Pseudomembranous colitis

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SUMMARY  Three basic histopathological patterns which may be seen in rectal biopsies from patients with pseudomembranous colitis are described, based on a study of 29 cases. The spectrum of change is illustrated and the problems of differential diagnosis are discussed—from a non-diagnostic proctitis at one extreme to acute ischaemia at the other. In the differential diagnosis of the acute colitic, the importance of urgent rectal biopsy and a carefully taken drug history is stressed. The association of pseudomembranous colitis with pre-existing disease and antibiotic therapy is confirmed. It is suggested that these cause local mucosal damage and may trigger the first part of a local Shwartzman reaction. Capillary microthrombosis may then play a part in producing the mucosal necrosis seen later in the disease.

Pseudomembranous colitis has a typical pathological appearance which can be distinguished not only from Crohn’s disease and ulcerative colitis but also, in most instances, from the confusing group of ischaemic bowel conditions (Goulston and McGovern, 1965). It is a mucosal disease typified by multiple discrete yellow plaques, 0.2 to 2.0 cm in diameter, adherent to the mucosal surface of a variable length of colon. Histologically, each plaque comprises a ‘pseudomembrane’ of mucous debris, inflammatory cells, and exude overlying groups of partially disrupted glands, and separated by almost normal mucosa from an adjacent plaque. Ultimately complete mucosal necrosis may occur and the plaques coalesce. The gross pathology is unlike Crohn’s disease and ulcerative colitis while the focal mucosal lesions seen on histology are also in contrast to the transmural disease of Crohn’s colitis and the diffuse mucosal inflammation of ulcerative colitis. Diagnostic difficulty, discussed later in this paper, may arise between the advanced stages of pseudomembranous colitis and certain forms of ischaemic colitis.

The diagnosis of pseudomembranous colitis was formerly made only at necropsy, usually in elderly debilitated or postoperative patients (Kay et al., 1958), but in recent years it has become an urgent histopathological problem in the differential diagnosis of acute colitis. The spate of articles linking this form of colitis to lincomycin or clindamycin therapy has also brought it to prominence (eg, Cohen et al., 1973; Scott et al., 1973). As pseudomembranous colitis usually responds to active conservative management and is a non-recurrent disease, an accurate biopsy diagnosis is important.

The aim of this study, on 29 patients, was to define more clearly the minimal histopathological criteria necessary for a diagnosis of pseudomembranous colitis in rectal biopsy material, to examine the relationship between it and ‘antibiotic-associated colitis’, and to follow the clinical course of the disease.

Methods

We studied 29 patients in whom a final histopathological diagnosis of pseudomembranous colitis was made on biopsy, colectomy or necropsy material. In some of these cases earlier ‘non-diagnostic’ or wrongly diagnosed material was available. Most cases were seen at St. Thomas’ and St. Mark’s Hospitals between 1973 and 1975, and we were also able to study some from other hospitals. Full clinical details of preceding illness and surgery were obtained on all patients. Particular attention was given to any recent antibiotic therapy and its relationship to the onset of diarrhoea. The results of sigmoidoscopy and barium examination, as well as the haematological and bacteriological findings, were recorded.

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From a total of 29 cases, rectal biopsies were available in 23, and colectomy and/or necropsy tissue in 13. Routine 5 μm paraffin-embedded sections, stained with haematoxylin and eosin, were examined in all instances. Where the paraffin blocks were available, step sections were cut on the biopsy material. A Martius Scarlet Blue stain to demonstrate fibrin was carried out on all cases. In the case of referred sections, this had to follow bleaching of the original slides. In addition to the diagnostic features described by Goulston and McGovern (1965), the presence of other accompanying mucosal abnormalities was noted. These included crypt abscesses, the degree of goblet cell depletion, the nature of any adjacent inflammatory infiltrate, and the occurrence of capillary microthrombi.

Rectal biopsies were also examined from 25 cases of proven Crohn's disease, 25 cases of proven ulcerative colitis, and 10 patients with a variety of other bowel disorders, for example, Hirschsprung's disease, diverticular disease, and 'functional diarrhoea'. These acted as control observations.

Results

Clinical features

The main clinical features are summarised in Figures 1 and 2. The age range was wide, 12-77 years with a mean of 51 years. Eighteen cases were in females and 11 cases in males. Sixteen patients recovered on conservative management, nine required a colectomy, and there were eight deaths. Four of these eight had undergone colectomy.

Twenty-seven of the 29 patients had received a recent course of antibiotics and had developed symptoms within three weeks of completing the course. The details are given in Figure 2A and D. Only one antibiotic had been administered in 11 cases. In these, the antibiotic was administered for a trivial illness in six, and to cover extra-abdominal surgery in three. Only one of this group had clinically apparent cardiovascular disease. Of the 16 patients for whom a mixture of antibiotics had been prescribed, all were either chronically ill or recovering from major surgery. Six had overt cardiovascular disease. Two patients had not received antibiotics recently, but only one was in perfect health before presentation.

Diarrhoea was the major presenting symptom in 25 cases; three presented with an acute abdomen and one with chronic abdominal pain and a change of bowel habit.

The major sigmoidoscopic findings, where available, are summarised in Fig. 1D and the results of stool cultures in Figure 1E. No quantitative bacteriology was performed.

Histopathology

We were able to classify lesions into types I, II, or III, depending on the degree of change observed.

Biopsies were classed type 1 (T1) when the main inflammatory changes were restricted to the interglandular surface epithelium and immediately subjacent lamina propria (Fig. 3). This took the form of focal epithelial necrosis or irregularity, together with the presence of polymorphs, nuclear dust, and eosinophilic exudate in the lamina propria. Small luminal showers of fibrin and polymorphs were also seen splaying out from these foci. Serial sections, wherever possible, were cut on all T1 lesions to eliminate the possibility that a larger lesion was present in the specimen.

Lesions were classified type 2 (T2) when the typical appearances described by Goulston and McGovern (1965) were present (Fig. 4). The major feature was a well-defined group of disrupted glands. These were distended by mucus and polymorphs and had usually lost the superficial half of their epithelial lining. They were surmounted by a cloud of epithelial debris, fibrin, mucus, and polymorphs, 'the pseudomembrane'. Within this the polymorphs were often held in columns by strands of mucus (Fig. 4 (inset)). In the literature the terms membranous and pseudomembranous are confusing and used in differing senses. They are sometimes regarded as synonyms and sometimes distinguished, even in basic pathological texts. The term pseudomembranous is preferred in this paper and describes the pathological inflammatory covering that is raised up above the surface of the mucosa characterising the T2 lesion.

When complete structural necrosis of the mucosa was present, with a thick covering of fibrin, mucus, and inflammatory debris (Fig. 5), the lesion was classified as type 3 (T3).

Using the criteria outlined above, the 23 biopsies were classified as shown in Table 1. The presence of the other significant abnormalities is also presented in this table. Many of these did not apply to the T3 lesion which was dominated by the inflammatory membrane. The two cases from whom non-diagnostic biopsies were obtained were proven to have pseudomembranous colitis on subsequent examination of the gross specimen.

Certain helpful but non-diagnostic features were present in both T1 and T2 biopsies. Areas of normal mucosa were present in all. Where the epithelium and glands were intact, inflammation was limited to the superficial half of the lamina propria, and frequently it was immediately subepithelial (Fig. 6). The predominant inflammatory cell type was the polymorph and this was associated with nuclear debris. Plasma cells and lymphocytes, although increased, were never present in large numbers. In-
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**Fig. 1**

**Salient Clinical Details in 29 Patients with Pseudomembranous Colitis**

**A**

- **Age Range:** 12-77 yrs mean 51 yrs
- **Sex Distribution:** M. II F. 18

**B**

- **Main Presenting Symptoms:**
  - Diarrhoea 25
  - Acute Abdomen 3
  - Change of bowel habit 1

**C**

- **Associated Diseases:**
  - Seriously ill or post major surgery 14
  - Trivial infection 8
  - Orthopaedic case 6
  - Well 1

**D**

- **Sigmoidoscopy Findings in 21 Patients:**
  - Plaques yellow/white 14
  - Non-specific abnormality 6
  - Normal 1

**E**

- **Stool Cultures in 24 Patients:**
  - No pathogens 19
  - Candida 2
  - Bacteroides 1
  - Staph. Albus 1
  - Klebsiella 1

**F**

- **Outcome:**
  - Deaths 8 (all over 55 yrs)
  - Recoveries 21
  - Colectomies 8 (4 died)

**Fig. 2**

**Antibiotic Details Preceding Onset of Pseudomembranous Colitis (29 Patients)**

**A**

- **History:**
  - No recent course 2
  - Finished course within previous 21 days 27

**B**

- **16 Cases Received a Mixture of Antibiotics Which Included:**
  - Clindamycin 12
  - Lincomycin 3
  - Ampicillin 8
  - Cloxacin 3
  - Gentamicin 2
  - Nearam 2
  - Fucidin I
  - Fucidacin, I Ceporin, I Tetracycline, I Septrin, I Sulphonamide

**C**

- **II Cases Received Only a Single Antibiotic:**
  - Clindamycin 3
  - Ampicillin 3
  - Lincomycin 2
  - Cloxacin 1
  - Gentamicin 1
  - Nearam 1
  - Fucidin I
  - Fucidacin 1
  - Ceporin 1
  - Tetracycline 1
  - Septrin 1
  - Sulphonamide 1

**D**

- **Diarrhoea:**
  - Commenced during course 17
  - After course finished 10
Fig. 3  A rectal biopsy showing the type 1 lesion. A small spray of fibrin, polymorphs, and epithelial debris is seen arising from the superficial interglandular area in close proximity to a dilated capillary (arrow). (Haematoxylin and eosin × 105:5)

Fig. 4  The type 2 lesion. A well-defined focus of disrupted glands distended by mucin and polymorphs but flanked by normal mucosa. Inset: a detail from the overlying 'pseudomembrane' not in the main picture, showing the characteristic column pattern of the polymorphs and mucin. (H and E × 55)
Mucosal ulceration was not prominent in either T1 or T2 lesions. Where the surface epithelium was lost this was very localised while at other sites the epithelium often showed a serrated appearance.

Discussion

CLINICAL FEATURES
Although pseudomembranous colitis is now seen in younger patients with milder forms of illness, it is still in the older patient who is chronically sick or postoperative that it poses the most serious danger. All the deaths in this series occurred in patients over 50 years of age (Fig. 7). In addition, all but one were seriously ill from other causes, or recovering from major surgery. There were six patients under 40...
years of age and the youngest was aged 12. Two of this group required colectomy but there were no deaths.

Sigmoidoscopy showed white or yellow plaques in 14 cases. Even when plaques are seen, a biopsy may not be diagnostic because of sampling error. Tedesco et al. (1974) point out the importance of choosing the correct site and taking a biopsy of the plaque. Unless specifically sought, the smaller lesions of Type I are easily overlooked at sigmoidoscopy. For this reason a carefully taken drug history in mild cases of diarrhoea may alert the clinician. Even so we have seen Type I lesions when the sigmoidoscopy appearance of the mucosa has been reported as normal. In those coming to surgery a confident diagnosis of pseudomembranous colitis had been made in only one of the five in whom preoperative biopsies were available. The urgency of diagnosis when surgery is imminent justifies asking for a rapid frozen section on a carefully taken biopsy in order to prevent too radical a procedure.

Two of the 13 patients with Type I lesions underwent colectomy (15%) and two also of the seven with Type II lesions (29%). Type I lesions were more common among those who developed diarrhoea during the course of antibiotic therapy (9 of 14, 64%) than in those who developed diarrhoea after treatment had finished (3 of 7, 43%).

Type II lesions did occur in those presenting during the course of antibiotics (3 of 14, 21%) but were relatively more common (4 of 7, 57%) in those presenting subsequently (Table 2). However, we were unable to use the histological classification as a guide to clinical prognosis.

These observations confirm the close association between pseudomembranous colitis and antibiotics, in particular lincomycin and clindamycin (Schapiro and Newman, 1973; Viteri et al., 1974). Of the 29 cases, only two had not completed a course of antibiotics within the previous month. Twenty of 27 had received lincomycin or clindamycin, singly or in combination, while 11 had received ampicillin, alone or with another antibiotic. Ten patients gave a history of diarrhoea or a skin rash associated with previous antibiotic courses.

It is questionable whether all 'antibiotic induced
Pseudomembranous colitis is of the pseudomembranous pattern (Gibson et al., 1975). If one excludes proven infective lesions, such as staphylococcal colitis, it is possible that this is the case. The inflammatory 'non-diagnostic' biopsies described in the literature (Cohen et al., 1973; Scott et al., 1973; Le Frock et al., 1975) may well have had the pattern of variants of T1 lesions. Such cases, when progressive, terminate in pseudomembranous colitis. Other forms of chronic non-specific inflammatory bowel disease precipitated by antibiotic-associated diarrhoea have not been described. This supports the idea that the type 1 lesions in antibiotic-associated colitis are early forms of pseudomembranous colitis. More work on biopsies from early cases may clarify the problem.

**HISTOPATHOLOGY**

For the histopathologist the classification of lesions as types 1, 2, and 3 emphasises the spectrum of biopsy appearances found in pseudomembranous colitis and the need for improved histological criteria with which to distinguish different types of mild colitis which are usually diagnosed as 'non-specific' or 'non-diagnostic'.

Currently the 'summit-lesion', of the type 1 change (Fig. 3), is the earliest recognisable abnormality on which to make a positive diagnosis of pseudomembranous colitis. It is well illustrated in other papers and is not simply an artefact of sectioning (as serial sections in this study have shown) (Goulston and McGovern, 1965; Gibson et al., 1975; Steer, 1975). It occurs immediately beneath the surface epithelium between the glandular openings. The lamina propria shows the presence of eosinophilic material along with the focal accumulation of polymorphs and nuclear debris. The overlying epithelium usually becomes irregular, crenated or degenerate and a pin-point microscopic eruptive focus develops (Figs. 3 and 6). These lesions are small and may be revealed only on step sections. Indeed, in some of these cases many levels were cut through a block before the type 1 lesion was found. It is also important to pay attention to the adjacent mucosa, for similar 'summit-lesions' were noted in three biopsies from the control group (2 ulcerative colitis, 1 Crohn's disease). In pseudomembranous colitis adjacent mucosa is either normal or shows superficial and focal accumulation of polymorphs and nuclear debris. Oedema of the lamina propria and occasional poorly formed crypt abscesses may be present. When similar surface lesions were seen in Crohn's disease or ulcerative colitis the accompanying inflammatory changes in the mucosa were more severe, corresponding to the descriptions of Morson and Dawson (1972). The 'summit-lesion' is therefore only diagnostic in the presence of minimal inflammatory changes. Unlike Sumner and Tedesco (1975), we found that inflammation in the lamina propria was marked only in the type 3 case.

It was confirmed by subsequent examination of the operative or necropsy specimen in three type 1 cases that summit lesions are part of the developing picture of pseudomembranous colitis. In addition, nine other colons that were examined showed these lesions alongside the classical appearances of pseudomembranous colitis.

As described in this paper the type 2 or glandular lesion of pseudomembranous colitis should present no diagnostic problem on rectal biopsy (Fig. 4). It was seen in nine of the 23 biopsies. Typically, there is a well circumscribed focus of from two to six distended, partially disrupted glands. The ghost outlines of glands remain, often with the deeper epithelial cells still intact. Above, like a volcanic eruption, lies the 'pseudomembrane', a loose network of mucin, polymorphs, nuclear debris, and fibrin. The polymorphs are frequently held in linear streaks by the mucin, a small but sometimes helpful point in poor quality biopsies (Fig. 4, inset). The paucity of inflammation and hence the relatively normal appearance of the adjacent mucosa is again a striking feature.

Only one type 3 lesion was present in the biopsy material (Fig. 5). This appearance results from more complete structural necrosis of the mucosa. Study of the colectomy and necropsy specimens gave evidence that it was a progression from type 2 lesions. When this mucosal necrosis predominates and becomes confluent, it is difficult to distinguish it from the other varieties of colitis which cause extensive necrosis (McGovern and Goulston, 1965). The intestinal mucosa may become opaque and yellow when it is necrotic and infiltrated by inflammatory cells, as in the more acute forms of ischaemic colitis (Fig. 8). When the discrete focal plaques of pseudomembranous colitis (Fig. 9) coalesce it can therefore
resemble these forms of ischaemic disease. A confluent yellow membrane means mucosal necrosis and is not diagnostic of pseudomembranous colitis. At this stage a positive diagnosis from biopsy material is often impossible, for the presence of the inflammatory membrane is not specific and may even be seen in severe Crohn's disease or ulcerative colitis. Three of the control biopsies from the group with ulcerative colitis showed complete structural mucosal necrosis and an overlying membrane of necrotic debris and inflamed granulation tissue. In our experience, however, there is usually some surviving mucosa remaining on the biopsy that offers a clue to the diagnosis.

Operative and necropsy specimens from varieties of ischaemic colitis may also resemble pseudomembranous colitis very closely (Whitehead, 1972), especially if the presence of a pseudomembrane is used as the main diagnostic criterion. It is this resemblance, coupled with the occurrence of capillary microthrombi, that has been the basis of the theory of an ischaemic aetiology for pseudomembranous colitis (Margaretten and McKay, 1971). However, some mucosal abnormalities such as haemorrhage
Fig. 10  Ischaemic colitis. The microscopy of the specimen shown in Figure 8. There is structural necrosis of the mucosa with membrane formation resembling the type 3 lesion in pseudomembranous colitis. However, there is prominent intramucosal haemorrhage (arrowed) and there is no evidence of classical type 2 foci. (H and E × 45)

Fig. 11  Pseudomembranous colitis. Compare with Figure 10. This shows the close resemblance between the ischaemic and pseudomembranous lesions once structural necrosis has occurred. Here there are sharp margins to the lesions, no haemorrhage and elsewhere in the specimen typical type 2 appearances were present. (H and E × 55)
and intense congestion are a prominent feature of the acute varieties of ischaemic colitis (Wilson and Qualheim, 1954; Ming, 1965) (Fig. 10), and we have found this feature only rarely in pseudomembranous colitis, and even then the ghost outlines of the distended glands remain. In the chronic forms of ischaemia there is glandular atrophy accompanied by fibrosis and hyalinisation of the lamina propria adjacent to the necrotic zones (Marston et al., 1966). In pseudomembranous colitis the transition from necrotic zones to relatively normal mucosa is more sudden (Fig. 11), and in addition type 2 lesions are usually seen at some point. Poor fixation or autolysis, with loss of glands but not lamina propria, can occasionally present an appearance easily confused with the glandular ghost outlines of pseudomembranous colitis.

**PATHOGENESIS**

The aetiology of pseudomembranous colitis is unknown. It has been recorded in a variety of clinical states, and primary roles for infection, antibiotics, ischaemia, and toxins have all been put forward, but no one agent offers a wholly satisfactory explanation (Goulston and McGovern, 1965; Hardaway and McKay, 1959). A viral aetiology for clindamycin-associated disease is among the most recent of theories (Steer, 1975).

This series offered no support for a simple infective bacteriological aetiology, culture for pathogenic organisms being unrewarding. However, studies on quantitative alterations in the faecal or mucosal flora were not carried out (Marr et al., 1975). Along with many other recent papers we confirm that antibiotics, in particular, clindamycin and lincomycin, have a role in the pathogenesis (Groll et al., 1970; Smart et al., 1976; Unger et al., 1975). But whether they act directly, via metabolites, or just provide a suitable ambiance for the development of the colitis is still conjecture.

In the literature, there is frequent reference to the association between chronic cardiovascular disease, states of shock, and pseudomembranous colitis (Drucker et al., 1964). The experimental work on vascular occlusion and low flow states, however, produces a haemorrhagic picture of total or incipient infarction (Robinson et al., 1972), and many earlier clinical reports would today be categorised as pure ischaemic enterocolitis or haemorrhagic necrotising enterocolitis. A non-occlusive ischaemic pathogenesis for pseudomembranous colitis is still favoured by many workers based on the frequency with which mucosal capillary thrombi are found. McKay et al. (1955) have tried to produce the disease experimentally by inducing mucosal 'capillary thrombosis', and Whitehead (1971) has supported this concept with human necropsy observations. Capillary microthrombi were not seen in any of the type 1 lesions and in only three type 2 biopsies (Table 1). They were, however, present in six of the 10 colectomy specimens.

If capillary microthrombi do initiate the disease, then one would expect to find them in type 1 biopsies. On the other hand, if they are solely the consequence of severe ulceration why are they not seen more frequently in severe Crohn's disease and ulcerative colitis? Sumner and Tedesco's (1975) observations on mild cases of pseudomembranous colitis did not reveal microthrombi and they are not mentioned in several other studies (Goulston and McGovern, 1965; Smart et al., 1976; Scott et al., 1973). The evidence, therefore, suggests that while capillary microthrombi may be responsible for the features of the later stages of pseudomembranous colitis, they are unlikely to be the initiating cause.

While the precise aetiology is unknown, a local Shwartzman phenomenon has been proposed for the pathogenesis of pseudomembranous colitis (Hjort and Rapaport, 1965). This is also a two-stage process involving a preparatory phase in which there is focal necrosis and aggregation of granulocytes, followed by a provoking phase in which localised intravascular coagulation occurs. In the majority of the type 1 lesions we noticed vascular margination of polymorphs and there was a distinct impression that capillary leakage was responsible for the eosinophilic material and inflammatory debris in the lamina propria (Fig. 12). This exudation, an early event in the production of the type 1 lesion and possibly a trigger to the glandular disruption that follows, might correspond to the preparatory phase in a localised Shwartzman reaction. This epithelial disorganisation would then act to localise capillary microthrombi in the provoking phase and allow access to the circulation of agents previously excluded by the intact mucosa. It is also an explanation for the characteristic focal nature of the lesions.

The clinical observations lend some support to this two-stage concept. Only rare case reports exist of pseudomembranous colitis arising in previously fit individuals (Jackson and Anders, 1972). A preceding 'preparatory' history of chronic disease, major surgery, or antibiotics is required. After this, in only a select group of patients, does the disease arise, we suggest as a response to a second stimulus, now potentiated by the clinical situation.

The localised Shwartzman phenomenon is entirely non-specific, and little information exists on the mechanism by which the above factors might initiate their effect on the intestinal mucosa, although qualitative alterations in intestinal flora, mucosal enzymes, or bile salt metabolism are possibilities.
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While these are only speculations based on our histological observations, and many anomalies exist, future experimental work aimed at inducing a localised Shwartzman reaction in the intestine by these means would seem a fruitful path (Goldgraber and Kirsner, 1959). For at present there is no evidence to support a specific immunological reaction, such as the Arthus phenomenon, and little support for a solely infective or ischaemic aetiology.

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