

Pseudomembranous colitis associated with a triple therapy for *Helicobacter pylori* eradication

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Abstract

Helicobacter pylori (*H. pylori*) is one of the most common chronic bacterial infections in humans, affecting half of world's population. Therapy for *H. pylori* infection has proven to be both effective and safe. The one-week triple therapy including proton pump inhibitor, clarithromycin, and amoxicillin or metronidazole is still recommended as a first-line treatment to eradicate *H. pylori* infection in countries with low clarithromycin resistance. Generally, this therapy is well-tolerated, with only a few and usually minor side effects. However, rare but severe adverse effects such as pseudomembranous colitis have been reported, *Clostridium difficile* (*C. difficile*) infection being the main causative factor in all cases. We report the cases of two women who developed pseudomembranous colitis after a 1-wk triple

therapy consisting of pantoprazole 20 mg *bid*, clarithromycin 500 mg *bid*, and amoxicillin 1 g *bid* to eradicate *H. pylori* infection. A limited colonoscopy showed typical appearance of pseudomembranous colitis, and the stool test for *C. difficile* toxins was positive. Rapid resolution of symptoms and negative *C. difficile* toxins were obtained in both patients with oral vancomycin. No relapse occurred during a four and eleven-month, respectively, follow up. These cases suggest that physicians should have a high index of suspicion for pseudomembranous colitis when evaluate patients with diarrhea following *H. pylori* eradication therapy.

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Key words: *Helicobacter pylori* eradication; Triple therapy; *Clostridium difficile*; Pseudomembranous colitis; Vancomycin

Core tip: Herein are described the cases of two elderly women who developed pseudomembranous colitis after one-week triple therapy consisting of pantoprazole (20 mg *bid*), clarithromycin (500 mg *bid*), and amoxicillin (1 g *bid*) to eradicate *Helicobacter pylori* (*H. pylori*) infection. After a 10-d treatment with oral vancomycin (125 mg every 6 h) both patients had complete resolution of symptoms and negative stool test for *Clostridium difficile* toxins. Clinicians should have a high index of suspicion of pseudomembranous colitis as a rare, but severe complication of *H. pylori* therapy.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is one of the most common chronic bacterial infections in humans, affecting half of the world's population. Its prevalence is high in developing countries and low in the developed ones^[1]. *H. pylori* eradication therapy is supported by numerous consensus groups around the world, and the treatment of millions of infected subjects has demonstrated that such strategy is both effective and safe. The spectrum of indications for *H. pylori* eradication therapy has steadily extended over the last decade^[2] with a resultant increase in its use. The one-week triple therapy including proton pump inhibitor (PPI), clarithromycin and amoxicillin or metronidazole proposed at the first Maastricht conference^[3] to eradicate *H. pylori* is still recommended as the first-line treatment by the recent Maastricht IV consensus conference^[2] in countries with clarithromycin resistance rate under 15%-20% (e.g., Northern European countries)^[4]. Eradication rates with standard triple therapy have fallen to 70%-80% over the past few years, mainly due to increasing resistance to clarithromycin^[5]. Generally, this therapy is well-tolerated, with only a few and usually minor side effects (e.g., nausea, metallic taste). However, severe adverse effects such as pseudomembranous colitis have been reported^[6-13], *Clostridium difficile* (*C. difficile*) being the main causative agent in all cases.

We report the cases of two elderly women who developed pseudomembranous colitis after one-week triple therapy with pantoprazole, clarithromycin, and amoxicillin for *H. pylori* infection.

CASE REPORT

The first case is a 70-year-old woman who was referred to our department with a 10-d history of watery diarrhea (6-12 stools per day) and crampy abdominal pain. Her medical history included hypertension, chronic gastritis *H. pylori* positive, and colonic diverticulosis (previously diagnosed on colonoscopy). Three weeks before admission she completed a one-week triple therapy (pantoprazole 20 mg *bid*, clarithromycin 500 mg *bid* and amoxicillin 1 g *bid*) for *H. pylori* infection. On physical examination, she looked unwell, and her abdomen was mildly tender, with no masses. Temperature and vital signs were normal. Laboratory investigations revealed leukocytosis (14800/mm³) with neutrophilia, high C-reactive protein (11.5 mg/dL), and low levels of serum albumin (2.4 mg/dL), sodium (133 mEq/L), and potassium (2.7 mEq/L). Two days before admission, stool samples examination excluded enteric bacterial pathogens (*Shigella*, *Salmonella*, *Yersinia* spp.) as well as *C. difficile* toxins. Without any prior preparation, the patient underwent a limited colonoscopy, which showed diffusely scattered off-white pseudomembranes attached to the hyperemic underlying mucosa and multiple diverticula (Figure 1). Repeated stool sample examination was positive for *C. difficile* toxins A and B. Treatment with oral metronidazole 500 mg every 8 h was initiated, replaced 72 h later with oral vancomycin 125



Figure 1 Pre-treatment endoscopic examination. Colonoscopy revealed scattered off-white pseudomembranes, some of them around a diverticulum.

mg every 6 h due to unfavorable response. After a 10-d treatment with vancomycin, the patient had a complete resolution of the symptoms and was discharged from hospital with negative results for *C. difficile* toxins and one stool per day. During a four-month follow-up, patient remained asymptomatic.

The second case concerns a 71-year-old woman who was admitted with profuse watery diarrhea (up to 10 stools daily) and abdominal pain. Her prior medical history was unremarkable. Symptoms occurred 5 d after a one-week triple therapy (pantoprazole 20 mg *bid*, clarithromycin 500 mg *bid* and amoxicillin 1 g *bid*) for *H. pylori* eradication. Physical examination was normal, except for signs of dehydration. Microbiological examination of stools was negative for *Salmonella*, *Shigella* and *Yersinia* spp., and did not reveal any parasites. The patient had leukocytosis (12400/mm³), hypokalemia (2.8 mEq/L), and mild inflammatory syndrome. Sigmoidoscopy showed typical signs of pseudomembranous colitis, while a stool test for *C. difficile* toxins A and B proved positive. The patient received 10-d treatment with oral vancomycin 125 mg every 6 h, followed by prompt improvement in symptoms and negative test for *C. difficile* toxins. No relapse occurred during an 11-mo follow-up.

DISCUSSION

Eradication therapy for *H. pylori* provides enormous benefits and has proved to be both effective and safe. Except from the rare and mild side-effects, eradication therapy is generally well-tolerated. Severe adverse effects such as pseudomembranous colitis following eradication therapy have very rarely been reported^[6-13] which is quite surprising, taken into account the immense number of subjects treated worldwide. It is difficult to find a clear explanation why are so rare cases of pseudomembranous colitis after eradication therapy reported in the literature, but some hypotheses were put forward: (1) the use of metronidazole, an efficient drug against *C. difficile*; however, several cases of pseudomembranous colitis, as published, occurred after a regimen containing metronidazole^[8-10]; (2) the short duration of the therapy; (3) almost all treat-

ments are carried out in outpatients (hospitalization is a risk factor for *C. difficile* infection); and (4) many cases with mild clinical disease were most likely not diagnosed, either because the patients did not consult a physician or the physician did not suspect the development of *C. difficile* infection^[10].

Over the last decade, *C. difficile* infection rate has increased dramatically worldwide both in incidence and severity^[14,15]. In addition to broad-spectrum antibiotic therapy, there have been identified many other potential risk factors for *C. difficile* infection (advanced age, female gender, comorbidities, admission to ICU, long hospital stay, immunosuppressive therapy, and PPI use)^[16-21]. Several studies and recent meta-analyses have shown that PPI therapy is associated with increased risk of *C. difficile* infection^[20-27], and United States Food and Drug Administration even issued a safety announcement to inform the public about this possible risk^[28]. Newly published studies have found that *C. difficile* infection can occur outside the above mentioned well-known risk groups, in the absence of any hospitalization and even in young patients with no comorbidities^[29].

All the components of the triple eradication therapy for *H. pylori* (PPI and two antibiotics: clarithromycin and amoxicillin or metronidazole) are potential risk factors for *C. difficile* infection. The most responsible for development of pseudomembranous colitis seems to be clarithromycin, used in both our cases and in most of the published reports^[6,7,10,13].

The spectrum of *C. difficile* infection is wide, ranging from mild, self-limiting diarrhea to fulminant pseudomembranous colitis which is associated with significant morbidity and mortality. Most patients with *C. difficile* infection have a mild-to-moderate disease, but some may develop severe forms of disease such as pseudomembranous colitis, or even complicated by toxic megacolon^[7]. Among variables used to define severe disease, the most important are the presence of pseudomembranes at endoscopy and age over 65 years. Both our cases met the criteria for a severe form of disease, and were treated with vancomycin according to current guidelines recommendations^[30].

Our cases, in addition to the ones published, demonstrate that pseudomembranous colitis can occur after a usually well-tolerated triple therapy for *H. pylori* eradication. Despite this very rare complication, it should be underlined that *H. pylori* eradication therapy provides huge benefits and remains effective and generally safe. However, *C. difficile* infection may occur with an eradication therapy for *H. pylori* consisting of two antibiotics and a PPI. Most likely, *C. difficile* infection cases following *H. pylori* eradication therapy are not as rare as reported by literature, considering that a significant proportion of mild form of disease does not come to physician's attention and thus may remain undiagnosed^[31]. Clinicians should be aware of such complication when prescribing triple therapy for *H. pylori* eradication, and should inform the patients that they may have diarrhea during or after

treatment, and therefore should seek medical advice.

In conclusion, pseudomembranous colitis should be suspected in any patient with watery diarrhea during or after triple therapy for *H. pylori* eradication. Awareness of such complication is particularly important in the actual context when both duration and indications for *H. pylori* eradication therapy have been extended.

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