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

A 30 - YEAR - OLD WOMAN WITH FEVER, DIARRHOEA, AND WASTING

CASE 1 - 1991

Presentation of Case

A 30 - year - old woman was admitted to the Dhaka based clinical facility of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) because of low grade fever of 3 months, diarrhoea of 10 days, and poor appetite of 7 days duration.

The patient came from a very low socio - economic strata. She worked as a daily labourer and lived in the city slum. Her husband had died one year previously with swelling of the legs and face, and her only son (3 years old) disappeared a few months before her admission.

Her state of health prior to the present illness was not known. Her fever was irregular, appearing in the evening but was not associated with chills. The diarrhoea was characterized by watery motions without any blood, 15 to 20 times a day. Her menstruation has been regular, the last menstrual period being 20 days before admission. Further details of the history were not elicited at admission.

On physical examination the patient appeared cachectic weighing 34 kilograms. Her body temperature was 36.5 °C; pulse, 80/minute; respirations, 26/minute; and blood pressure, systolic, 80 and diastolic, 40 mm Hg. She was moderately dehydrated, pale and had gross pitting oedema of her legs and face. She had no cyanosis or jaundice.

The patient was conscious. Her abdomen was soft, and not distended, but the costovertebral angles at the back were tender. Bowel sounds were audible. Liver and spleen were not palpable. No lymphadenopathy was found. The heart and lungs were apparently normal, as also were other systems.

A random blood sugar measured by a glucometer (Reflolux, Mannheim Boehringer, West Germany) was 1.9 mmol/L. The patient was given 200 ml of 25% glucose by vein, and was maintained with 5% dextrose in normal saline. Subsequently the blood sugar was normal. She passed no urine for 16 hours after admission; thereafter she passed a normal volume of urine.

A microscopic examination of stool showed ova of *Ascaris lumbricoides* and larvae of *Strongyloides stercoralis*. Stool culture was negative for *Salmonellae*, *Shigellae*, *Vibrio cholerae* and *Campylobacter jejuni*. Laboratory examination of blood showed haematocrit 26%, total leukocyte count of 42,000/mm^3 with 88% neutrophils, 2% band forms, 7% lymphocytes, 1% monocytes and 2% metamyelocytes in the differentials; there were mild to moderate amounts of toxic granules. A chest radiograph showed patchy opacities on both lungs and obliteration of the right costophrenic angle with evidence of pleural thickening on the right side, suggestive of bilateral pulmonary tuberculosis with right sided pleural effusion. Sputum for acid fast bacilli was not obtained. She was rehydrated and maintained with oral rehydration solution. Anti - tuberculosis therapy with daily doses of streptomycin 750 mg, rifampicin 450 mg and isoniazide 300 mg was initiated; but streptomycin was temporarily replaced by intramuscular injections of gentamicin, 30 mg every 8 hours, due to a clinical suspicion of septicaemia. A blood sample was sterile on admission. On the third hospital day, the urine was positive (1+) for protein, and contained 2 to 3 red blood cells, 60 to 70 pus cells, 6 to 8 epithelial cells, and a moderate number of bacteria per high - power field. A catheterised urine sample was sterile on culture. A repeat haematocrit on the sixth hospital day was 23%. The patient was transfused with 450 ml of whole human blood. She had, after

admission, frequent brownish liquid stools and one bout of bloody watery stool, all having an offensive smell.

On the ninth hospital day, she suddenly developed distension and tenderness of the abdomen with absent bowel sounds, and signs of peripheral circulatory failure. The blood pressure was not recordable. Radiologic examination of the abdomen revealed a raised left dome of the diaphragm due to collection of gas in the stomach, and a distended large bowel without fluid levels. An oval opacity of approximately 10x5 mm was seen at the level of the 3rd lumber vertebra on the left, suggesting a calcified lymph node. She was then placed on continuous nasogastric suction, intravenous ampicillin 500 mg every 6 hours, metronidazole 250 mg every 8 hours, and intravenous fluids. Her condition did not improve and she died the next day.

Differential Diagnosis

Dr. Amal K. Mitra*: This case presents the problem of a 30-year-old cachectic woman who presented with a history of 3-months of low grade irregular fever, 10-days of watery diarrhoea, and 7-days of anorexia. She died 10 days after hospital admission. The fact that she was a day-labourer, a widow, and that she lived in a slum having no access to good sanitation and hygiene suggest her poor socioeconomic background, and susceptibility to malnutrition and infections. Before proceeding to a discussion of this case, we will review the radiographic findings in the chest.

Dr. Habibur Rahman**: This is a posteroanterior radiograph of the chest obtained on admission to this hospital. The right hemisphere of the diaphragm is shaggy in outline. The costophrenic angle in the right side is hazy. The cardiophrenic angles are clear. Patchy opacities are seen in the upper, middle and lower zones of both lung parenchyma, with some scattered translucent areas in the upper and mid zones. There is also pleural thickening in the right costophrenic region. The heart is normal in size, but slightly shifted to the left, due to rotation of the patient to the left side. The radiograph illustrates typical findings of pulmonary tuberculosis with pleural effusion in the right side. The important differential diagnosis could be neoplasm or fungal infiltrates.

Dr. Mitra: The major diagnostic features of the case then are the clinical presentations with irregular fever and wasting associated with suggestive radiological findings. In Bangladesh, tuberculosis should be the initial diagnosis in such a patient who is poor and probably immunocompromized, and who lives in an environment of poverty and poor sanitation. The diagnosis was, however, not conclusive in the absence of a positive history of exposure to persons with known tuberculosis, a positive tuberculin skin test, or isolation of acid fast bacilli (AFB). However, her husband had died one year earlier of an unknown cause. We do not know whether other persons in the neighbourhood suffered from a similar illness. Tuberculin skin test was not done in this case. A negative test would not have precluded the diagnosis of tuberculosis since she was severely malnourished and could have been anergic. In any event, the simplest and most reliable test would have been to perform an acid fast stain on sputum. Unfortunately this also was not done.

Constitutional symptoms such as fever, nonproductive cough and extensive patchy nonlobar infiltrates on the chest radiograph might suggest atypical pneumonia, the most common causes being *Mycoplasma pneumoniae* and adenoviruses in adults. A close association of pneumonia due to cytomegalovirus and *Pneumocyctis carinii* in immunocompromised hosts, such as in acquired immunodeficiency syndrome (AIDS) has been reported (1). Fortunately no patient with AIDS has been reported so far from Bangladesh. Anorexia, weight loss and pleural effusion are suggestive of bronchogenic carcinoma. However, there was no radiological evidence of discrete mass or atelectasis.

I shall now consider the probable causes of death in this patient who was treated for tuberculosis. Acute disseminated tuberculosis is usually of rapid onset and fatal. The diagnosis is all too often missed and revealed only at autopsy (2). The chest radiograph classically shows miliary mottling, but it may take about 4 to 6 weeks to become recognizable. As with tuberculosis in the immunocompetent host, extrapulmonary tuberculosis can occur at virtually any site in the body. I can reasonably exclude tuberculous meningitis

* Senior Medical Officer, Clinical Research Centre (CRC), ICDDR,B, Dhaka, Bangladesh.
** Radiologist, ICDDR,B.

and tuberculomas involving the central nervous system on the basis that the patient had no altered sensorium, headache, convulsions, signs of meningeal irritation, focal neurological signs or cranial nerve palsies. History of loose motions, abdominal distension and loss of appetite could suggest intestinal and peritoneal dissemination of tuberculosis (2). We are not sure whether she had recurrent attacks of bowel irregularities. She terminally developed ileus. May I ask Dr. Lutfor Rahman whether the patient had any ascitis.

Dr. Lutfor Rahman*: Ascitis was not recognized in the clinical findings.

Dr. Mitra: One can only speculate that abdominal distension could be due to a collection of ascitic fluid or an acute abdomen or both.

Oliguria of the patient for an initial period of 16 hours could be due to dehydration; however such symptoms as impaired renal function along with tenderness at the renal angles may suggest urinary tract infection or tuberculosis of the urinary tract. Microscopic haematuria and pyuria in apparently sterile urine could be due to an existing urinary tract tuberculosis which, by itself, does not lead to growth of any bacteria by ordinary culture. The other explanation of the sterile urine could be the fact that the patient already received gentamicin.

Haematogenous spread of tubercle bacilli to the adrenals may lead to adrenal insufficiency. I cannot exclude adrenal tuberculosis conclusively, since the patient had gastrointestinal symptoms, lethargy, weight loss, hypotension and hypoglycaemia on admission. However she was conscious.

Regarding treatment it is very difficult to comment whether the addition of pyrazinamide could alter the course of the disease. In very severely ill patients some authors claim the additional benefit of using prednisolone (2).

I shall now consider another prominent diagnostic possibility in this case. Although the patient presented with watery diarrhoea, it is important to notice that she passed several motions of brownish liquid stools and one bloody stool after admission. In addition, her stools were very offensive in smell. Infection due to *Entamoeba histolytica* is quite prevalent in Bangladesh (3). Amoebiasis should be suspected in hospitalized patients with poor socioeconomic background, because such undernourished populations have a heavier load of intestinal parasites (4). Haematophagous trophozoites of *E. histolytica* are the most important pointers to the diagnosis. Stool microscopy may fail to detect the parasite, but specimens obtained by scraping mucosa of the rectum have a greater chance of detecting *E. histolytica*. Metronidazole was given to this patient for a suspicion of toxic colitis, but it was started only 24 hours before the patient died. Features of toxic colitis are not uncommon in fulminating cases of amoebiasis (5). The sudden deterioration of her general condition on the ninth hospital day, together with features of circulatory collapse and acute abdomen, were probably due to perforation of the colon with acute peritonitis. Haemorrhagic watery stool detected on one occasion after admission suggests necrotizing enterocolitis as a complication of invasive amoebiasis (6).

The other important clinical problem of the patient was hypoglycaemia detected at admission. Hypoglycemia can occur in diarrhoeal patients due to a number of factors, such as anorexia, increased catabolism, elevation of glucose counter-regulatory hormones and improper gluconeogenesis (7). Butler *et al* in their autopsy series reported a similar observation of hypoglycaemia as the immediate cause of death in 9% of 140 patients (8).

Did the patient have septicemia? The synergistic interaction of infection and malnutrition is well recognized on the basis of clinical observations and epidemiologic data (9). Chandra suggested that several facets of immunocompetence are adversely affected in states of malnutrition leading to increased susceptibility to severe infections (10). Butler *et al* in their autopsy study found septicemia to be the immediate cause of death in 27% of cases (8). In our patient, the presence of high leukocytosis with a shift to the left indicated the possibility of sepsis which, of course, could not be ruled out by a single sterile blood culture. A similar blood picture could also be due to a condition of disseminated tuberculosis (11).

The generalised oedema of this patient was not due to cardiac failure because there was no dyspnoea, raised jugular venous pressure or enlarged tender liver. Moreover, her heart sounds were normal, and there was no cardiomegaly on chest x-ray. The chance of

* Medical Officer, CRC, ICDDR,B.

hepatic cirrhosis can also be ruled out because the patient had no clinically apparent jaundice or hepatosplenomegaly or other signs of portal hypertension. There was abdominal distension, but ascitis was not clinically marked. Could it be glomerulonephritis? There was no hypertension, and microscopic examination of urine did not show gross haematuria. Oedema is more likely to be nutritional, resulting from a number of contributing factors like poverty, prolonged illness, anorexia and anaemia. The husband also had swelling of his legs and face at the time of death. This important family history could suggest that the man also suffered from severe malnutrition.

Dr. Tahmeed Ahmed: Was the diagnosis of amoebiasis considered during treatment of this patient?

Dr. Mitra: No, this diagnosis was not considered, presumably because the patient on admission had only watery diarrhoea in absence of the parasite in the stool by microscopic examination. But the frequent passage of brownish liquid stools having an offensive smell should have raised a suspicion of intestinal amoebiasis. A previous published report from ICDDR,B showed that 51% of patients with amoebiasis had non-bloody, watery, or mucoid stools (12).

Dr. N. H. Alam: Did you try to isolate acid fast bacilli from other specimens?

Dr. Mitra: Other diagnostic procedures, such as naso-tracheal aspirate, bronchoscopy or biopsy were not done in this case.

Clinical Diagnoses

Pulmonary tuberculosis with probable dissemination into the abdomen and urinary tract.
Septicaemia.
Intestinal amoebiasis with ?perforation of large intestine.

Pathological Discussion

Dr. A. N. Alam*: Dr. M. Islam, will you give us your postmortem findings?

Dr. M. Islam**: Postmortem examination of the cadaver was carried out after obtaining signed informed consent of the next of kin. On opening the abdomen, approximately 500 ml of thick fibrino-purulent fluid was found in the lower part of the peritoneal cavity. Also scattered thin patches of purulent exudate were seen on surface of mesentery, mesocolon, greater omentum and transverse colon. Small bowel wall and mucosa were unremarkable, but a few scattered tubercles were seen on its serosal surface. Numerous discrete and large confluent deep ulcers with geographical contours consistent with amoebic colitis were present throughout the large intestine. Two perforated ulcers were seen in the ascending and transverse colons.

Mesenteric lymph nodes were enlarged and showed caseation. The liver was enlarged, soft and fatty; it revealed multiple small abscesses. Trophozoites of *E. histolytica* were seen in exudate within the abscesses in the liver (Fig. 1). The kidneys showed pale cortex and no other abnormalities. Both lungs were indurated and fibrotic, and had fibrous pleural adhesions and caseations. Tuberculous granulomata (presence of AFB confirmed by Ziehl-Neelsen stain) were found in the lungs, small intestine, and hilar and mesenteric lymph nodes.

Dr. A. N. Alam: We have seen similar patients in the past, whose stool did not show the presence of *E. histolytica* on repeated microscopy, although the patients were clinically suspected for amoebiasis. Dr. Islam, what is your experience with these postmortem examinations?

Dr. Islam: I can remember a few cases in which *E. histolytica* were detected only at autopsy. These patients generally had severe pancolitis, associated with diffuse superficial mucosal necrosis. The amoebae were seen

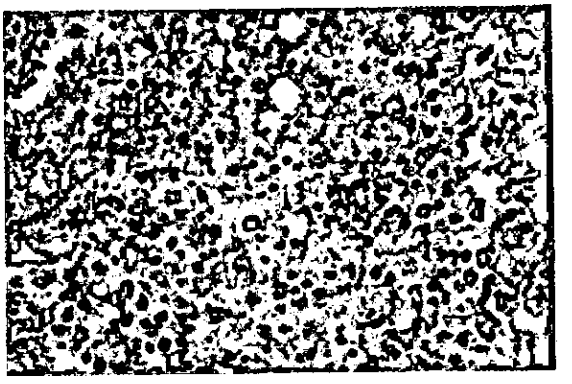

Fig. 1 – Amoeba in necrotic liver abscess (PAS stain, x120).

* Head, CRC, ICDDR,B
** Pathologist, ICDDR,B

invading healthier tissue deeper to the necrotic mucosal layer (Fig. 2). Amoebae were absent in the necrotic layer as well as in the luminal contents.

Fig. 2 – Amoeba in colonic submucosa, lying deeper to the necrotic mucosa (PAS stain, x120).

Dr. M. S. Akbar: Dr. Islam, why did the clinicians miss the diagnosis of amoebiasis?

Dr. Islam: Perhaps the necrotic layer formed a barrier to free shedding of amoebae and pus cells in the faeces. Also, colonic function might have been lost in these patients due to diffuse mucosal necrosis in the large bowel, resulting in watery diarrhoea which misled the clinicians. Serological tests (e.g. precipitin test or counterimmunoelectrophoresis) should be more widely used to diagnose amoebiasis in such patients (13).

Dr. Rafiqul Islam: Dr. Mitra, why was the clinical diagnosis of hepatic amoebiasis missed in this patient?

Dr. Mitra: The patient did not have the classical signs and symptoms, such as high fever, chills and enlarged tender liver. Moreover, the incidence of hepatic amoebiasis has been greatly reduced in our country, probably due to indiscriminate use of metronidazole in diarrhoeal patients (14). At this hospital, hepatic amoebiasis was not seen in 140 autopsies of patients who died with diarrhoea including 22 having invasive amoebiasis (8).

Dr. Aminul Islam: Urinary seeding of tuberculosis, suspected clinically, was not confirmed at autopsy. Dr. Islam, do pyuria and haematuria in this case suggest urinary tract infection?

Dr. Islam: Urinary tract infection in women of poor socioeconomic background is quite common. But similar urinary abnormalities have also been reported in 25% of patients with acute hepatic amoebiasis. This has been explained by the effect of circulating "immune complexes" formed with amoebic antigens on kidney function of the patients (13).

Dr. A. N. Alam: Dr. Mitra, what would be your recommendation from the experience of this patient?

Dr. Mitra: I would conclude that in very sick patients with prolonged diarrhoea in a developing country, the possibility of invasive amoebiasis should be considered even in the absence of pus cells and trophozoites of *E. histolytica* in the stool.

Anatomical diagnoses

Pulmonary fibrocaseous tuberculosis with dissemination to hilar and mesenteric lymph nodes and small intestine.
Severe amoebic colitis with perforation and acute peritonitis.
Hepatic amoebiasis with formation of multiple small abscesses.

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