues(1979) noted that results of premortem blood cultures were negative in 7 of 39 infants (18 percent) with unequivocal infection at autopsy. Thus some infant with significant systemic bacterial infection may not be identified by the usual culture technologies.

A variety of organisms, including viruses, fungi, protozoa, chlamydia and mycoplasma, as well as bacteria, can cause neonatal infections. Infections in neonates are acquired from one of four sources. First, a small percent of infections are acquired transplacentally; toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, syphilis, rarely congenital tuberculosis, early onset listeriosis, etc. Second, some infections are acquired from mother during labor and delivery; early- and late-onset group B streptococcus, late-onset listeriosis, chlamydia, etc. Third, most infections are produced by organisms acquired from maternal or hospital source; most gram negative organisms, *S. aureus, S. epidermidis*, etc. Finally, a small portions are acquired outside the hospital in case of home delivery, or readmission to the nursery.

TORCH infections usually manifest with hepatosplenomegaly, microcephaly, chorioretinitis, etc, which are not evident in this patient. Congenital syphilis may be virtually excluded by negative VDRL test. Congenital tuberculosis is usually infected via the umbilical cord or by aspiration of the infected amniotic fluid. In these cases, more prominent hepatomegaly or persistent, rather than transient, pulmonary infiltrate would be expected at birth. When exposed postnatally, signs usually develop within 4 to 8 weeks and include fever, rapid respiration, weight loss, anemia and, in some cases, hepatosplenomegaly (Kendig and Rodgers 1958). *Chlamydia trachomatis* acquired during passage through the birth canal may cause pneumonia as well as conjunctivitis. Pneumonia usually manifests between the fourth and eleventh weeks of life, and in some cases, as early as the second week. It presents staccato cough occurring in paroxysm. Some infants have apneic episodes. Crepitant inspiratory rales are commonly heard; on the other hand expiratory wheezes are distinctly uncommon. A small number require oxygen and even some ventilatory support but mortality is exceptional (Beem *et al.* 1979).

Over the past decades, the major organisms responsible for sepsis neonatorum have changed. Group A streptococci were most common in the 1930s and early 1940s and were replaced by coliform organisms in the late 1940s and 1950s. In the late 1950s and early

1960s coagulase-positive S. aureus caused significant neonatal disease. Group B beta-hemolytic streptococci and coliforms, particularly *E. coli*, have been the most common causative organisms since 1970s. And group D streptococci, *H. influenzae* and Klebsiella-Enterobacter species have also been incriminated. Recently coagulase-negative staphylococci and candida species have emerged as important pathogen, particularly in low birth weight infants.

Two patterns of diseases, early-onset and late-onset, have been associated with systemic bacterial infections during the first month of life. Early-onset disease presents as a fulminant process involving multiple organs in the 1st week of life, while late-onset disease is often manifested as meningitis after the 1st week. This pattern is distinct especially in case of group B streptococcal infection or listeriosis. E coli infections usually do not fit into two distinct clinical syndromes. In early-onset group B streptococcal infection, onset is sudden and follows a fulminant course with the primary focus of inflammation in the lung. The chest roentgenogram shows a reticulogranular pattern with air bronchograms indistinguishable from that seen with uncomplicated hyaline membrane disease.

The patient initially showed respiratory distress with diffuse streaky increased densities on the chest roentgenogram, but improved by the 3rd day with CPAP, though briefly. This course suggests hyaline membrane disease rather than early onset group B streptococcus or listeria disease. In early-onset literiosis, the chest roentgenogram shows infiltrates suggestive of aspiration pneumonitis in most infants (McCraken 1981).

Her main respiratory disease progressed rather slowly over more than 10 days despite combination antibiotic therapy with cefotaxime and gentamicin, or ceftriaxone and amikin. The chest roentgenogram showed patch densities rather than homogeneous infiltration of segments or lobes. These pictures are unusual for common bacteria such as S. aureus or gram negative enteric organisms. In addition, no pathogen was isolated from blood, urine and CSF. Though the culture of endotracheal secretion grew *E. cloacae*, the possibility of contamination by oropharyngeal flora is high when the specimen is obtained through the oral cavity.

Another issue in this patient is the significance of CSF abnormalities. She was shown to have germinal matrix hemorrhage on day 4 of admission by sonography, grade III intraventricular hemorrhage on day 10, both of which are frequently observed in low birth weight infants. On day 10, CSF examination disclosed RBC 34,000/mm^3, WBC 145/mm^3 (poly 30%, lymphocytes 70%), protein 1,100 mg%. The interpretation of these abnormalities are complicated by intracranial hemorrhage. We have no available data regarding interpretation of CSF pleocytosis in a patient with intraventricular hemorrhage. The closest situation as far as we can have would be CSF pleocytosis in a suspected meningitis patient with a traumatic tap. Although the normal number of WBCs in CSF contaminated with blood has not been studied systematically, suggested definitions for normal values include a comparable WBC/RBC ratio in CSF and in peripheral blood (Feigin 1981), or the use of an arbitrary WBC/RBC ratio of 300 (Moffet 1981). Both of these definitions imply that when CSF is contaminated with blood there exist a fixed relationship between the number of RBCs and WBCs in CSF and peripheral blood, in the absence of preexisting CSF pleocytosis. But Rubenstein and Yogev (1985) have shown that the actual WBC counts were approximately 20% of the expected WBC counts in patients without bacterial meningitis, though the actuality was reported to be far higher than the expected in 90% of patients with bacterial meningitis (Mayefsky and Roghmann 1987). Assuming the patient's peripheral blood RBC 4,500,000/mm^3, the expected CSF WBC count is 226/mm^3, while the actual count is 62% of the expected, 145/mm^3. Considering the high protein content in addition to borderline CSF pleocytosis, the patient may be considered to have inflammatory reaction in the

CNS.

During the past decade, advances in intensive care have made the survival of critically ill neonate possible. However, intensive care is not without hazards, and nosocomial infection has been recognized as a major problem in neonatal intensive care units. Recently, coagulase-negative staphylococci and candida species have emerged as important pathogens in neonatal intensive care units. Coagulase-negative staphylococci accounted for as much as 60% of sepsis in a neonatal ICU in a recent report (Freeman *et al.* 1990a). This apparent increase has been associated with increased survival of very-low-birth weight and premature infants, the introduction of invasive procedures for maintaining and monitoring in infants, and prolonged stays in the neonatal ICUs. Infants with bacteremia due to coagulase-negative staphylococci have signs similar to those of bacteremia caused by other invasive organisms, such as group B streptococci and gram-negative enteric bacilli. Two thirds of infants had apnea and bradycardia, and alf had a depressed platelet count or an elevated proportion of immature neutrophils in the differential white cell count. Most infants with neonatal sepsis due to coagulase-negative staphylococci do not have associated focal disease, but bacteremia has been associated with pleural effusion, abscess of the skin and subcutis, meningitis, endocarditis, and necrotizing enterocolitis. Mortality appears to be lower in this disease than in sepsis due to group B streptococci or gramnegative enteric bacilli. In 1982 data set by Freeman and colleagues (1990a), all but 1 of the 38 infants with coagulase-negative staphylococci survived. But hospital stays are prolonged (Freeman *et al.* 1990b).

The possibility of candida infection should be seriously considered. Baley *et al.* (1984) reported 9 clinically-diagnosed and 4 autopsy-diagnosed systemic candida infections in premature infants. All thirteen infants initially had respiratory distress syndrome, and 12 infants developed respiratory deterioration at the onset of candida infection. Eleven of them developed significant pulmonary infiltrate on the chest roentgenogram. Radiologic picture was nonspecific but five infants developed radiologic changes reminiscent of bronchopulmonary dysplasia with infiltrates, atelectasis and overexpansion. Additional presentations included abdominal distension and guaiac positive stools, carbohydrate intolerance, leukocytosis, erythematous rash, hypotension, temperature instability, meningitis, endophthalmitis, etc. The autopsy-diagnosed cases presented at 7 days of mean age, in contrast to 33 day of clinically-diagnosed cases, and may have been heavily colonized at or immediately after birth, leading to the early acute and more fulminant onset. Out of 4 autopsy-diagnosed cases the lungs were involved in three, the CNS and kidney in two.

Kassner and colleagues (1981) reviewed the autopsies of 15 infants dying of systemic candidiasis and noted pulmonary involvement in 14 infants. Eight of them were premature infants, with gestational age of 26 to 33 weeks. Shortly after birth each infant had respiratory distress owing to respiratory distress syndrome or perinatal sepsis with pneumonia. The initial radiologic findings were consistent with respiratory distress syndrome in most of the infants. Six infants showed complete or partial radiologic clearing within a few days. Within a few days after the onset of sepsis and respiratory deterioration, all the infants had patch areas of consolidation; these became confluent over days or weeks.

Reviewing 27 infants with systemic candidiasis, Faix (1984) concluded that CNS infection is very common (64%) in infants with systemic candidiasis, and that abnormal CSF in infants with positive blood, urine, or deep-tissue cultures for candida suggests CNS infection even if cultures are negative. Analysis of CSF in cases with CNS involvement revealed that CSF leukocyte ranged 2-260/mm^3, erythrocyte 0-2800/mm^3, protein 15-825 mg%. He suggested that computed tomography or ultrasonography may facilitate detection of parenchymal abscess or granuloma, but the microscopic size of

many of these lesions may preclude detection by such technique.

Pneumocystis carinii pneumonia in infants may progress slowly over 1 to 4 weeks, and patients exhibit increasingl severely tachypnea, dyspnea, intercostal retractions, and flaring of ala nasi. The initial roentgenogram often shows haziness spreading from the hilar region to the periphery, which assumes a finely granular, interstitial pattern. The peripheral granularity may progress to coalescent nodules. CNS involvement in *Pneumocystis carinii* infection is unknown.

As a possible etiologic agent of infection in this patient, I have mentioned TORCH, congenital and neonatal tuberculosis, chlamydia, gram-negative enteric bacilli, group B streptococci, coagulase-positive and -negative staphylococci, candida and pneumocystis. Of these, candida is the most probable cause of pneumonia and probably associated meningitis and sepsis in the patient. Candida albicans account for most of candidiasis in the newborn, though *C. tropicalis* and *C. parapsilopsis* have been reported.

Clinical diagnosis:

1. Prematurity
2. Hyaline membrane disease
3. Pneumothorax, tension
4. Hyperbilirubinemia
5. Intraventricular hemorrhage
6. *Candida albicans* infection, involving the lung, CNS, and possibly other organs

Pathological findings (Dr. Chi)

Postmortem examination revealed patchy consolidations of the lungs, a small thymus and a subcapsular hematoma of the liver. Microscopically, multiple foci of candidal abscesses and granulomas were found scattered through the lungs (Fig. 3), kidneys, liver, brain and heart. Vessels were often stuffed with candidal organisms (Fig. 4). Postmortem blood and lung culture grew *Candida albicans*. There were multiple fibrin thrombi in the lungs and brain. The thymus showed acute involution. However, no evidence of thymic dysplasia was noted. The heart showed patent ductus arteriosus and multifocal candidal abscesses (Fig. 5) in the myocardium. The brain showed diffuse dilatation of the ventricular system. There was bilateral germinal matrix hemorrhage with extension into the ventricles and subarachnoid space(Fig. 6). The ependymal lining was stained with old blood. Microscopically numerous focal granulomas with candidal organisms were seen in the brain and cerebellum.

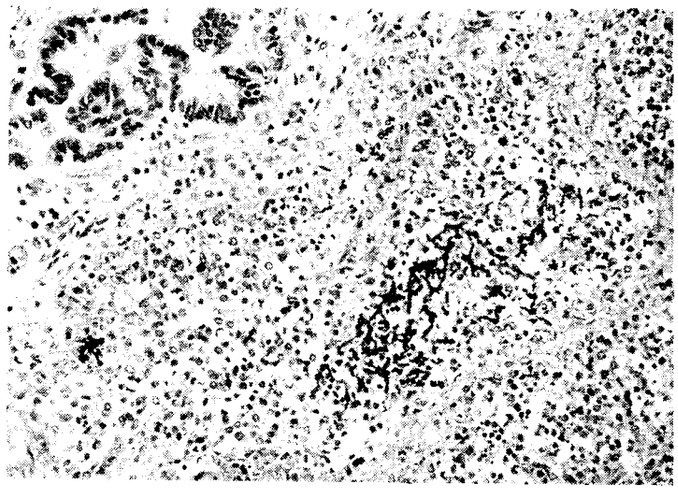

Fig. 3

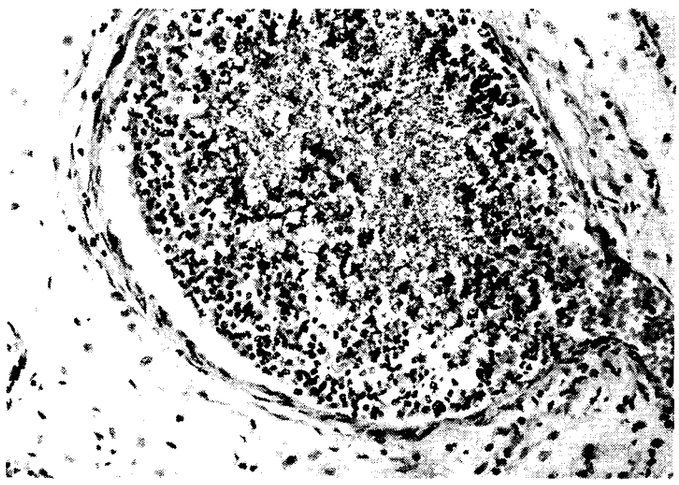

Fig. 4

In summary, this 16 days old female baby's fatal clinical course was complicated by systemic candidiasis, mimicking clinically hyaline membrane disease and secondary pneumonia. The source of primary infection is undetermined. However, based on the history of intubation and most severe involvement of the lung,

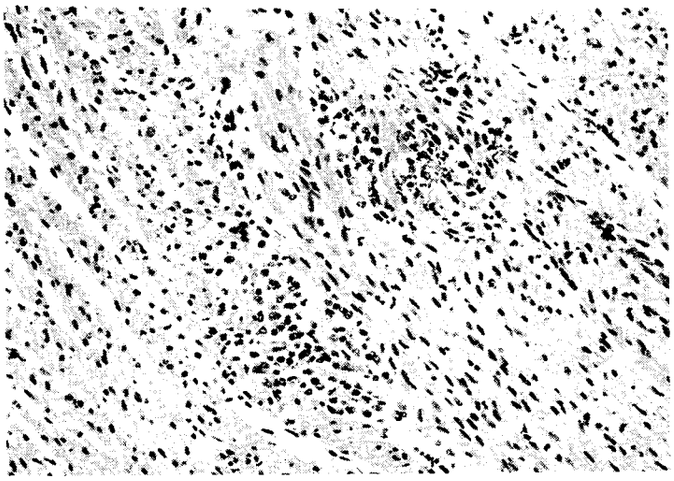

Fig. 5

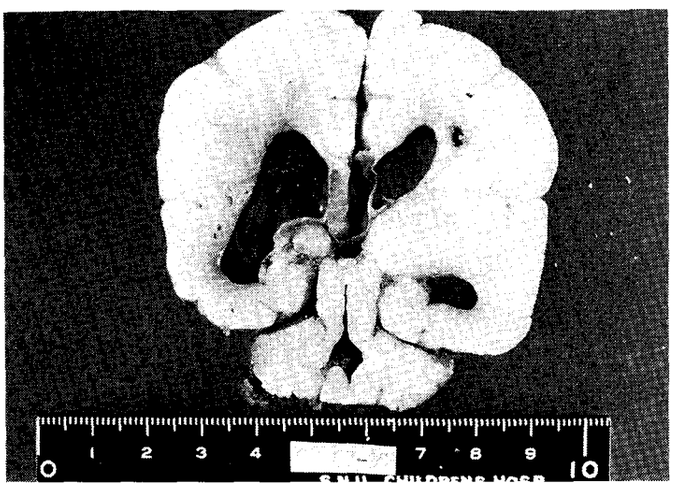

Fig. 6

the respiratory tract is the probable source. The candidal organisms are proved to be candida albicans by culture. The pattern of dissemination, involving the lung, brain, kidney, myocardium, etc suggested the immunocompromised host. However, The thymus was normal, and sufficient neutrophilic or granulomatous inflammation around fungal organisms were present. This case would be grouped into neonatal disseminated candidiasis. Disseminated intravascular coagulation, demonstrated microscopically as intravascular fibrin microthrombi could be the sequence of event of the infection.

Pathological diagnosis

1. Systemic candidiasis (*Candida albicans*), involving lungs, kidney, liver, brain and heart

2. Disseminated intravascular coagulation with multiple fibrin thrombi in the lungs and brain

3. Intraventricular hemorrhage, brain

4. Patent ductus arteriosus

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