Pseudomembranous colitis without diarrhoea following *Helicobacter pylori* eradication therapy

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INTRODUCTION

In recent years, there has been an increasing acceptance of *Helicobacter pylori* eradication therapy for the treatment of *H. pylori*-positive peptic ulcer disease not only by gastroenterologists but also by primary care physicians, especially following the 1994 National Institutes of Health (NIH) Consensus Conference and the Maastricht Consensus Report by the European *Helicobacter Pylori* Study Group (Malfertheiner et al, 1997). One possible serious side-effect of *H. pylori* eradication therapy is pseudomembranous colitis, which usually presents with diarrhoea (Awad et al, 1994). This article reports a case of pseudomembranous colitis presenting with a fall in haemoglobin level but without diarrhoea following *H. pylori* eradication therapy.

CASE REPORT

A 73-year-old man with a known history of hypertension and gout was admitted into hospital having had chest and epigastric discomfort for 3 days. His chest discomfort was not related to exertion, and there was no recent history of antibiotic or non-steroidal anti-inflammatory drug intake. His bowel habit was normal. Physical examination was unremarkable except for mild ankle oedema. Per rectum examination revealed brownish stool and no mass was felt.

Serial electrocardiograms revealed non-specific flattening of T-waves over the lateral chest leads with no serial change. Chest X-ray revealed normal heart size and clear lung fields. Full blood count revealed a mild normochromic normocytic anaemia with haemoglobin concentration of 10.3 g/dl (normal range: 13.0–18.0 g/dl), a normal leukocyte count of 6.0×10^9/litre (normal range: 4.0–11.0×10^9/litre) and a normal platelet count of 176 x 10^9/litre (normal range: 150–400×10^9/litre). Renal function tests revealed mild renal impairment, with urea and creatinine levels being 19.2 mmol/litre (normal range: 2.5–7.5 mmol/litre) and 0.181 mmol/litre (normal range: 0.05–0.14 mmol/litre) respectively. The serum sodium, potassium, calcium and phosphate levels were normal. Liver function tests were normal. Ultrasound scan of the kidneys revealed bilateral small kidneys, and there was no hydronephrosis. An upper gastrointestinal endoscopy revealed antral gastritis with erosions as well as duodenitis. Histological examination of antral biopsies revealed the presence of *Helicobacter pylori*.

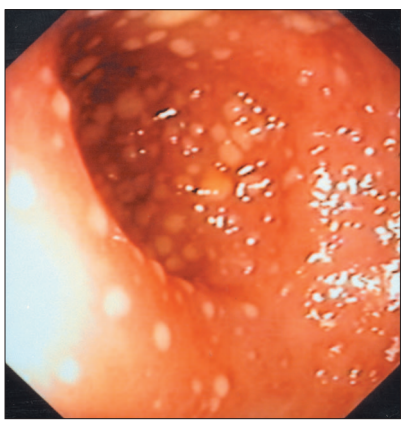
The patient was prescribed a 1-week course of lansoprazole 30 mg twice daily, amoxycillin 1 g twice daily and clarithromycin 500 mg twice daily, which he tolerated well. His epigastric discomfort subsided following treatment. However, on follow-up 6 weeks after the initial upper gastrointestinal endoscopy, the patient was noted to have pallor, and a full blood count revealed a significant drop of his haemoglobin concentration to 7.8 g/dl. There was no history of passing tarry stool, and there was no diarrhoea all along, nor did he experience any abdominal pain or distension. Stool test for occult blood was positive. A second upper gastrointestinal endoscopy revealed no abnormality, indicating that the previous erosive gastritis and duodenitis had healed already. However, colonoscopy revealed the presence of numerous raised light-yellowish plaques, 1–5 mm in diameter, scattered throughout the entire colon and rectum, which were compatible with pseudomembranous colitis (*Figure 1*). Colonic biopsies revealed mucopurulent substance overlying oedematous mucosa (*Figure 2*). Foci of dilated necrotic glands filled with mucus and neutrophils were identified, but the intervening mucosa showed only oedema and a mild increase in inflammatory cells (*Figure 3*). Special stains for acid fast bacilli and fungi were negative. The features were consistent with pseudomembranous colitis. A subsequent stool test for *Clostridium difficile* cytotoxin was also positive.

The patient was treated with a 10-day course of oral vancomycin 125 mg four times a day. Around 8 weeks after the initial colonoscopy, a follow-up colonoscopy revealed the complete disappearance of the light-yellowish plaques observed at initial colonoscopy (*Figure 4*). At the time of the second colonoscopy, his haemoglobin concentration had risen back to 10.4 g/dl.

DISCUSSION

H. pylori eradication therapies are now widely prescribed not only by gastroenterologists but also by internists and family practitioners (Milne et al, 1995; Boekema et al, 1997; Breuer et al, 1998). Many different therapeutic regimens for *H. pylori* eradication have been tried. One of the most favoured regimens, which is recommended by most countries as first-line treatment for the eradication of *H. pylori,* comprises a proton pump inhibitor plus two of the following antibiotics: amoxycillin, clarithromycin and metronida-

Figure 1. Endoscopic view of the colon showing multiple light-yellowish plaques of various sizes on the mucosal surface, compatible with pseudomembranous colitis.



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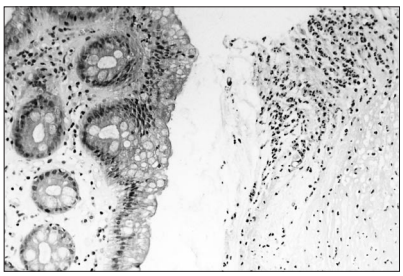


Figure 2. Photomicrograph of colonic biopsy demonstrating mucus and polymorphs overlying oedematous mucosa (haematoxylin eosin stain, original magnification x125).

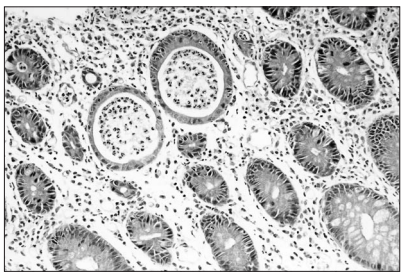


Figure 3. Photomicrograph of colonic biopsy demonstrating distension of colonic crypts by mucopurulent material (haematoxylin eosin stain, original magnification x125).

zole (Lee and O'Morain, 1997; Misiewicz, 1997).

Current *H. pylori* eradication therapies are generally safe, although mild side-effects, such as gastrointestinal upset, are common during treatment. One serious side-effect of such therapies is pseudomembranous colitis. In a trial of *H. pylori* eradication using omeprazole plus amoxicillin and metronidazole for 1 week (Hudson et al, 1995), the incidence of pseudomembranous colitis was 0.8% (1 in 132).

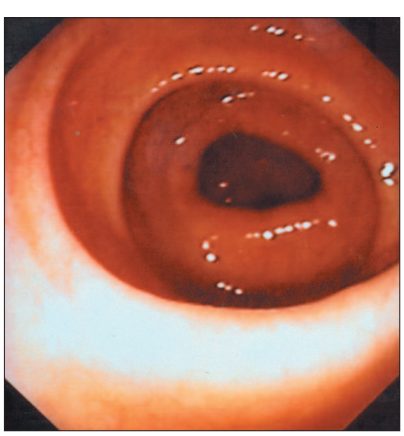
Pseudomembranous colitis can be induced by virtually all antibiotics except aminoglycosides and vancomycin (Amin, 1985; Carbon et al, 1994), but among the antibiotics commonly used for *H. pylori* eradication, amoxicillin is the most likely culprit. Clarithromycin alone is very rarely associated with pseudomembranous colitis, but clarithromycin in combination with omeprazole in the absence of amoxicillin has been reported to induce pseudomembranous colitis (Teare et al, 1995).

The profound acid suppression of proton pump inhibitors can theoretically weaken the body's defense against enteric infections. In a case control study by Neal et al (1996), proton pump inhibitors were found to significantly increase the risk of *Campylobacter* infections in people aged 45 years or over, an effect not seen with histamine-2 antagonists or previous gastric surgery. On the other hand, another case control study by Garcia Rodriguez and Ruigomez (1997) did not support a major role for acid suppression in the development of bacterial gastroenteritis. In addition, long-term omeprazole therapy was not found to lead to small intestinal bacterial overgrowth (Nelis et al, 1994). It is still uncertain whether the likelihood of inducing pseudomembranous colitis by antibiotics is increased by the concomitant administration of a proton pump inhibitor.

Patients with pseudomembranous colitis usually present with profuse watery diarrhoea within 6 weeks of antibiotic therapy (Fekety and Akshay, 1993). However, this patient did not have any diarrhoea nor abdominal pain during the course of his illness, and it was not until colonoscopy that pseudomembranous colitis was detected.

Another category of patients who suffer from pseudomembranous colitis and yet often do not have diarrhoea are those who present with acute abdomen as a result of *Clostridium difficile*-associated fulminant colitis (Triadafilopoulos and Hallstone, 1991; Medich et al, 1992). These latter patients usually have severe abdominal pain, fever, leukocytosis and paralytic ileus, none of which were present in this patient. To the authors' knowledge, pseudomembranous colitis presenting with anaemia and occult intestinal blood loss in the absence of diarrhoea and abdominal pain has not been reported previously.

Figure 4. Repeat colonoscopy about 2 months after treatment showing complete disappearance of pseudomembranous plaques.



Nowadays, the gold standard for diagnosing *C. difficile* enterocolitis is by the detection of *C. difficile* toxin(s) in stools. The classical method of detecting *C. difficile* toxin B is by demonstrating its cytopathic effect in cell culture monolayers, but this test has the disadvantages of being expensive and time-consuming (Fekety and Akshay, 1993). Commercially available enzyme immunoassay tests for detection of *C. difficile* toxin A and/or toxin B are now widely used for diagnosing *C. difficile* infection. These assays have the advantages of rapidity and simplicity but have a lower sensitivity than cytotoxicity assay (Barbut et al, 1993). More recently, polymerase chain reaction assays of *C. difficile* toxin genes have been reported to be capable of diagnosing *C. difficile* infection with sensitivity and specificity comparable to those of cytotoxicity assay, and have the added advantages of speed and not requiring special equipment (Alonso et al, 1999; Karasawa et al, 1999).

Regarding the endoscopic diagnosis of pseudomembranous colitis, it must be noted that in some patients with pseudomembranous colitis, the typical endoscopic features are limited to the colon above the rectosigmoid area so that the diagnosis may be missed if sigmoidoscopy alone is performed (Seppala et al, 1981; Tedesco et al, 1982).

For patients with documented pseudomembranous colitis, both oral metronidazole and vancomycin are effective therapies (Teasley et al, 1983), but general supportive treatment and discontinuation of other antibiotics, if possible, should not be overlooked. Although most cases of pseudomembranous colitis respond to medical therapy, surgery is indicated for those who fail to respond to medical therapy or present with signs of

peritonitis (Waddell et al, 1992; Agnifili et al, 1994; Morris et al, 1994). In a series of cases of *C. difficile*-associated colitis, Lipsett et al (1994) reported that 0.39% (13 out of 3300) of patients required surgical intervention. The mortality rate of pseudomembranous colitis has been reported to be around 4% in those treated medically, while the mortality rate ranges from 14% to 100% in those who require surgical intervention (Lipsett et al, 1994; Synnott et al, 1998).

CONCLUSIONS

This article has presented a case of pseudomembranous colitis without diarrhoea following *H. pylori* eradication therapy. With the widespread treatment of *H. pylori* infection nowadays, this rare but potentially serious complication should be borne in mind. Clinicians must also be aware that pseudomembranous colitis can present with occult gastrointestinal blood loss and anaemia in the absence of diarrhoea. HM

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