ANTIBIOTIC ASSOCIATED PSEUDOMEMBRANOUS COLITIS — REPORT OF FIVE CASES AND REVIEW OF THE LITERATURE

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SYNOPSIS

Five cases of pseudomembranous colitis are presented. The clinical and pathological features of this condition are reviewed. Specific therapy is available, and it is hoped that increased awareness of this condition may allow more cases to be diagnosed in Singapore.

INTRODUCTION

While pseudomembranous colitis (PMC) was first described ninety years ago, the last decade has seen major advances in the understanding of its aetiology, pathogenesis and treatment. However, this condition seems to be uncommon in Singapore. We report five patients seen in one medical unit over a 3-year period.

CASE REPORTS

CASE 1

A 36-year-old Chinese man was admitted with Henoch-Schonlein purpura. Two days later, he became febrile and oral Ampicillin, 500 mg 6-hourly was prescribed. Six days later, he developed upper gastrointestinal haemorrhage. Gastroscopy showed a bleeding gastric ulcer and partial gastrectomy was performed. He developed a high fever the day after surgery. Blood cultures grew Acinobacter. Ampicillin was continued, and in addition Cloxacillin and Gentamycin were commenced. On the third postoperative day, profuse watery diarrhoea occurred up to ten times daily. Sigmoidoscopy showed yellow plaques on an edematous rectal mucosa. Biopsy confirmed pseudomembranous colitis. Stool cultures for enteric pathogens were negative, but Clostridium culture was unavailable at the time.

Ampicillin and Cloxacillin were withdrawn. Vancomycin 500 mg six hourly and Metronidazole 800 mg eight hourly were given orally. Diarrhoea and fever subsided rapidly and repeat sigmoidoscopy six days later was normal. All antibiotics were withdrawn after 10 days and the patient made an uneventful recovery.

CASE 2

A 40-year-old Indian man was admitted with a five-day history of profuse watery diarrhoea up to twenty times daily associated with abdominal cramps, vomiting and fever. He had been on oral Ampicillin and Cloxacillin for the past one month for aseptic necrosis of the left hip. Sigmoidoscopy revealed a patchy proctitis with pseudomembranes. Biopsy showed fragments of exudates, consistent with pseudomembranes. Stool cultures were negative for enteric pathogens but positive for Clostridium difficile. All symptoms subsided rapidly on withdrawal of the antibotics and repeat sigmoidoscopy 4 days later was normal.

CASE 3

A 33-year-old Malay man was admitted with a ten-day history of profuse watery diarrhoea up to 15 times daily. He took oral Tetracycline 250 mg 6-hourly for 3 days for tonsillitis. Diarrhoea started nine days later. Sigmoidoscopy revealed mucosal edema with adherent pseudomembranes both in the rectum and in the lower sigmoid colon. Biopsy showed focal volcano-like exudates of mucus and polymorphs typical of pseudomembranous colitis (Figure 1). Stool culture was negative for enteric pathogens but positive for Clostridium difficile. The diarrhoea resolved spontaneously and repeat sigmoidoscopy three days later was normal.

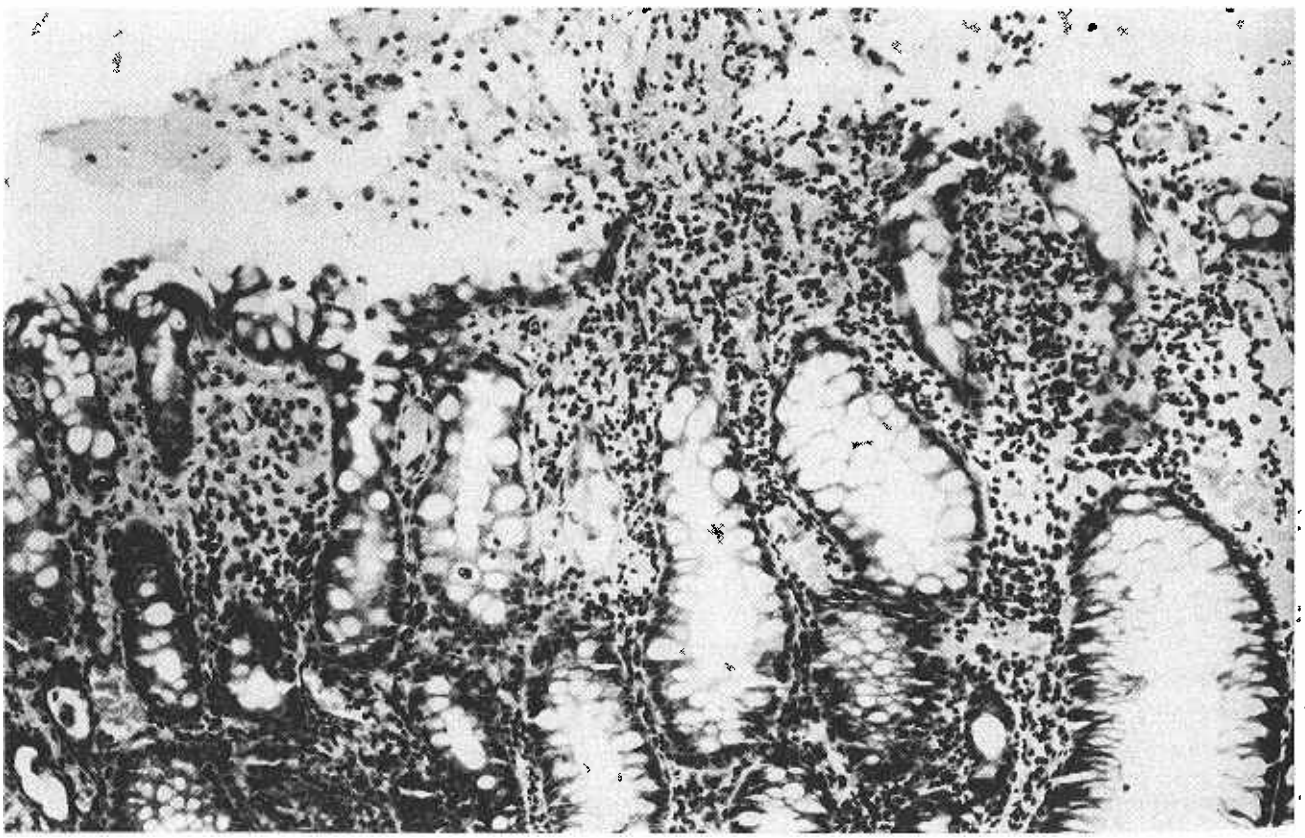

FIGURE 1 Pseudomembranous colitis. There is a "volcano-like" eruption of mucus, polymorphs and fibrin from the lamina propria where there is surface epithelial ulceration. There is also inflammation in the adjacent lamina propria and marked loss of mucin from the goblet cells.

CASE 4

A 48-year-old Chinese man with chronic renal failure underwent a cadaveric renal transplant. On the 5th post-operative day, he developed a swinging fever and a five-day course of intravenous Cefoperazone, 1 gm 12-hourly was given. The fever returned one week later and Cefotaxime, 1 gm 12-hourly was started. Two days later, the patient developed profuse watery diarrhoea up to ten times daily with occasional streaks of blood. The diarrhoea was associated with abdominal cramps. Sigmoidoscopy two days later revealed mild proctitis with pseudomembranous plaques. Biopsy showed polymorph infiltration of an intact mucosa with a heavy exudate of mucus and polymorphs. The picture was volcanic in quality in places and typical of pseudomembranous colitis. Stool cultures were negative for both enteric pathogens and Clostridium difficile. The Cefotaxime was stopped and oral Vancomycin 250 mg 6-hourly was started. The diarrhoea subsided over the next ten days and repeat sigmoidoscopy was normal. The Vancomycin was given for a total of one week. However, there were signs of rejection and the kidney had to be removed.

CASE 5

A 80 year old Chinese man was admitted with fever and jaundice suggestive of cholangitis and blood cultures grew Proteus mirabilis. He was started on parenteral Ampicillin and Gentamycin. Cefotaxime was started one week later. He had a stormy hospital course, developing transient acute renal failure and right hemiparesis. Two weeks after admission he developed watery diarrhoea up to 10 times daily. Sigmoidoscopy to 15 cm showed plaques consistent with pseudomembranes. Biopsy showed non-specific changes. Stool culture was negative for enteric organisms but positive for Clostridium. The Gentamycin and Ampicillin were stopped but the Cefotaxime continued for another week. Vancomycin 250 mg qds and Metronidazole 400 mg tds were given for seven days. The diarrhoea gradually improved; his bowel habits became normal and he was discharged. Investigations for the source of his septicemia are still in progress.

DISCUSSION

Pseudomembranous colitis (PMC) was first described in 1893 (1). Initial reports indicated an association with shock, recent abdominal surgery, and other serious underlying disease. PMC was then a serious condition with a high mortality rate. In the 1950s an association with antibiotics was described and Staphylococcus aureus was implicated as the causative agent. It was not until 1977 that PMC was shown to be due in most instances to toxins produced by Clostridium difficile.

Clostridium difficile is a spore-forming gram positive anaerobe. It can be cultured from the stools of up to 60% of normal infants and 3% of healthy adults (2). It is postulated that antibiotic therapy leads to an alteration in the normal gut flora allowing the proliferation of Clostridium difficile. This organism then produces toxins and cause PMC.

The antibiotic therapy which leads to PMC may be oral or parenteral. Nearly all antibiotics have been known to lead to PMC but Clindamycin and Ampicillin appear to account for a large proportion of cases (2).

The illness may start during or after the antibiotic therapy. Typically, there is profuse watery diarrhoea without blood. Crampy hypogastric pains and fever are common. Sigmoidoscopy shows yellowish white plaques with normal or mildly inflammed intervening mucosa. Microscopic changes vary from mild mucosal inflammation to fibrinoid necrosis of the surface mucosa with firmly adherent material composed of fibrin and leucocytes. In some cases, sigmoidoscopy may be unhelpful as pseudomembranes may only occur in the proximal colon requiring colonoscopy for visualization (3). Barium studies are not generally indicated.

The diagnosis can be further confirmed by the identification of Clostridium difficile cytotoxin in the stools. This test is positive in 95% of patients with confirmed antibiotic associated PMC (2). Stool culture for Clostridium difficile is positive in 90% of patients with antibiotic associated PMC (2).

Treatment consists of stopping the offending antibiotic if possible. Specific drug therapy includes the use of oral Vancomycin, Metronidazole or Bacitracin General measures, such as replacement of fluid, electrolytes, and albumin may be required. Anti-diarrhoeal agents are contra-indicated. The illness vary in severity from a mild diarrhoea which resolves after cessation of antibiotic or exhibition of Vancomycin, to a fulminant colitis which can progress to toxic megacolon. Older patients and those with severe underlying disease tend to develop severe colitis.

Although much is now known about PMC, several questions remain unanswered. It is not known why a high proportion of infants harbour Clostridium difficile and its toxins without apparent ill effects. Clostridium difficile often shows in-vitro sensitivity to the same antibiotics which has resulted in its overgrowth. Metronidazole, known to be an effective treatment for PMC, has also been implicated in its causation. Although a sizeable proportion of patients on antibiotics develop diarrhoea, only some of these will be positive for Clostridium difficile toxin. Of these, only a proportion will have PMC. There appears to be a continuous spectrum from the mild antibiotic related diarrhoea negative for Clostridium difficile, on the one hand, to PMC on the other. The exact proportion of patients in each category and the factors determining which end of the spectrum each patient belongs to, remain to be elucidated.

To diagnose PMC, a high index of suspicion is required. Sigmoidoscopy and biopsy should be performed in all patients developing diarrhoea during or shortly after antibiotic therapy. It is unfortunate that the toxin assay cannot be performed in Singapore but stool culture for Clostridium difficile is available and should be performed in appropriate cases. The five cases reported here have been seen by one gastroenterologist over a three-year period and it seems likely tht the rarity of PMC in Singapore is at least partly due to underdiagnosis.

Recognition of PMC and prompt cessation of the offending antibiotic may allow rapid relief of the patient's symptoms. Specific therapy with Vancomycin or Metronidazole can be life-saving. PMC is a diagnosis worth bearing in mind in a patient with acute diarrhoea.

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