GASTRO-INTESTINAL MUCORMYCOSIS IN INFANCY

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Recently there have been increasing numbers of reports of mucormycosis in man. Most of the cases have occurred in adults who were also suffering from some form of malignant disease or diabetes mellitus, or who were having prolonged steroid and/or antibiotic treatment.[1] Among children, cerebral mucormycosis has been reported and reviewed by Borland.[2] There are, however, only a few recorded cases of gastro-intestinal mucormycosis in infancy.[3,4]

The following is a report of 5 African children, whose ages ranged from 12 days to 1 year, with fatal mucormycosis in various parts of the alimentary tract.

CASE 1

This male infant, aged 1 year, weight 16 lb., was admitted to hospital with a history of 2 weeks' diarrhoea. The stools were blood-streaked, and the infant was said to have been vomiting, coughing, and short of breath for 1 week before admission.

On examination the temperature was 100°F. (rectal), the pulse rate was 138 per minute and respirations were 36 per minute. The child was malnourished, having thin, sparse hair with wasting of the muscles. There was clinical evidence of severe dehydration. Apart from the finding of bilateral Harrison's sulci of the chest, the rest of the physical examination was normal.

Treatment consisted of intravenous fluid replacement, 2-hourly feeds of a half-cream milk formula, and chloramphenicol ('chloromycetin palmitate') orally in doses of 125 mg. every 6 hours. The patient was still passing frequent stools on the 4th hospital day, when he began to vomit. As a result, signs of dehydration re-appeared. The vomiting increased in severity on the 5th hospital day and the rectal temperature rose to 102·2°F. The child became tachypnoeic, there was reduced air entry at the right base, and the abdomen became distended. Serum-electrolyte estimations at this stage revealed a hyponatraemia (Na—117 mEq./litre). The sodium content of the intravenous fluid was increased and the oral milk feeds were reduced in amount. Despite these measures, the child died suddenly on the morning of the 6th hospital day.

Postmortem Findings

The body was that of a poorly nourished African male child. The abdomen was distended and the skin showed areas of depigmentation. The hair was sparse and receded at the temples. There was mild oedema of both legs. The peritoneal cavity contained 4 oz. of purulent fluid and showed an acute peritonitis. There were flakes of purulent and fibrinous material on the visceral and parietal peritoneum. The oesophagus showed slight mucosal congestion, but was otherwise normal. There was no evidence of ulceration. The stomach contained a large perforation, 4·5×3 cm., on the posterior wall. The serosal surface in this region was dark black in colour and the discolouration had spread to the surface of the pancreas in contact with the stomach. There was an extensive area of blackish necrosis involving the whole of the greater curvature and almost the entire posterior wall. This had extended onto the middle third of the lesser curvature and for a small distance onto the anterior wall. The necrotic zone was surrounded by an area of intense hyperaemia. The small bowel appeared healthy. A small area of black necrosis, 2 cm. in diameter, was present on the surface of the transverse colon in contact with the pancreas and posterior wall of the stomach. The appendix was healthy. The splenic artery was thrombosed throughout its length. The spleen weighed 25 G. and showed large areas of recent infarction. The liver (257 G.) presented the diffuse light-yellow colour of fatty change.

Microscopic examination of the stomach showed ulceration of the mucosa and diffuse necrosis of the sub-mucosa and muscle with infiltration by numerous neutrophils, lymphocytes and

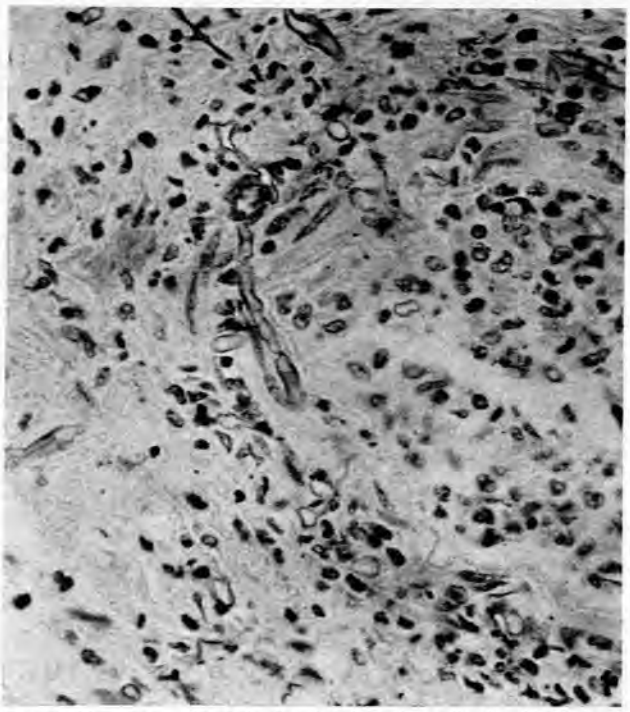

Fig. 1. Non-septate fungal hyphae invading the wall of a blood vessel (haematoxylin and eosin × 480).

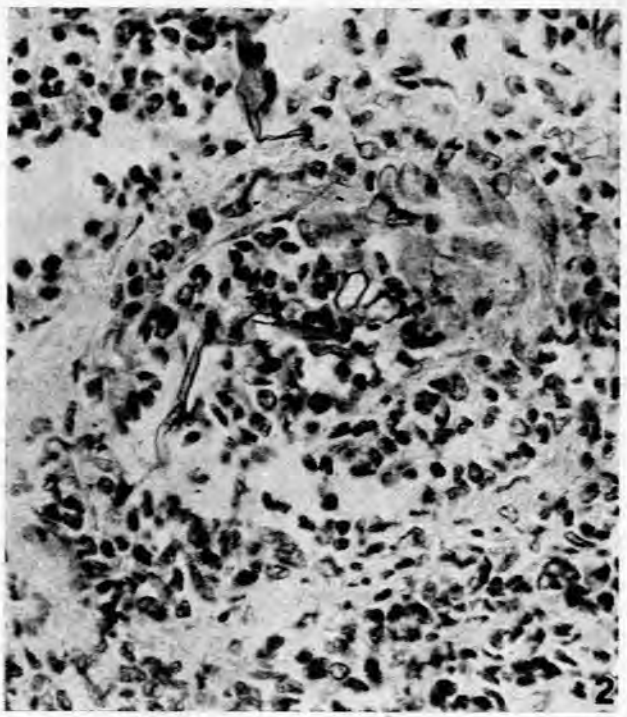

Fig. 2. Section through oesophageal ulcer showing fungal hyphae and inflammatory infiltrate in the submucosa (haematoxylin and eosin × 480).

histiocytes. The smaller vessels contained antemortem thrombi. Scattered throughout these areas of necrosis, and especially marked in the region of the small blood vessels, were many branching non-septate fungal hyphae (Fig. 1). Microscopic examination of the transverse colon through the area of necrosis showed an appearance similar to that seen in the stomach. Fungal hyphae were present throughout the wall, and the serosal surface showed the presence of an acute peritonitis. The pancreas showed some atrophy of the parenchymal cells. The superficial surface was necrotic and contained numerous neutrophils; in this area there were also fungal hyphae similar to those noted in the stomach. The spleen showed severe congestion of the pulp with widespread infarction of the parenchyma, especially at the periphery. The splenic artery contained a recent antemortem thrombus and fungal hyphae were noted in the wall of the vessel. The liver showed moderate, diffuse, fatty change.

CASE 2

A male infant, aged 7 months, was admitted to Baragwanath Hospital with a week's history of diarrhoea, vomiting and sores in the mouth.

Physical examination revealed a moribund infant with signs of protein malnutrition, viz. atrophic scalp hair and a nutritional dermatosis. The child was severely dehydrated, with acidotic respiration. The tongue was dry and the lips were cracked. There was a purulent discharge from the left ear. The child was stuporose and had a poor muscle tone. The serum-sodium level was 116 mEq./litre, serum-potassium level 3·2 mEq./litre, and the carbon dioxide combining power 7·5 mEq./litre. Intravenous-fluid therapy was started immediately, but the infant died 6 hours after admission.

Postmortem Findings

The body showed evidence of severe malnutrition. A pressure ulcer was present over the occiput. The oesophagus showed marked mucosal congestion, and an ulcer 3 cm. in length was present immediately above the cardiac sphincter. The floor of the ulcer contained necrotic material. The wall surrounding the ulcer presented a blackish discolouration and at one point this had involved the trachea. The mediastinum appeared normal. The remainder of the gastro-intestinal tract showed no obvious lesion. The liver (240 G.) was soft and smooth and diffusely yellow in colour. Apart from bilateral bronchopneumonia the remaining morbid anatomical findings were essentially negative.

Microscopic examination of the oesophagus in the region of the ulcer showed destruction of the mucosa and infiltration of the submucosa and muscularis by neutrophils, lymphocytes, and histiocytes. Branching non-septate fungal hyphae were present throughout the wall and were seen invading the blood vessels (Fig. 2). Areas of necrosis were present and the inflammatory process involved the mediastinal surface of the trachea. The lungs showed a diffuse confluent bronchopneumonia. Section of the liver showed the presence of marked diffuse fatty change with congestion of the sinusoids.

The histological findings in the remaining organs were essentially negative.

CASE 3

This male twin infant, aged 4½ months, was admitted to hospital with a 3 weeks' history of diarrhoea and anorexia.

His weight on admission was 6¾ lb., and he was thin, rachitic and undernourished. There was clinical evidence of dehydration. The stools contained blood and mucus. *Shigella flexneri* and a salmonella organism were cultured from them.

The child was in hospital for 46 days, during which period he required intravenous infusions of saline, blood and plasma on no less than 6 separate occasions for relapses of diarrhoea and recurrence of dehydration. The following antibiotics were administered in turn during the 6½ weeks he was in hospital: procaine penicillin, 1 ml. intramuscularly, daily for 5 days; oxytetracycline, 50 mg. every 6 hours, for 3 days; chloramphenicol, 62·5 mg. every 6 hours, for a period of 10 days, and a further period of 5 days; sulphatriad, 0·25 G. every 6 hours, for 6 days; and streptomycin, 0·25 G. daily by intramuscular injection, and 30 mg. orally every 4 hours, for 3 days.

The weight of the patient had risen from 6¾ lb. on admission to 10¾ lb. by the 27th hospital day. The haemoglobin level at this

stage was 9·5 G. per 100 ml. Thereafter there was steady deterioration in the condition of the infant. His weight fell progressively to 6¾ lb. while the haemoglobin level fell to 6·5 G. per 100 ml. by the 41st hospital day. The patient developed oral thrush and a pressure sore on the scalp, and he began to vomit. Clinical signs of pneumonia with crepitations at the right base and left apex appeared 48 hours before death. For this the patient was treated with penicillin in doses of 250,000 units every 6 hours by intramuscular injection.

Postmortem Findings

The body was that of a poorly nourished African male infant. Both lungs showed early bronchopneumonic consolidation and atelectasis. The oesophagus and stomach appeared normal. The duodenum, jejunum and colon showed marked mucosal hyperaemia. In the ileum there was a small mucosal ulcer 0·4 cm. in diameter. The remaining morbid anatomical findings were essentially negative.

Microscopic examination of the jejunum showed some congestion and oedema of the mucosa with diffuse infiltration by lymphocytes, plasma cells, neutrophils and eosinophils. Section of the ileum showed a small mucosal ulcer, the floor of which was composed of necrotic debris. The base of the ulcer was heavily infiltrated by branching non-septate fungal elements. Numerous sporing bodies were also observed. The surrounding sub-epithelial tissues showed infiltration by acute and chronic inflammatory cells. Section of the lungs showed acute bronchopneumonic consolidation.

CASE 4

A female infant was admitted to hospital on the 10th day of life with a history of diarrhoea for 5 days.

The birth weight had been 7 lb. 2 oz., but on admission to hospital her weight had fallen to 5 lb. 1 oz. The anterior fontanelle was depressed and there was marked loss of elasticity of the skin. The tongue was dry. Respirations were rapid, but the lungs were clinically clear. The abdomen was distended with gas. A rectal swab culture resulted in a growth of *B. proteus* and coliform organisms.

Intravenous fluid was given, and by the second hospital day the weight had risen to 6 lb. 4 oz. and oral feeds with expressed breast milk were started. However, later in the day the child collapsed suddenly. Intramuscular coramine was injected, but the child died the following day with clinical evidence of sclerema of the subcutaneous tissues.

Postmortem Findings

The body was that of a poorly nourished African female infant. There was marked diminution in the subcutaneous fat and there was some depression of the anterior fontanelle. The abdomen was slightly distended. Both pleural sacs contained 30 ml. of blood-stained serous fluid. The peritoneal cavity contained 90 ml. of viscid, yellow, purulent material which was adherent to the loops of bowel and the parietal peritoneum. The oesophagus and the cardia of the stomach showed mild mucosal congestion and oedema. There was an elliptical perforation 1½ × 1 cm. on the posterior wall of the stomach near the upper third of the greater curvature. The wall of the stomach surrounding the perforation showed intense congestion and oedema. The small and large bowel were both normal. The remainder of the morbid anatomical findings were essentially negative.

Microscopic examination of the stomach at the edge of the perforation showed a coagulative necrosis of all 3 layers of the wall, with acute inflammatory-cell infiltration. The blood vessels showed an acute arteritis and contained numerous polymorphonuclear leucocytes. Scattered throughout the walls of these vessels were numerous non-septate fungal hyphae similar to those seen in the previous cases.

CASE 5[5]

This premature male infant was born at Baragwanath Hospital and weighed 3 lb. Meconium was passed normally until the 6th day of life. Then no stools were passed for the succeeding 3 days. On the 9th day the infant vomited a feed of expressed breast milk and some slight abdominal distension was noted. Two watery brown stools were passed: one of them was blood-stained. An X-ray picture of the abdomen showed a gross pneumoperitoneum.

Perforation of the bowel was diagnosed and the child was given antibiotic cover with intramuscular penicillin and streptomycin. Oedema of the abdominal wall and scrotum was noted on the 11th day, together with persistence of the abdominal distension. Thrush had appeared in the mouth. This was treated with nystatin, 50,000 units, every 8 hours. Despite these measures the child deteriorated steadily and died on the 12th day of life.

Postmortem Findings

There was a severe meconium peritonitis. The peritoneal cavity contained 100 ml. of green purulent fluid. A large perforation, 2 cm. in diameter, was present 1 inch below the splenic flexure on the anterior wall of the descending colon. There were some yellow flecks of inspissated meconium adjacent to the perforation and free in the peritoneal cavity. Loops of bowel were densely adherent to the lateral abdominal wall on the left. The remaining morbid anatomical findings were negative.

Microscopic examination of the colon at the site of the perfora-

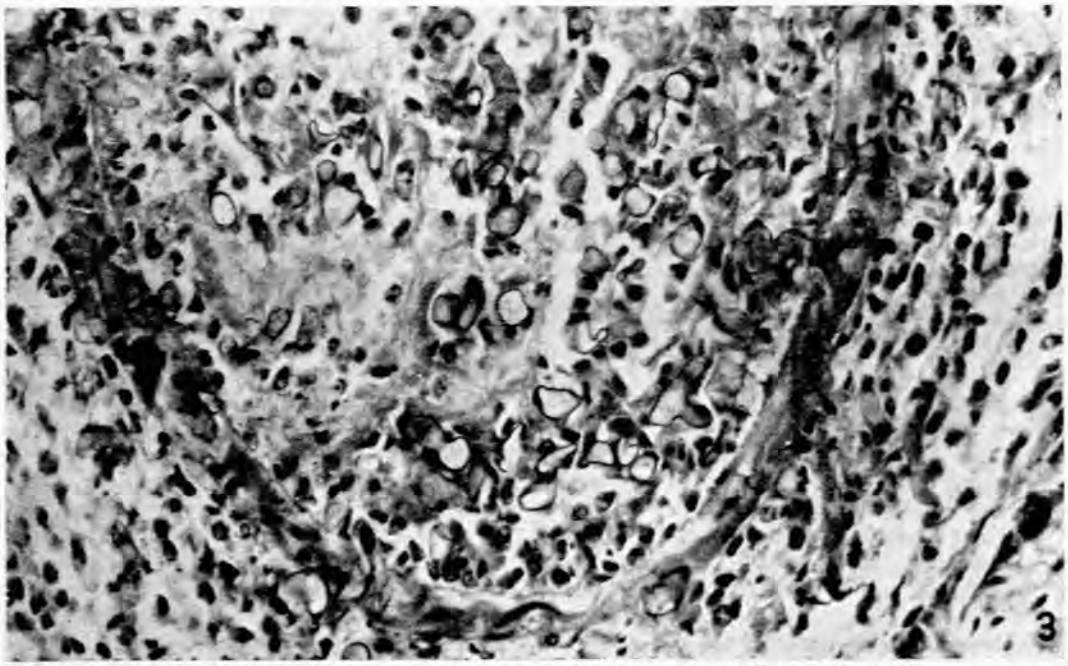

Fig. 3. Thrombosed vessel invaded by fungal hyphae in the submucosa of the colon (haematoxylin and eosin × 480).

tion showed the surrounding mucosa to be necrotic and haemorrhagic. There was haemorrhage into the submucosa and infiltration of the entire wall by neutrophils. The serosa was acutely inflamed and covered by necrotic debris. Non-septate branching fungal hyphae were present in the lumen of the bowel, in the wall, and on the serosa (Fig. 3). The fungal filaments were large and showed absence of cross-wall formation with free and irregular branching, features suggesting origin from the mucoraceae. In many areas the hyphae were invading the walls of blood vessels and had come to lie within their lumens.

COMMENT

Approximately 150 autopsies are carried out on children at Baragwanath Hospital every year, and these 5 cases of mucormycosis were seen over a period of 5 years. The condition is therefore relatively rare. There have been previous reports of infection with mucor in the Bantu. Watson[3] reported a case of gastric perforation due to mucor in a 26-month-old Bantu child suffering from malnutrition. Sutherland and Jones[6] have suggested that the type of food given to malnourished Bantu children may facilitate the growth of fungal spores because of fermentation either before or after cooking.

Of the 5 infants reported here, 2 were newborn while the remaining 3 were grossly undernourished. Furthermore, in 4 of the 5 infants there was an associated gastro-enteritis. Thus it would appear, in our experience, that 2 categories of infants are particularly liable to develop infection with the fungus mucor, viz. malnourished and newborn infants, especially if these children suffer from gastro-enteritis. It has been suggested that acidosis in some way predisposes to infection with mucor. Diarrhoeal disease is a well-recognized cause of acidosis. In case 2 there was clinical and biochemical evidence of such an acidotic state, which may have favoured proliferation of mucor.

Four of the children were receiving antibiotics. Torack[1] has pointed out the rôle of antibiotics in precipitating fungus infections. It is possible that antibiotics may stimulate the growth of fungi, or they may produce their effect by altering the immunologic response of the host, by changing the gastro-intestinal flora or by a direct toxic effect on the host's tissues. Actual stimulation of fungal growth has been demonstrated in experiments using neomycin, bacitracin and aureomycin.[7] The reduction of competitive bacterial flora probably allows normally harmless saprophytic fungi to proliferate. The family mucoraceae consists of 3 genera, viz. Mucor, Absidia and Rhizopus.

The characteristic histological finding in mucor is the presence of large non-septate hyphae invading the tissues and particularly blood-vessel walls, which become thrombosed with resultant infarction.[8]

All our cases showed the typical invasion of the walls of blood vessels, but there was no evidence of spread of the infection through the blood stream. Spread appeared to be taking place by direct extension through the tissues and not along the mucosal surfaces; this confirms the findings of Gatling.[4] In none of our cases was the organism cultured.

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