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Klebsiella Sepsis in a Premature Baby†

(SNUCH CPC-45)

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CASE HISTORY

This male baby was born to a 39 year old mother via Caesarian section because of breech presentation and premature rupture of the membrane. The gestation period was 30 weeks and the birth weight was 1200gm. The mother had had 3 spontaneous abortions and 4 therapeutic abortions. During this pregnancy she suffered from a severe toxemia of pregnancy for which she received magnesium sulfate and hydralazine.

The immediate postnatal activity of the baby was fair although Moro and sucking reflexes were poor. Apgar scores at 1 minute and 5 minutes were 3 and 7, respectively. The muscle tone was very poor and he was slightly cyanotic. Because of respiratory difficulty the baby was intubated and intermittent positive pressure breathing was applied.

Physical examination of the baby at nursery showed a pulse rate of 142 per minute. The skin was not cyanotic, and response to tactile stimuli was poor. Respiration was irregular, and intercostal retraction was noted. The chest X-ray film at nursery showed findings of respiratory distress syndrome. Therefore surfactant was given through the trachea. The chest X-ray film after surfactant instillation showed improvement on the next day. However, on the third day he showed pulmonary interstitial emphysema, and arterial blood gas analysis showed acidemia and retention of carbon dioxide.

The laboratory data showed hemoglobin 15.1 gm%, red blood cells 4.45 m/cmm, white blood cells 1150/cmm with 57% segmented, 38% lymphocyte and 8% monocyte. The platelet count was 230x103 /cmm and reticulocyte was 7.1%. Blood glucose was 148 mg/dl on the first day. Remaining laboratory data including blood chemistry were unremarkable. The blood gas data are summarized in Table 1.

On the 7th day the baby showed hyperbilirubinemia (total bilirubin 15.4 mg/dl), for which an exchange transfusion was done. On the same day he was noted to have a grade II-III/IV systolic murmur along the left sternal border. Mefenamic acid was given with the suspicion of patent ductus arteriosus, and the murmur subsided subsequently. The patient remained stationary until the 15th day when

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abdominal distention and signs of upper gastrointestinal hemorrhage were noted. He was placed on vancomycin for this. On the 21st day both chest X-ray film and blood gas analysis data showed some improvement. He was extubated and thereafter remained in relatively stable condition until the 46th day, when sudden pallor was noted. He became flaccid. A blood transfusion was given. However, the patient did not respond to management and lapsed into a lethargic state. He expired on the next day.

DISCUSSION

Discussant(Dr. Chang); In summary, this 1.20-kg male infant who was born at 30 weeks gestation to a 39-year-old mother had many problems during the obstetric, perinatal, and neonatal periods, such as perinatal asphyxia, RDS, PIE, PDA, gastrointestinal hemorrhage, and hyperbilirubinemia. These problems had been resolved sucessfully through the neonatal period and he remained in a relatively stable condition until the 46th hospital day. However, on the 46th hospital day, his general condition suddenly deteriorated. In spite of the management, including a blood transfusion, he succumbed in the relatively short period of 24 hours. So, I think that the main concern of this discussion is the differential diagnosis of the various causes of the postneonatal sudden death of this VLBW infant.

In general, many different categories of diseases and conditions should be considered in differential diagnosis of sudden infant death (Table 2). But, in this case protocol, some problems including congenital heart disease, arrhythmia, or anomalies that may cause acute airway obstruction can easily be excluded by the physical findings and clinical history. Also, hypoglycemia or electrolyte disturbance associated with the endocrine or metabolic diseases were never supported by any laboratory findings or clinical history. So, I can narrow the range of the causes of death into the common problems encountered during the post-extubated period of VLBW infant; infection, anemia, apnea, chronic hypoxemia associated with BPD, feeding intolerance or GER, and aspiration, etc.

May I see the radiologic findings of this infant at this point?

Dr. Yeon(Radiology); The initial chest X-ray film shows a diffuse bilateral haziness with air bronchogram and deteriorated cardiac border compatible with severe respiratory distress syndrome. The follow up chest X-ray film after surfactant instillation shows some improvement, but the chest X-ray film on the 3rd day

Table 1. Summary of hospital course and findings

		Ventilator mode				ABGA			
		FiO_2	RR	PIP	IT	pH	PCO_2	PO_2	HCO_3
# 1HD Surfactant	2 hrs after	1.0	60	30	0.30	7.113	60.3	202.4	19.3
	6 hrs after	0.9	60	27	0.30	6.87	98.7	181.0	18.3
# 2HD	12 hrs after	0.75	90	27	0.30	7.209	49.7	180.3	19.6
	24 hrs after	0.6	90	27	0.30	7.366	37.2	89.2	21.3
# 3HD	7 AM	0.6	90	27	0.30	7.225	53.8	106.3	22.2
	12 MD	0.6	100	30	0.25	7.074	77.0	53.4	22.5
# 7HD		0.62	60	30	0.17	7.360	53.1	63.0	30.3
#15HD		0.68	69.8	24	0.15	7.291	56.6	48.5	27.2
#21HD		CPAP				7.335	43.2	178.2	23.0
#22HD	After extubation					7.322	489.7	156.2	28.2

HD: Hospital day; ABGA : Arterial blood gas analysis

Table 2. Differential diagnosis of postneonatal sudden death

Congenital problems; CHD, arrhythmia, other anomalies of the head and neck
Infection; bacterial or viral infection
Endocrine or Metabolic diseases; electrolyte disturbance or hypoglycemia
Anemia;physiologic or pathologic
Apnea associated with sudden death; idiopathic or symptomatic
Chronic hypoxemia associated with BPD
Other conditions; seizure, drug abuse or withdrawal
Other conditions that may cause airway obstruction or suffocation; tumorous conditions or aspiration

suggests the findings of pulmonary interstitial emphysema. On the 7th hospital day, cardiomegaly and increased pulmonary vascularity appeared. Thereafter, the subsequent follow-up chest X-ray shows streaky densities on both lower lung fields and the hilar area, and these findings are compatible with the radiologic findings of BPD. On the 15th hospital day, the radiologic findings of the abdomen show the dilatation of the bowel gas.

Dr. Chang: I have some questions about the clinical history. First, was there any event associated with the sudden deterioration of this infant? Second, how long was the oxygen therapy continued after extubation?"

Dr. Kim(Cheil Hospital); After extubation, he was relatively stable until the 46th hospital day. On the 46th hospital day, retinal examination was done for the evaluation of retinopathy of prematurity. Immediately after the examination, a sudden pallor developed and he became flaccid and lethargic. On the next day, he expired. Duration of oxygen therapy after extubation was about 10 days. So, I thought that his clinical course after extubation was compatible with the classic BPD, but its severity was not enough to cause sudden death.

Dr. Chang: Thank you. Because of the history of blood transfusion and the radiologic findings of BPD, I have to consider two possibilities; anemia and BPD.

Anemia during the neonatal period and ensuing several months has many different etiologies(Table 3). Among these hemolysis and bleeding associated with the perinatal event can easily be excluded by the clinical history and laboratory findings. Catastrophic massive intracranial hemorrhage, especially intraventricular hemorrhage of the preterm infant, often cause severe anemia and sudden death in infants(Table 4). But intracranial hemorrhage of a preterm infant is usually associated with a perinatal or neonatal event, and the clinical course of this infant after extubation had been stable for a relatively long period until he died. So, it is less likely that intracranial hemorrhage caused the anemia and death of this infant. Frequent sampling and nutritional deficiency during the neonatal period may often aggravate in physiologic anemia or anemia of prema-

Table 3. Etiologies of anemia in the neonatal period and ensuing months

Bleeding	1. Fetal or placental hemorrhage
	2. Postpartum hemorrhage
	· cephalhematoma
	· liver or spleen rupture
	· GI bleeding
	· intracranial hemorrhage: massive IVH
Hemolysis	1. Immune hemolysis; ABO or RH incompatibility
	2. Nonimmune hemolysis
	· infection;CMV, toxoplasmosis, syphilis bacterial sepsis
	· DIC
	· hereditary RBC disorder; spherocytosis, enzyme defect hemoglobinopathies
Diminished RBC production	1. Diamond-Blackfan syndrome
	2. Congenital leukemia
	3. Infection; especially Rubella
	4. Drug
	5. Physiologic anemia or anemia of prematurity

Table 4. Clinical features of periventricular-intraventricular hemorrhage

Three basic syndromes	Clinical features
Catastrophic deterioration	Inexorable evolution in minutes to hours
	Neurologic features
	Stupor -- coma
	Respiratory disturbance--apnea
	Generalizes tonic seizure
	"Decerebrate" posturing
	Pupils fixed to light
	Eyes fixed to vestibular stimulation
	Flaccid quadriparesis
Saltatory deterioration	Stuttering evolution;hours to day
	Neurologic features
	Altered level of consciousness
	Altered motility(usually decreased)
	Hypotonia
	Abnormal tight popliteal angle
	Abnormally eye position or movement or Both
	Respiratory disturbance(?)
Clinically silent syndrome	Unexplained fall in hematocrit
	Failure of hematocrit to rise after transfusion

turity. So, I think that the cause of anemia in this infant is aggravated physiologic anemia or anemia of prematurity. Other listed etiologies on the table associated with decreased RBC production are not compatible with the clinical course of this infant. Because anemia is one of the many contributing factors of symptomatic apnea, and apnea could be associated with the sudden death of an infant, I consider the anemia of this infant to be one of the factors that may have caused sudden death.

Data from Stanford NICU graduates show that BPD represents 50% of postneonatal deaths in infants between 1001 and 1500 gm birth weight, and accounts for 20% of infant deaths. These data suggest that pulmonary dysfunction, chronic respiratory failure, and other associated problems, such as pulmonary hypertension, may be the important risk factors for sudden death. The last radiologic findings of this infant are compatible with those of BPD, but it is less likely that BPD is the main cause of death, because the duration of O_2 therapy after extubation was only 10 days, further O_2 therapy was not required, and its severity was not enough to cause death. I think that BPD may be one of the possible contributing factors, but it's not a main factor.

As mentioned above several conditions have already been excluded by the physical findings, such as airway anomalies or tumorous conditions of the head and neck that may cause airway obstruction or suffocation. But, aspiration of food material may occasionally occur and causes acute airway obstruction, especially in the preterm infant, due to cricopharyngeal incoordination or GER etc. Although no event was mentioned associated with aspiration or suffocation in this protocol, I want to include aspiration as one of the possible causative factors, since I have frequently experienced these problems during the feeding of sick infants.

Because neonatal infection, especially bacterial sepsis, may often have insidious onset and subclinical symptoms, infectious disease should not be excluded in differential diagnosis of the cause of sudden infant death. If this infant had an infectious disease, it is more likely that it was a bacterial and hospital infection. Viral infectious diseases of congenital or acquired are not compatible with the clinical, physical and laboratory findings of this infant.

Apnea is a common problem in the newborn infant, especially in the preterm infant (Table 5). Idiopathic apnea of prematurity is commonly encountered in the early neonatal period and persists for a variable period, and it occurs mainly because of immaturity of the respiratory center and respiratory muscle. Symptomatic apnea is a frequent manifestation of general problems in newborn infants; infection, anemia, GER, BPD, metabolic disorder such as hypoglycemia, and convulsion etc. If this infant has apnea, it is more likely to be symptomatic

Table 5. Etiologies of apnea in the newborn

Idiopathic apnea of prematurity
Symptomatic apnea with causes
1. RDS
2. Anemia
3. GER
4. PDA
5. Hypoxia or Hypercarbia
6. Metabolic disorders
7. BPD
8. Drug
9. convulsion

apnea. I have already discussed the several possible causative factors for the sudden death of this infant, and I think that all of these factors discussed above may cause symptomatic apnea. In general, the risk of SIDS increases in siblings of infants with SIDS, infants with apnea with infancy, and prematurely born infants. So, I think that it is possible that apnea is one of the main causative factors of sudden death.

At this point, I want to summarize and tabulate the discussed possible causative factors because it is impossile to exclude completely any of them due to the limited nature of the available clinical information(Table 6). So I conclude that apnea was the main causative factor of death and, that the interaction and contribution of other factors such as sepsis, BPD, anemia, GER, and aspiration contributed to the onset of the apnea and the sudden death of this infant. But, if all of these factors are completely excluded by the autopy findings, the diagnosis of sudden death of this infant will be categorized as SIDS by exclusion diagnosis.

Table 6. Summary of possible causative factors associated with the sudden death of this infant

1) Bacterial sepsis
2) Chronic hypoxemia associated with BPD
3) Anemia probably due to aggravated anemia of prematurity
4) Symptomatic apnea associated with infection, anemia, GER, BPD, aspiration
5) Aspiration that may cause suffocation

PATHOLOGICAL FINDINGS(Dr. Chi)

Postmortem examination showed an emaciated boy with a mild scrotal edema and jaundice. The heart showed patent ductus arteriosis and foramen ovale, signifying persistent fetal circulation. The lungs were somewhat consolidated grossly, and microscopically showed patchy bronchopneumonia and intra-alveolar hemorrhage(Fig 1). There were scattered foci of lipid-laden multinucleate giant cells in the alveoli, indicating milk aspiration(Fig 2). The pneumonia was more in the left lung. No aspirated material was seen in tracheo-bronchial trees. The alveolar septa were not particularly thickened anywhere. In other words no evidence of bronchopulmonary dysplasia was present. The liver was grossly enlarged and dusky gray with congestion. Histologically fatty change and marked intracellular cholestasis were seen. The kidneys showed findings of acute tubular necrosis grossly and microscopically(Fig 3). The stomach showed hemorrhagic gastropathy but remaining G-I tract was unremarkable. The brain showed no intraventricular hemorrhage. There were however,

Fig 1. Microscopic picture of the lung, showing intra-alveolar hemorrhage and bronchopneumonia. H&E, X40

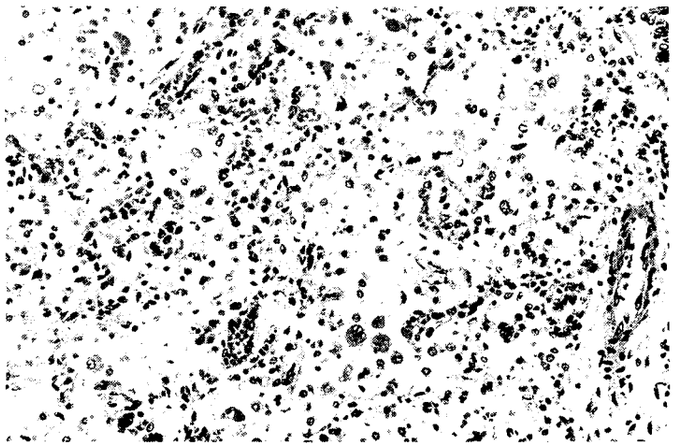

Fig 2. Photomicrograph of the lung shows an increased number of alveolar macrophage and occasional inflammatory cells. H&E X100

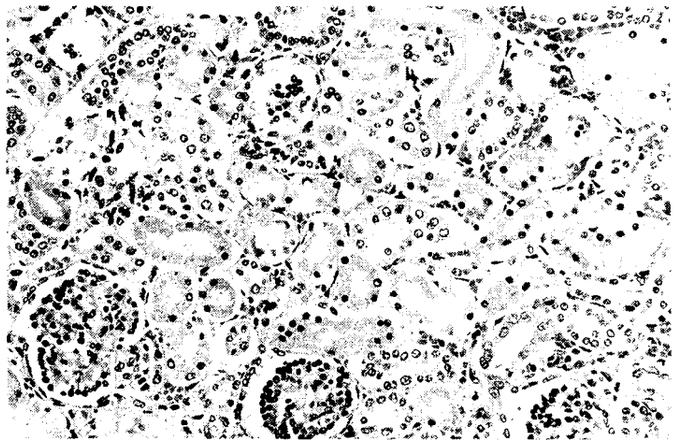

Fig 3. Kidney section reveals necrotic tubular epithelia, indicating acute tubular necrosis. The glomeruli are intact. H&E X100

Fig 4. Retinal section shows proliferative angiopathy showing numerous spindle cells and blood vessels. H&E X250

findings of hypoxic-ischemic encephalopathy. Both eyeball showed proliferative angioretinopathy (Fig 4). Postmortem blood culture and lung culture showed Klebsiella pneumoniae in both samples.

Pathologic diagnosis

1. Klebsiella pneumoniae sepsis
   - Bronchopneumonia with intraalveolar hemorrhage, lungs
   - Massive cholestasis with fatty change, liver
   - Hemorrhagic gastropathy
   - Hypoxic ischemic encephalopathy
2. Persistent fetal circulation
   - Patent ductus arteriosus
   - Patent foramen ovale
3. Proliferative retinopathy, bilateral
4. Milk aspiration, terminal
5. Acute tubular necrosis, kidneys
6. Pleural and peritoneal effusion
7. Accessory spleen(2), hilum
8. Inguinal hernia, right
9. (Prematurity)

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