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RECORD OF CLINICOPATHOLOGICAL CONFERENCE OF THE INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASE RESEARCH, BANGLADESH

A ONE - YEAR - OLD FEMALE CHILD WITH MALNUTRITION, PERSISTENT DIARRHOEA, AND SHOCK

CASE 2 - - 1991

Presentation of Case

A one - year - old girl was admitted to the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) with diarrhoea of two months and fever of two days duration.

The infant belonged to a poor family, the father earning about US $120 per month. She was said to have had no major illnesses in the past but had not received any immunisations. She was breast - fed and also given a dilute preparation of cow's milk, rice powder, sugar and water at home. She was the sixth child; three siblings died during the first month of life.

The present illness started 2 months before admission with passage of loose or liquid stools 5 - 7 times a day without blood, mucus, fever, or vomiting. The infant was given oral rehydration saline and various unspecified medications at home. The diarrhoea persisted and 2 days before admission, the patient developed a mild grade fever.

In examination, her peripheral pulses were imperceptible, the heart rate was 160 per minute, respirations were deep with a rate of 40 per minute. Rectal temperature was 34.0°C. The infant was severely dehydrated, lethargic, pale and wasted. She weighed 4.55 kg and had bilateral pitting oedema. (Her weight for age was 47% of NCHS median (1). There were intercostal retractions with a few crepitatins in the base of the right lung. The abdomen was distended and tense with sluggish bowel sounds. Liver and spleen were not palpable.

The child was admitted to the Intensive Care Unit. A random blood sugar was normal. Dehydration was rapidly corrected by an intravenous solution containing Na^+ 133 mmol/l, K^+ 13 mmol/l, Cl^- 98 mmol/l and HCO_3 - 48 mmol/l. Despite hydration the child remained lethargic and hypothermic with imperceptible peripheral pulses. A clinical diagnosis of septicaemia was made and ampicillin and tobramycin were started intravenously after drawing a blood sample for culture (later turned out to be sterile). The haematocrit was 26% for which she was transfused with 60 ml of fresh blood. The white cell count was 14,954/cmm with polymorphs 48%, bands 04%, lymphocytes 43%, monocytes 04%, metamyelocytes 01%, serum potassium was 2.25 mmol/l, TCO_2 8.8 mmol/l and protein 37 g/l. The electrolyte abnormalities were corrected with additional intravenous potassium and bicarbonate solutions. An X - ray of the chest on admission showed opacities in the right paracardiac region suggestive of bronchopneumonia. A plain X - ray of the abdomen in erect posture done on the same day revealed multiple fluid levels. The child was kept on nothing - by - mouth with nasogastric suction and intravenous fluid ration of a polyelectrolyte solution with 5% dextrose. Metronidazole was started by injection for possible anaerobic organisms causing enterocolitis. Stool microscopic examination revealed many fat globules and a stool culture did not yield *Salmonella*, *Shigella* or *Vibrio*.

The features of paralytic ileus improved on the second hospital day and the child was given a low lactose diet containing milk and rice powder which she tolerated. On the third hospital day the stool became soft. However, her respiratory status progressively deteriorated with the appearance of coarse crepitations and a gasping respiration on the 4th hospital day requiring oxygen. There was no improvement in peripheral perfusion. A repeat chest x - ray showed bilateral diffuse

infiltrate. On suspicion of either a Gram negative pneumonia resistant to tobramycin or a staphylococcal pneumonia, ceftriaxone and cloxacillin were started intravenously. In spite of all these efforts she died on the same day.

Differential diagnosis

Dr.S.M. Akramuzzaman*: In summary, this problem concerns an infant with marasmic kwashiorkor, persistent diarrhoea, severe bronchopneumonia, septicaemia, hypothermia, electrolyte imbalance and paralytic ileus. The details of her dietary history and nutritional status before the onset of diarrhoea were not known. She might have become malnourished either by getting feeds of low nutrient density or from the consequences of persistent diarrhoea where there is substantial loss of macro (2) and micronutrients (3). A decreased intake of food due to poor appetite, withholding of food and increased catabolism during diarrhoea might have further added to the development of severe malnutrition.

Acquisition of infection leading to severe pneumonia and septicaemia, hypothermia, and electrolyte abnormalities can all be explained by the severity of malnutrition. The interaction between nutritional status and resistance to infectious disease has long been recognised (4). Due to the poor immune status, the offending pathogen could easily colonise and invade the respiratory and gastrointestinal epithelium, giving rise to bronchopneumonia, septicaemia and persistent diarrhoea.

The aetiopathology of persistent diarrhoea is multifactorial. Preexisting malnutrition might have resulted in prolongation of diarrhoea (5) in this child. Lactose digestion and absorption is decreased in persistent diarrhoea (6). The diarrhoea improved following introduction of low lactose diet and antibiotic therapy. Therefore, the child possibly had lactase deficiency which could be due to continued damage of the intestinal brush border by a pathogen which was adequately treated by broad spectrum antibiotics.

Hypothermia in this child could be due to a decreased basal metabolic rate (7) and alteration in thermoregulation which are frequently found in malnutrition (8) and also in septicaemic condition. Decrease in cardiac output (9), a prolongation of the systemic circulation time (8), and a decreased peripheral blood flow might have contributed to hypothermia.

Total body potassium is decreased in malnutrition (10) and this was further aggravated by the loss of potassium with diarrhoeal stool. Diarrhoea, septicaemic shock or hypothermia all might have contributed to the development of metabolic acidosis.

Now I shall try to focus on the probable causes of severe and progressive pneumonia and septicaemia in this child. The child deteriorated even after administration of intravenous ampicillin, tobramycin and metronidazole for four days. *Haemophilus influenzae* and Pneumococcus which are usually sensitive to ampicillin and Gram negative bacilli sensitive to tobramycin or an anaerobe can be excluded. The X-ray of the chest was not suggestive of staphylococcal pneumonia because of the absence of pneumatocelles, pleural effusion or pneumothorax which are commonly present in this condition. However, considering the immunocompromized condition, a rapidly progressive and fulminating course (11) and predominant involvement of the right lung, staphylococcal pneumonia can not be excluded in this child. A Gram negative organism could have caused such progressive fatal pneumonia in this severely malnourished infant. Pseudomonas infection may be ruled out as most of the strains are sensitive to tobramycin. Klebsiella pneumonia was not considered because typically there should have been involvement of the upper lobe (12) associated with bulging of fissure or abscess formation or cavitation and is usually sensitive to tobramycin.

It is also possible that the infant had viral pneumonia which is difficult to diagnose. Respiratory syncitial virus (RSV) is the commonest viral pathogen amongst children admitted to out hospital (13) with diarrhoea and acute respiratory infection. It causes a patchy type of bronchopneumonia and rarely causes severe pneumonia. Parainfluenza virus usually causes mild upper respiratory infection and is associated with croup. Therefore, these two viruses are unlikely to have caused such severe pneumonia in this child. Influenza virus (11) often causes fulminating pneumonia in children, but it is usually bilateral, occurs in epidemics and is commonly associated with croup which were absent in this patient. Adenovirus infection could be a possibility because it may cause severe pneumonia in children (14) and may be associated with gastroenteritis. Cytomega-

* Medical Officer, Clinical Research Centre, ICDDR,B, Dhaka, Bangladesh.

lovirus remains another cause of fulminating pneumonia in this immunocompromized host. However, it usually infects neonates who acquire the infection from the nursery or from the birth canal during delivery (15).

Atypical pneumonia is less likely in this patient as the onset of this condition is usually subacute and the chest signs are minimal but occasionally it causes an acute bilateral interstitial pneumonia (16). Again the immunocompromized state of the infant failure to respond to antibiotics, and an absence of leucocytosis point towards atypical pneumonia.

There is also a possibility of *Pneumocystis carinii* pneumonia (17) in this child because it usually occurs in an immunocompromized host, has an abrupt onset and follows a progressive fatal course.

Lastly, considering the endemicity of pulmonary tuberculosis in Bangladesh, it should also be considered a likely diagnosis since the patient was not vaccinated with BCG.

An aetiological diagnosis of pneumonia can rarely be made on clinical and radiological criteria. Isolation of the organism by culture is the best recourse. Conclusive sources of culture are blood, pleural fluid, material obtained by lung puncture or lung biopsy specimens. This patient had a negative blood culture but a single blood culture may not yield positive results in more than 60% of cases. Considering the fulminating nature of the pneumonia in this child where conventional antibiotics were ineffective, invasive diagnostic techniques such as lung puncture were indicated.

In conclusion, it seems to me that the child died of severe bronchopneumonia and septicaemia with underlying severe protein energy malnutrition. The probable etiology of pneumonia or septicaemia is either a virus, Gram negative bacilli or pneumocystis carinii.

Dr. S.A. Chowdhury: Why was lumbar puncture not done for spinal fluid examination?

Dr. Akramuzzaman: Lumbar puncture was not done as there were no definitive signs or symptoms of meningeal irritation. The lethargy was thought to be due to hypokalaemia, acidosis and shock. Moreover, a lumbar tap in this child with severely compromised respiration could have been fatal.

Dr. Chowdhury: How was a diagnosis of septicaemia made without a positive blood culture?

Dr. Akramuzzaman: This was a clinical diagnosis on the basis of one or more of the following findings: fever, toxicity, shock, disseminated intravascular coagulation, and, often a source of infection or a predisposing host defect. In my opinion, this child was correctly diagnosed as a case of septicaemia on clinical grounds.

Dr. Chowdhury: Were the ears examined?

Dr. Akramuzzaman: Yes, the ears were carefully examined and no abnormality could be detected.

Dr. R. B. Sack: I think Dr. Akram has discussed most of the possible etiologies of severe pneumonia and septicaemia in a severely malnourished child. To me, *Pneumocystis carinii* might have been the pathogen in this immunocompromized child.

Clinical diagnosis

Marasmic kwashiorkor
Bronchopneumonia
Persistent diarrhoea

Pathological discussion

Dr. Moyenul Islam*: The autopsy was done eleven and one-half hour after death on this pale and malnourished female infant. The abdomen and the peritoneal cavity appeared unremarkable. Stomach, small bowel and appendix appeared unremarkable. Caecum and proximal colon contained pale yellow faecal matter. Serosa and muscular coats of large bowel appeared unremarkable. The mucosa of the large bowel showed scattered congested patches but there was no obvious colitis or ulceration. The mesenteric lymph nodes were small and pale. The liver was soft, yellow and grossly appeared fatty. The gall-bladder appeared unremarkable. The spleen had a small gray indurated area with a geographic outline which I suspected to be an infarct. The kidney grossly appeared unremarkable. All areas of both lungs were diffusely consolidated with rubbery consistency and had brownish purple appearance on the cut surface. The heart appeared unremarkable. Microscopy of the lung showed interstitial inflammation, thickening of the septa, congestion, oedema and hyaline membrane formation within alvioli. These are features of viral pneumonia. There were also focal alveolar infiltration of polymorphs and macrophages. Inflammatory exudate was present within the lumen of the bronchi.

* Pathologist, ICDDR,B.

At the start of the autopsy we aspirated material from both lungs for culture by trans-thoracic puncture. The culture was sterile. Since very delicate bacteria like haemophilus or pneumococcus may not survive prolonged storage of the body in the cold room, Gram stains were done on lung sections to identify bacteria. Bacteria were not seen, instead yeasts were found (Fig. 1) which were also stained by PAS method. Many of these were inside macrophages within alveolar spaces. These yeasts were thought to be candida, but characteristic hyphae were absent. I considered the possibility of Histoplasma and Blastomycosis, but on morphological appearance, these were ruled out. In systemic candidates, blood stream invasion and dissemination to other organs of the body would be expected, but these were not seen. Probably it was a case of localised involvement of the lung where candida was inhaled through the respiratory tract. The spleen showed thrombosed vessels alongside a recent haemorrhagic infarct. Sections of the large bowel from the congested patches showed haemorrhage in the lamina propria and there were thrombi in the underlying venules and capillaris. We have noticed similar thrombi in a few other patients with diarrhoea particularly in infants, where no diarrhoeal pathogens were identified. We wonder if these lesions represent Shwartzman reaction. The small intestine showed slight to moderate autolysis but, in spite of that, intranuclear inclusions, characteristic of cytomegalovirus (CMV) were seen in epithelial cells. Perhaps CMV infection has been the cause of persistent diarrhoea in this child. Inclusions were also seen in tubular epithelial cells of the kidney (Fig. 2), confirming that the child had disseminated CMV infection. The child had marked fatty change in the liver. Lymphoid tissue was hypoplastic in lymph nodes and in intestinal mucosa.

In my opinion the primary underlying disease in this patient was severe malnutrition with an immunocompromized status, associated with CMV infection, leading to persistent diarrhoea and superinfection with candida, probably by endobronchial inhalation, leading to pulmonary candidiasis.

Dr. M.R. Khan: Does CMV cause persistent diarrhoea?

Dr. Islam: All of our previous cases which

Fig. 1. Candida *(yeasts) in alveolar species of lung tissue. Gram Stain X 330.*

Fig. 2. Cytomegalovirus *inclusion in renal tubular epithelial cell. H and E Stain X 120.*

had CMV involvement of bowel, had persistent diarrhoea.

Dr. N.H. Alam: If the diarrhoea was due to CMV, how will you explain improvement with antibiotics in such a short time?

Dr. A.K. Azad: The patient did not have severe diarrhoea. Along with CMV infection of the small intestine, there was bacterial overgrowth, and I agree with Dr. Akram that the broad spectrum antibiotic therapy might have helped the patient in improving diarrhoea.

Dr. P.K. Bardhan: Did you find any CMV particularly in the colonic section?

Dr. Islam: No, I did not. For detection of CMV one has to examine multiple blocks from different parts of all organs. We normally examine a limited number of blocks from each organ.

Dr. M.A. Salam: To explain the cause of infarct in the spleen, can it be due to septicaemia?

Dr. Islam: It could be due to intravascular thrombosis. I found thrombi in the small bowel wall, in the large bowel wall and in the spleen. This could have been a consequence of a septic process.

Dr. Sack: Did you look for CMV in the lungs?

Dr. Islam: I have looked carefully in the lungs for CMV inclusions without success. But one has to examine multiple sections from different parts of the lung before one could be absolutely certain.

Dr. Sack: The pathology you showed in the lung really looks like a viral process rather than that of candida. Candida is a rare primary pathogen without being disseminated widely. We did not see inflammatory process and hyphae. So, I would question whether the candida you found was a secondary invader rather than a primary infection.

Dr. Islam: Yes, I agree. The findings of interstitial infiltration, the oedema, marked congestion and hyaline membrane formation are more in favour of a viral type of pneumonia and candida is probably a superinfection on that.

Dr. Salam: Finally, as to a cause of death, do you think that respiratory failure could be a primary cause of death in this particular child?

Dr. Islam: I would think so. The thickening of the alveolar septa, formation of hyaline membrane and pulmonary oedema would have impeded gaseous exchange in the lung.

Dr. Akramuzzaman: What could be the source of this virus?

Dr. Islam: This is an ubiquitous virus and almost our entire population by the age of two years would have acquired the virus. The virus is usually transmitted through saliva from mother or other siblings.

Anatomical diagnosis

a) Marasmic kwashiorkor with an immunocompromized status
b) Cytomegalovirus infection with persistent diarrhoea and pneumonia
c) Superinfection with candida leading to pulmonary candidiasis.

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