PAPERS AND ORIGINALS

Diagnosis of pseudomembranous colitis

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Summary and conclusions

Twenty-eight patients with histologically proved pseudomembranous colitis have been seen in one hospital since July 1975. All patients with the disease had received antibiotics, six for infections not requiring operations; the other 22 cases all occurred after major surgery. All the patients had diarrhoea; six patients also had fever with clinical signs of sepsis, and three had abdominal pain thought to be due to anastomotic dehiscence after colonic resection. Pseudomembranous colitis was associated with white blood counts over 15 000/mm³ in 17 patients and albumin concentrations of less than 30 g/l in 18. Pseudomembranous colitis was an incidental finding at necropsy in two of six patients who had not had an operation. Of the 22 patients who had had major surgery, nine died from this complication; in all except two of these cases the diagnosis was made only at necropsy.

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If pseudomembranous colitis is suspected on clinical grounds or if there is an unexplained complication after colorectal surgery repeat sigmoidoscopy and testing for faecal toxins should be carried out to establish the diagnosis so that prompt supportive treatment can be given.

Introduction

Pseudomembranous colitis is an uncommon condition usually associated with antibiotic treatment.[1] It is most frequently reported in elderly patients with malignant disease but many cases have occurred after intestinal operations.[2–5] Although clinicians have become more aware of it as a cause of severe diarrhoea, most reports have described few cases, and the condition is still regarded as rare.[6–13] In over 1000 orthopaedic operations only three of the 58 patients with antibiotic-associated diarrhoea had evidence of pseudomembranous colitis.[14] There has been only one large series of patients with the condition but this was collected from at least three London hospitals.[15] We saw 39 clinically suspected cases between July 1975 and December 1977; but in many of the patients the diagnosis was difficult to establish. This review of the clinical presentation and diagnostic features of pseudomembranous colitis, with the results of additional laboratory studies, may provide a basis for earlier diagnosis of the disease.

Patients and methods

We reviewed the 39 patients with clinically suspected pseudomembranous colitis seen since July 1975, and the histological material obtained from necropsy or biopsy (assessed by HT). Patients were included in the study if they showed specific diagnostic features[15]—notably inflammatory changes with fibrin and polymorphs splaying out from the lamina propria (T1); disrupted glands distended with

TABLE I—*Number of cases of pseudomembranous colitis seen per month during 1975-7*

1975		1976					1977							
June	July	April	May	July	Sept	Dec	March	April	June	July	Sept	Oct	Nov	Dec
4	2	1	1	2	2	1	1	1	2	2	1	4	2	2

TABLE II—*Antibiotic treatment in six patients with pseudomembraneous colitis without previous operation*

Case No	Diagnosis	Antibiotic
1	Respiratory infection, Septicaemia	Amoxycillin
2	Leukaemia, Septicaemia	Amphotericin, gentamicin, and clindamycin
3	Dental abscess	Clindamycin
4	Breast abscess	Clindamycin
5	Respiratory infection	Ampicillin
6	Fractured femur	Tetracycline

TABLE III—*Cases of pseudomembranous colitis by age (numbers of deaths in parentheses)*

Age (years):	10-	20-	30-	40-	50-	60-	70-	80-	90-
Group without operation (N=6)	1 (1)		1	2	2 (1)				
Postoperative group (N=22)				1	4	5 (2)	8 (4)	3 (2)	1 (1)

mucin and polymorphs covered with a pseudomembrane of epithelial debris, fibrin, mucus, and polymorphs (T2); or complete structural necrosis and a membrane (T3). Twenty-eight of the patients (of whom 16 were women) had unequivocal histological evidence of the disease; their ages ranged from 18 to 90 years (mean 63), and 15 were over 60. Table I shows the distribution of cases over the three years of the study.

The clinical presentation, sigmoidoscopic appearance, radiological features, and all available haematological and biochemical data were reviewed and analysed. Quantitative analysis of the faecal flora was also carried out for patients seen after July 1976. Serial dilutions of faecal samples were prepared in an anaerobic cabinet[16] and cultured aerobically and anaerobically for 72 hours before counting. Recently we have also included a test for a faecal toxin in HeLa cells, human embryonic lung fibroblasts, and rhesus monkey kidney cells.[17]

Results

CLINICAL FINDINGS

Six patients who had not had a recent operation developed pseudomembranous colitis, two of whom died (table II). Both were seriously

TABLE IV—*Prophylactic and postoperative antimicrobial agents given to 22 patients with pseudomembranous colitis*

Case No	Condition	Prophylaxis: Drug	Prophylaxis: Days	Duration of postoperative treatment (days): Cloxacillin	Ampicillin	Amoxycillin	Penicillin	Cefazolin	Cephaloridine	Cefuroxine	Gentamicin	Co-trimoxazole	Lincomycin	Clindamycin	Metronidazole	Amphotericin
1	Carcinoma of colon	Metronidazole*, Kanamycin*	(B†)													
2	„	Metronidazole*, Kanamycin*	(B†)				7				5			7		
3	„	Lincomycin, Tobramycin	1, 1									12				
4	„	Metronidazole*, Neomycin	(B†)								6				6	
5	„	Lincomycin, Gentamicin	3, 3													
6	„	Lincomycin, Gentamicin	3, 3													
7	„	Lincomycin, Tobramycin	1, 1													
8	„	Lincomycin, Gentamicin	3, 3													
9	„	Lincomycin, Gentamicin	1, 1		2							3			7	10
10	„								1			3			4	
11	„	Lincomycin, Tobramycin	1, 1		11						7					
12	„					3								3		
13	Rectal prolapse (abdominal rectopexy)	Lincomycin, Gentamicin	3, 3	4				13			5		7		2	
14	„	Lincomycin, Gentamicin	7, 7								7				2	
15	Villous papilloma (transacral excision)	Metronidazole*, Neomycin*	(B†)	1								12				5
16	Gall stones	Clindamycin							3							
17	Gastric carcinoma	Ampicillin	10					9			21	17				
18	Hepatoma	Neomycin‡	(B†)					1								
19	Bleeding duodenal ulcer				10					9	10				4	
20	Cancer of breast														3	
21	Crohn's disease											5				
22	Fractured femur				10							7				

*Oral
†Bowel preparation
‡For encephalopathy

ill, one being an alcoholic with respiratory sepsis and pneumococcal septicaemia and the other an 18-year-old girl with acute leukaemia and Gram-negative septicaemia. The other four patients had taken antibiotics—for dental abscess, breast abscess, and respiratory infection, and during conservative treatment of a fractured femur (table III). They developed diarrhoea from 6 to 10 days after starting antibiotics, and it continued for 5-12 days (mean 8·2). In the two who died pseudomembranous colitis was an incidental finding at necropsy. In the other cases the diagnosis was established by sigmoidoscopy and biopsy.

Twenty-two patients developed pseudomembranous colitis after operation. Twenty had been operated on for gastrointestinal disorders, 14 of them for malignant disease (12 colorectal cancers, gastric cancer, and hepatoma); the other eight operations were for breast cancer, rectal prolapse (two cases), rectal papilloma, gall stones, bleeding duodenal ulcer, fractured femur, and Crohn's disease.

All 22 patients had received antibiotics, 16 of them as prophylaxis and 17 for treating suspected postoperative sepsis (table IV).

Diarrhoea was the principal symptom in all these patients and began either during antibiotic treatment (eight cases) or less than 10 days after it was stopped (12 cases). The diarrhoea started on the fifth to twentieth day after operation and persisted for a mean of 20 days. Six patients had an intermittent pyrexia and were thought to have a pelvic abscess or septicaemia; three developed clinical signs of an acute abdomen mimicking anastomotic dehiscence.

Nine of the 22 patients in the postoperative group died (table III) and in all except two pseudomembranous colitis was diagnosed only at necropsy. Four cases were misdiagnosed as having either severe sepsis (one case) or dehiscence of an intestinal anastomosis (three cases), and the surgeon thought that sigmoidoscopy might be dangerous. Another patient, who had mild diarrhoea after an anterior resection, was readmitted five weeks after operation with severe electrolyte depletion and died soon afterwards; pseudomembranous colitis had never been considered. The diagnosis was considered on clinical grounds in two other patients who died, but the initial sigmoidoscopy and biopsy findings were not diagnostic; their clinical condition deteriorated despite intensive medical management and sigmoidoscopy was never repeated. Two patients (both over 80) had a confirmed diagnosis of pseudomembranous colitis before death; one was moribund after transfer from another hospital and the other had disseminated malignant disease. None of the deaths were caused by perforation or haemorrhage.

Thirteen of the postoperative patients survived; four had minimal symptoms, but nine had a protracted illness and remained in hospital with diarrhoea for over a month, and two had diarrhoea lasting more than two months. The diagnosis was established by sigmoidoscopic biopsy in 12 patients, but in one only from biopsy specimens obtained from a transverse colostomy—this patient was thought to have a pelvic abscess but laparotomy showed a dilated colon. In all the patients who survived, the appearances seen on sigmoidoscopy and biopsy returned to normal within 10 weeks of the onset of symptoms.

TABLE V—*Final sigmoidoscopy findings in 20 patients with pseudomembranous colitis*

	Membrane	Oedema and contact bleeding only	Normal
Group without operation (N = 4) ..	4		
Postoperative group (N = 16)	9*	5 (1†)	2 (1†)

*Initial examination showed non-specific change in three.
†Died.

INVESTIGATIONS

The sigmoidoscopic findings are summarised in table V. The characteristic membrane or patches of white material adherent to the mucosa were observed in only 13 patients—in three of them only as a result of a repeat sigmoidoscopy, the appearances at the initial examination having been normal or non-specific. Satisfactory sigmoidoscopy was often extremely difficult in patients with profuse watery diarrhoea.

The eight patients who had a barium enema examination had extensive mucosal changes thought to be due to ulceration, affecting the entire colon in five cases and the left colon in three. Two patients developed severe abdominal pain suggesting a perforated colon after the barium enema and one of them had subcutaneous emphysema of the abdominal wall. Two patients had plain *x*-rays, which showed dilatation of the colon (diameter >8 cm), but this abnormality did not persist or lead to perforation.

A leucocyte count over $15{\cdot}0 \times 10^9$/l (15 000/mm^3) was recorded in 17 patients. In the surgical group the mean white cell count was $7{\cdot}5 \times 10^9 \pm 1{\cdot}5 \times 10^9$/l before operation; this rose to a maximum of $15{\cdot}2 \times 10^9 \pm 1{\cdot}675 \times 10^9$/l after operation. Almost all the critically ill patients had electrolyte abnormalities, and 18 had an episode of hypoalbuminaemia (albumin 30 g/l) during their illness. In the surgical group the mean serum albumin concentration was $34{\cdot}9 \pm 5{\cdot}8$ g/l before operation and this fell to a minimum of $27{\cdot}0 \pm 4{\cdot}0$ g/l.

We obtained blood cultures from all patients with pseudomembranous colitis but isolated organisms (*Pneumococcus*, *Pseudomonas aeruginosa*, and *Klebsiella aerogenes*) in only two cases—from the two critically ill patients with septicaemia who had not had an operation. The bacterial counts from faecal samples taken from 11 patients with colitis were compared with mean counts from 15 medical personnel in our hospital. The bacterial flora was abnormal in all except one patient (table VI). The most striking abnormality was the reduced number of faecal anaerobes, particularly *Bacteroides fragilis* (six patients) and anaerobic streptococci (seven patients). Counts of lactobacilli were reduced in seven patients and of *Escherichia coli* and *Streptococcus faecalis* each in two patients. There was also evidence of overgrowth by *Staphylococcus aureus* in two patients and *Clostridium* spp in five. A faecal toxin was found in high titres in all seven patients with histological evidence of pseudomembranous colitis who were investigated for the presence of toxins (table VII). The titre of toxin did not appear to be related to the severity or duration of the clinical illness.

TABLE VII—*Toxin titres in stool samples from seven patients with pseudomembranous colitis*

Case No:	1	2	3	4	5	6	7
Toxin titre	1/500	1/4000	1/400 000	1/200 000	1/100 000	1/800	1/800

TABLE VI—*Bacterial counts in 11 patients with pseudomembranous colitis, with means of counts in 15 controls*

Case No	*E coli*	*Str faecalis*	*Staph aureus*	Lactobacilli	*B fragilis*	Anaerobic streptococci	*Clostridium* sp
1	5×10^8	5×10^4	—	3×10^6	(5×10^6)	(—)	5×10^6
2	3×10^9	(—)	—	(—)	(1×10^4)	(—)	(—)
3	1×10^9	1×10^7	—	(—)	8×10^5	(—)	(—)
4	5×10^6	5×10^7	—	(5×10^4)	(—)	(—)	5×10^7*
5	(5×10^4)	3×10^7	1×10^8**	5×10^9	1×10^{10}	5×10^8	5×10^9*
6	1×10^7	(—)	5×10^3	1×10^6	(—)	1×10^9	1×10^8*†
7	1×10^{10}	1×10^6	—	(5×10^5)	3×10^{10}	5×10^8	(—)
8	2×10^9	1×10^5	—	(—)	(—)	(—)	(—)
9	(—)	5×10^5	—	(—)	1×10^8	5×10^7	1×10^5
10	5×10^7	5×10^5	3×10^8*	(—)	(—)	(—)	5×10^7*†
11	1×10^{10}	1×10^{10}	—	1×10^{10}	1×10^{10}	(—)	5×10^7*†
Controls	4×10^7	5×10^4	1×10^1	7×10^8	9×10^9	4×10^4	9×10^4

( ) Bacteria reduced compared with controls.
*Possible overgrowth of organisms.
†More than one species present.

TREATMENT

All patients with histological evidence of the disease were treated initially by codeine and diphenoxylate hydrochloride. Only four of the 12 patients responded within five days of starting treatment. Four patients were treated intensively with steroids and intravenous fluids but only one improved during the first 72 hours. Only one of three patients responded to oral cholestyramine, but the one patient treated with vancomycin improved immediately.

Discussion

This study emphasises the difficulty of diagnosing pseudomembranous colitis, there having been at least seven unsuspected cases diagnosed only at necropsy. In our hospital there is a high necropsy rate, and elsewhere the true incidence of the disease may be unrecognised either because of a low necropsy rate or because the colon is not routinely opened during post-mortem examination. The condition is far more common in this hospital than the sporadic published reports[18–20] would suggest. We believe that it is being more frequently diagnosed as a result of its increasing recognition as a cause of postoperative diarrhoea.

Over the past nine months all patients in this unit with more than three loose stools a day have had sigmoidoscopy even if they had had a recent colonic resection. If a membrane is seen specimens of this and the underlying mucosa must be taken for biopsy. Specimens obtained from an area not macroscopically affected may be normal.[21] If the sigmoidoscopic and histological appearances are not diagnostic we recommend a repeat sigmoidoscopy. In seven of our patients the initial sigmoidoscopic appearances were non-specific and in two of them the diagnosis was made only at necropsy. In three patients the florid changes in the rectum were discovered only by repeat sigmoidoscopy. Moreover, the sigmoidoscopic findings in isolation are not a reliable guide since in two patients the rectum was apparently spared.

Many of the patients with pseudomembranous colitis had a grossly raised white cell count and were febrile. Some of them also had abdominal signs suggestive of a localised abscess from dehiscence of an anastomosis. Sigmoidoscopy was therefore often considered dangerous and unnecessarily meddlesome. This experience has taught us to use sigmoidoscopy much more readily in patients with a complicated convalescence after intestinal surgery. Of the survivors, the postoperative patients who developed pseudomembranous colitis had a much more protracted illness and greater morbidity than did the patients who had not had an operation. None of the deaths was due to perforation or haemorrhage, and we now believe that many could have been avoided in the postoperative group if the diagnosis had been established and the patients given intensive supportive measures[22 23] or specific treatment.[24 25]

Pseudomembranous colitis might have been detected in suspected cases by routine barium enema.[26] But in two of the eight patients who had it, this examination exacerbated the symptoms and perforation of the colon was feared. Colonoscopy has been advocated to establish the diagnosis,[27] but many of our patients were considered too ill for procedures requiring air insufflation of the colon. The faecal toxin[17] found in patients with the disease has not only enabled us to identify the causative agent[28] but also may provide a diagnostic test. We are now investigating the titres of faecal toxin in different groups of patients with diarrhoea to see whether high titres are specific to pseudomembranous colitis.

All the patients in this survey had received some antimicrobial agent and many had had more than one. One patient developed pseudomembranous colitis after only two doses of tobramycin and lincomycin. Antibiotics might seem to have been used excessively in these patients. But most were thought to have developed a serious infection after operation either because of fever and unexplained leucocytosis or because of abdominal signs suggesting a leak from an intestinal anastomosis. Almost any antibiotic may be associated with the disease,[5 6 20 29 30] lincomycin and clindamycin having been most often blamed. Although one or other had been given to 15 of the 28 patients, gentamicin and tobramycin had been used in 13 cases. These antibiotics probably suppress the normal flora of the colon and allow overgrowth of certain pathogenic bacteria.

Our microbiological findings support this hypothesis and provide evidence of superinfection by staphylococci or clostridia in seven out of 11 cases. Certain clostridial species can produce a toxin causing a similar disease in laboratory animals.[31] Rifkin *et al*[32] moreover identified a toxin in the stool of patients with pseudomembranous colitis that was lethal for hampsters, increased vascular permeability in rabbit skin, and was cytotoxic for cells in tissue culture. It was neutralised by *Clostridium sordellii* antitoxin.

We believe that the only means of avoiding a high mortality rate is to establish the diagnosis promptly and give early supportive treatment. Our results suggest that careful repeated sigmoidoscopy should be performed in all clinically suspected cases and in any patient with an unexplained complication after a colorectal operation. Testing for faecal toxin may also prove to be a useful aid to diagnosis.

Requests for reprints should be sent to MRBK.

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