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Fatal pseudomembranous enterocolitis following clindamycin therapy

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SUMMARY

A fatal case of pseudomembranous enterocolitis following oral and parenteral clindamycin therapy is presented. Interesting features in this case are involvement of the small bowel and complete sparing of the large bowel distal to a defunctioning transverse colostomy. The significance of the absence of disease in the defunctioned bowel is discussed in terms of aetiology and diagnosis of pseudomembranous enterocolitis.

A CASE is reported of pseudomembranous enterocolitis occurring after oral and parenteral clindamycin therapy in a patient who had undergone resection of the sigmoid colon for diverticular disease with a protecting transverse colostomy prior to starting clindamycin therapy. At autopsy the pseudomembranous enterocolitis involved the ileum and large bowel proximal to the colostomy, but the colon distal to the colostomy was normal. No previous report has been found of either small bowel involvement or sparing of the bowel distal to a defunctioning colostomy in pseudomembranous enterocolitis associated with clindamycin therapy.

Case report

A 55-year-old white male was admitted for surgical treatment of colonic diverticular disease. He had suffered intermittent attacks of left-sided abdominal pain with mucous diarrhoea for 12 years, but the severity and frequency of these attacks had increased during the 6 months before admission. Barium enema examination demonstrated marked diverticular disease involving the lower descending and sigmoid colon, and a small projection of barium outside the mucosal border of the sigmoid colon indicated a small intramural abscess. Preoperative estimations of haemoglobin, leucocytes, platelets and serum urea and electrolytes were all within normal limits. Bowel preparation with mechanical evacuation, succinylsulphathiazole (1·5 g by mouth 4-hourly) and neomycin sulphate (1·0 g by mouth 4-hourly) was performed for 5 days preoperatively.

At operation 10 cm of diseased bowel at the junction of the descending and sigmoid colon were resected with two-layer end-to-end anastomosis of the colon. A small abscess cavity (2 cm in diameter) was opened during mobilization of the diseased colon, and because of this the patient was given 300 mg clindamycin† intravenously and the anastomosis was protected by dividing the transverse colon and establishing the proximal end as an end colostomy. The pus collected from the abscess subsequently cultured a mixture of Gram-negative bacteria which were all sensitive to clindamycin.

Initial postoperative progress was satisfactory and clindamycin therapy was continued for 6 days (150 mg i.v. 4-hourly for 4 days and 300 mg orally 6-hourly for 2 days). Temperature, appetite and colostomy function were all normal until the eleventh postoperative day, when the patient vomited his supper for no apparent reason. Four hours later he complained of severe abdominal pain and vomited again; his temperature was 37·6 °C, pulse rate 100/minute and blood pressure 18·6/10·6 kPa (140/80 mm Hg), his abdomen was slightly distended and diffusely tender and bowel sounds were reduced. This deterioration in the patient's condition was attributed to intraperitoneal sepsis with septicaemia. Intravenous fluid therapy and nasogastric intubation were instituted, blood culture (subsequently yielded *Bacteroides fragilis* on culture), leucocyte count (7×10^9/litre—7000/mm^3) and blood urea estimation (8·17 mmol/litre—49 mg per cent) were performed and antibacterial therapy was started using clindamycin (450 mg i.v. 4-hourly) and kanamycin sulphate (500 mg i.m. 12-hourly). A plain X-ray of the abdomen showed diffuse haziness but no evidence of intestinal obstruction. During the next 48 hours there was no change in the patient's condition, but a catheter inserted into the colostomy stoma drained 1·9 litres of thin brown fluid containing yellow particulate matter.

On the fourteenth postoperative day the patient was admitted to the intensive care unit; at this time he had hypoperfusion, relative hypoxaemia, poor urine output and a compensated metabolic acidosis. His temperature was 36·0 °C, pulse rate 120/minute, blood pressure 18·6/10·6 kPa (140/80 mm Hg), central venous pressure less than 0·67 kPa (5 cm H_2O), leucocyte count $7{\cdot}9 \times 10^9$/litre (7900/mm^3) and blood urea 21·2 mmol/litre (128 mg per cent). Treatment continued with assisted ventilation, expansion of the circulating fluid volume, clindamycin (450 mg i.v. 4-hourly) and gentamicin sulphate (70 mg i.v. 8-hourly). This treatment restored peripheral perfusion, urine output and normal acid/base status, but continuing infusion of large volumes of fluid was necessary to maintain the improvement. The abdomen became more distended and remained tender and bowel sounds were absent. The colostomy drained large volumes (over 1·5 litre/day) of thin brown fluid containing yellow particulate matter. A peritoneal tap yielded 2·5 litres of straw-coloured fluid containing many polymorphonuclear leucocytes, but was sterile on culture. Barium enema examination via the rectum showed an intact normal bowel extending to the closed end of the transverse colon, but barium introduced into the colostomy stoma revealed a diffusely abnormal mucosal pattern in the proximal colon, caecum and terminal ileum (*Fig.* 1). At this time (sixteenth postoperative day) the patient remained ill with a temperature of 38·0 °C, leucocyte count $26{\cdot}5 \times 10^9$/litre (26 500/mm^3) and a blood culture (taken on the twelfth postoperative day) positive for *Bacteroides fragilis*. These data were interpreted to indicate an intraperitoneal source of sepsis with continuing septicaemia, and a repeat laparotomy was performed.

Laparotomy revealed free yellow intraperitoneal fluid, the caecum and terminal 180 cm of ileum were grossly oedematous and discoloured but the jejunum and the colon distal to the colostomy were normal. No source of sepsis was discovered and a diagnosis of pseudomembranous enterocolitis was considered most likely. The abdomen was closed. Sigmoidoscopy revealed normal rectal mucosa, and limited examination of the colon through a sigmoidoscope inserted via the colostomy stoma showed very inflamed mucosa with copious quantities of the thick brown fluid; mucosal biopsies of the colon and rectum were taken. After the laparotomy, clindamycin was discontinued and methylprednisolone‡ (1 g i.v.

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‡ Solu-Medrol: The Upjohn Company of Canada, Don Mills, Ontario, Canada.

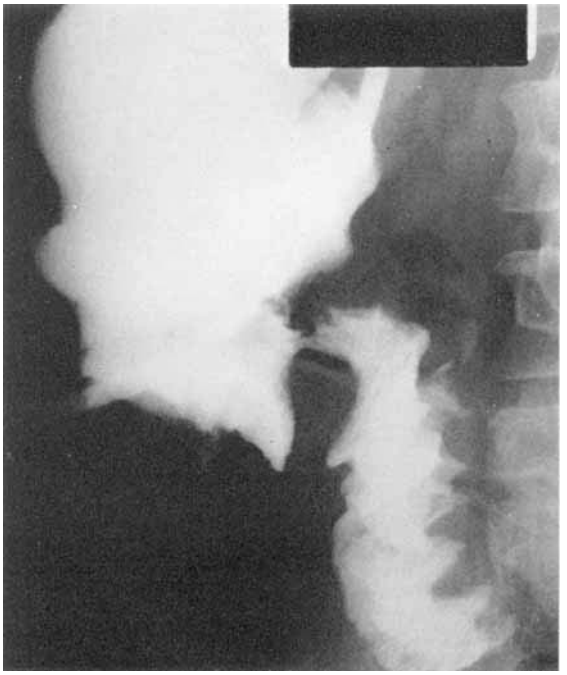

Fig. 1. Barium enema examination performed via the colostomy stoma. Spot film of the ileocaecal junction showing grossly abnormal mucosal pattern.

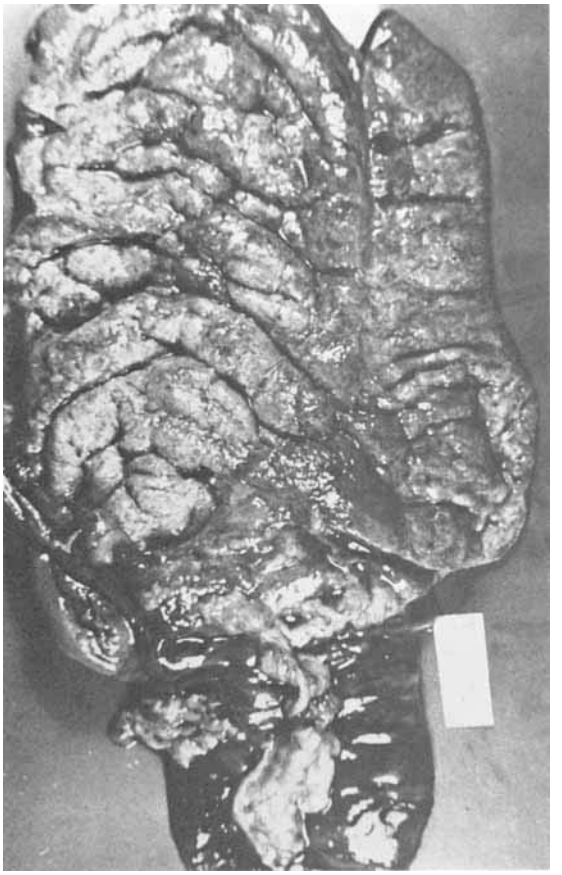

Fig. 2. Photograph of the ileocaecal region at autopsy. The mucosa of the ileum is separated as a cast and the caecal mucosa is grossly abnormal with yellow pseudomembrane formation.

6-hourly) added to the general supportive measures. Penicillin (2·5 million units i.v. 4-hourly) and chloramphenicol (750 mg i.v. 6-hourly) were given because of the proved Gram-negative septicaemia. The general condition of the patient improved, but peritoneal dialysis was started 24 hours after laparotomy because of oliguric renal failure. His condition remained stable until 36 hours after laparotomy, when a massive haematemesis led to cardiac arrest, and attempted resuscitation was unsuccessful.

The main finding at autopsy was marked oedema and thickening of the terminal 180 cm of ileum, caecum, ascending colon and the transverse colon proximal to the colostomy. When the wall of this bowel was opened practically all the mucosa of the ileum was separated as a tubular cast and the mucosa of the caecum and colon was grossly abnormal with yellow pseudomembranes (*Fig.* 2). The upper small bowel and the large bowel distal to the colostomy were grossly normal. The striking contrast in appearance between the diseased bowel proximal to the colostomy and the normal distal colon is illustrated in *Fig.* 3. The stomach contained fresh blood and its mucosa had many superficial erosions. Other findings included a small abscess cavity in the original operation wound, small bilateral pleural effusions and moderately severe atheroma. Histological examination of the diseased bowel showed marked submucosal oedema and infiltration of the bowel wall, with loss of mucosa and a pseudomembrane consisting of fibrinous exudate and inflammatory cells (*Fig.* 4). Review of the colonic wall biopsies taken previously via the colostomy stoma showed a similar appearance. Biopsies of the distal colon and rectum taken at autopsy (*Fig.* 5) and before death all showed normal mucosa and bowel wall. The mesenteric vessels were all patent when examined at autopsy.

Discussion

Pseudomembranous enterocolitis is recognized as a complication of many different types of illness, including pneumonia, uraemia, septicaemia (Goulston and McGovern, 1965), intravascular coagulation and infection (Hardaway and McKay, 1959), intestinal obstruction and carcinoma of the colon (Pettet et al., 1954; Goulston and McGovern, 1965) and postoperatively after both abdominal and non-abdominal procedures (Birnbaum et al., 1961). Recently, however, many cases of pseudomembranous colitis associated with lincomycin and clindamycin therapy have been reported (Benner and Tellman, 1970; Cohen et al., 1973; Scott et al., 1973; Shimkin and Link, 1973; Cohen et al., 1974; Davis, 1974; DeFord et al., 1974; Pittman et al., 1974; Steer, 1974; Sissons et al., 1974; Stanley et al., 1974; Stroehlein et al., 1974; Tedesco, Barton and Alpers, 1974; Tedesco, Stanley and Alpers, 1974; Viteri et al., 1974; Wise et al., 1974; Wolfe, 1974).

The gross pathological and histological findings in the present case were typical of those found in pseudomembranous enterocolitis, and review of the clinical findings suggest that this disease process presented on the twelfth postoperative day with abdominal pain, vomiting and subsequent watery colostomy drainage and vascular collapse. Before the onset of these symptoms the patient had received parenteral and oral clindamycin, he had no evidence of bowel obstruction and was clinically well. These facts

Fig. 3. Photograph of the ileocaecal region (left) and the descending colon (right) taken at autopsy. The striking difference in the macroscopic appearance of the two segments of bowel is demonstrated.

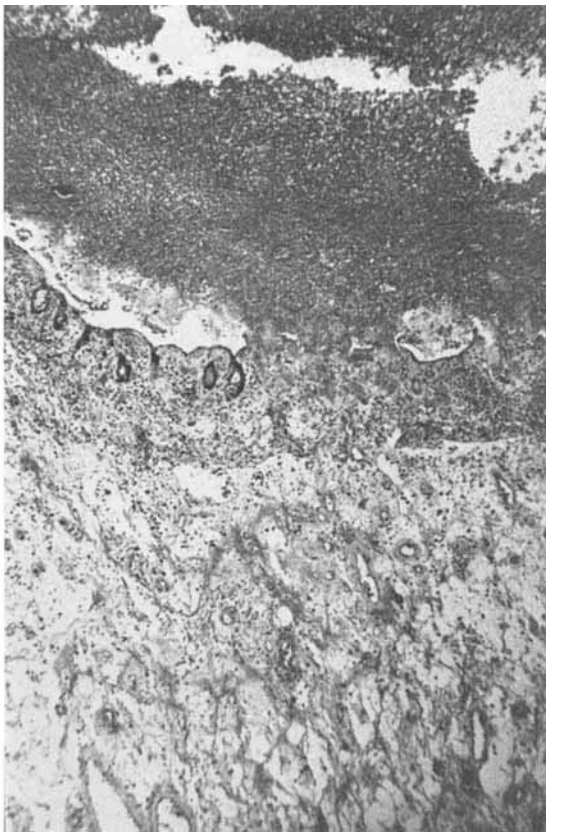

Fig. 4. Photomicrograph of the caecal wall biopsy taken at autopsy. The submucosa (below) contains a dense infiltrate of inflammatory cells, the mucosa is destroyed and the pseudomembrane (above) consists of fibrin and inflammatory cells. (×28.)

suggest that this is an example of clindamycin-associated pseudomembranous enterocolitis, with the onset of symptoms 5 days after completing a 6-day course of clindamycin. The subsequent course of the disease process was complicated by delayed recognition of the pseudomembranous enterocolitis, further therapy with clindamycin, sepsis and renal failure. It seems likely that the final event of gastric haemorrhage from superficial gastric erosions was related to stress and corticosteroid therapy.

The most interesting features of this case are the extensive small bowel involvement by the disease and the sharp demarcation of the process by the transverse colostomy with complete sparing of the distal bowel. As far as we are aware, these features have not been previously described in clindamycin-associated pseudomembranous enterocolitis, although small bowel involvement and demarcation of the disease by bowel obstruction have been recorded in pseudomembranous enterocolitis attributed to factors other than clindamycin therapy (Pettet et al., 1954; Goulston and McGovern, 1965). In this patient the whole bowel was exposed to the preoperative preparation, the parenterally administered clindamycin and any systemic haemodynamic or toxic process, while the

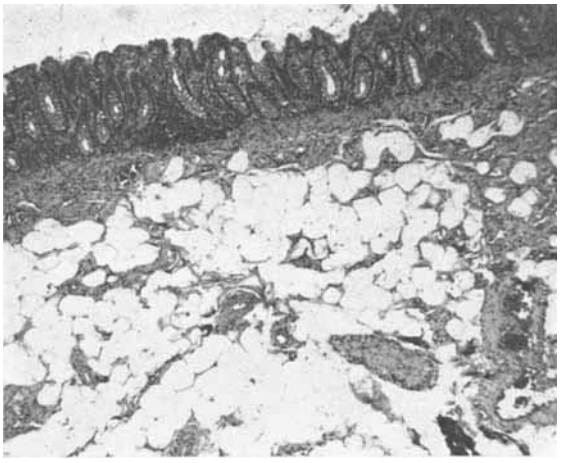

Fig. 5. Photomicrograph of the colon wall distal to the colostomy. The bowel wall and mucosa are histologically normal. (×25.)

bowel proximal to the colostomy was in addition exposed to the orally administered clindamycin and the faecal stream. The oral clindamycin therapy may be an important factor, as Tedesco, Barton and

Alpers (1974) have recorded that clindamycin-associated colitis is approximately four times more common after oral compared with parenteral therapy. The complete sparing of the bowel distal to the colostomy in our case suggests that local factors in the bowel are at least contributory in the pathophysiology of clindamycin-associated pseudomembranous enterocolitis. The local factor could be direct toxicity of clindamycin on the bowel mucosa, as suggested by Pittman et al. (1974), continued exposure to the faecal stream or some other factor. It seems likely that if an immunological mechanism is involved in the production of this disease (Davis, 1974) it acts in association with local factors within the bowel.

The complete sparing of the defunctioned bowel from the disease process in this case illustrates an important problem in the early diagnosis of the disease. Sigmoidoscopic or proctoscopic examination (Price and Davies, 1974; Tedesco, Barton and Alpers, 1974; Tedesco, Stanley and Alpers, 1974) and barium enema examination (Shimkin and Link, 1973; Tedesco, Stanley and Alpers, 1974) are described as useful methods of establishing the diagnosis of pseudomembranous enterocolitis. In cases with a segment of bowel defunctioned by colostomy it may be necessary to perform these examinations via the colostomy stoma to obtain evidence of the disease process.

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