



EDUCATIONAL OBJECTIVE: Readers will consider causes other than *Clostridium difficile* infection in cases of pseudomembranous colitis when testing is negative or treatment brings no response

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Pseudomembranous colitis: Not always *Clostridium difficile*

ABSTRACT

Although *Clostridium difficile* infection is the cause of most cases of pseudomembranous colitis, clinicians should consider less common causes, especially if pseudomembranes are seen on endoscopy but testing remains negative for *C difficile* or if presumed *C difficile* infection does not respond to treatment. Histologic review of colonic mucosal biopsy specimens can provide clues to the underlying cause.

KEY POINTS

Pseudomembranous colitis is a nonspecific pattern of injury resulting from decreased oxygenation, endothelial damage, and impaired blood flow to the mucosa that can be triggered by a number of disease states.

Chemicals, medications, ischemia, microscopic colitis, other infectious organisms, and inflammatory conditions can all predispose to pseudomembrane formation and should be included in the differential diagnosis.

As most patients with pseudomembranous colitis have *C difficile* infection, it should be excluded first. Empiric treatment for *C difficile* should be started if the patient is seriously ill.

Testing for *C difficile* is with polymerase chain reaction, enzyme immunoassay for toxins A and B, and glutamate dehydrogenase measurement.

PSEUDOMEMBRANOUS COLITIS is most often due to *Clostridium difficile* infection, but it has a variety of other causes, including other infections, ischemia, medications, and inflammatory mucosal diseases (Table 1). When pseudomembranes are found, one should consider these other causes if tests for *C difficile* are negative or if anti-*C difficile* therapy does not produce a response.

These less common causes are important to consider to avoid needlessly escalating anti-*C difficile* antibiotic therapy and to provide appropriate treatment. Pseudomembranous colitis is a nonspecific finding that suggests a larger disease process. Associated signs and symptoms, including fever, abdominal pain, leukocytosis, diarrhea, toxic megacolon, and electrolyte imbalances, may portend a life-threatening condition.¹ Awareness of causes of pseudomembranous colitis other than *C difficile* infection, the focus of this review, is key to prompt diagnosis and potentially life-saving patient care.

■ PSEUDOMEMBRANES ARE NONSPECIFIC

A pseudomembrane is a layer of fibropurulent exudate composed of acute inflammatory cells and mucus originating from inflamed and erupting crypts.² Although most often seen in *C difficile* infection, pseudomembranous colitis is a nonspecific pattern of injury resulting from decreased oxygenation, endothelial damage, and impaired blood flow to the mucosa that can be triggered by a number of disease states.²

On endoscopy, pseudomembranes appear as raised whitish or yellowish plaques that may be scattered or confluent in distribution (Figure 1).² They are usually found in the recto-

Nathalie H. Urrunaga, MD, MS, was supported by Grant Number 5 T32 DK067872-07 from the National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Disease (NIDDK). This document was also supported by the Intramural Research Program of the NIDDK, NIH.

doi:10.3949/ccjm.83a.14183

Colon ischemia usually affects elderly or debilitated patients who have multiple comorbidities

TABLE 1

Conditions associated with pseudomembranous colitis

Chemicals and illicit drugs

Cocaine
Glutaraldehyde

Medications

Cisplatin
Cyclosporine A
Docetaxel
5-Fluorouracil
Nonsteroidal anti-inflammatory drugs (diclofenac, indomethacin)

Infections

Clostridium difficile
Clostridium ramosum
Cytomegalovirus
Entamoeba histolytica
Escherichia coli O157:H7
Klebsiella oxytoca
Plesiomonas shigelloides
Salmonella species
Schistosoma mansoni
Shigella species
Staphylococcus aureus
Strongyloides stercoralis

Inflammatory conditions

Behçet disease
Collagenous colitis
Inflammatory bowel disease
Ischemic colitis

sigmoid colon but may be isolated to more proximal segments.³ Lower endoscopy is often performed in the diagnostic evaluation of patients with unexplained diarrhea, hematochezia, and abnormal abdominal computed tomographic findings (eg, colonic thickening).

CAUSES OF NON-*C DIFFICILE* PSEUDOMEMBRANOUS COLITIS

When pseudomembranous colitis is confirmed endoscopically, *C difficile* infection naturally comes to mind, but the two terms are not interchangeable. A wide differential diagnosis should be maintained, especially when there are clues that *C difficile* infection may not be the correct diagnosis.

Chemicals and medications

Several chemicals and medications can injure the bowel and predispose to pseudomembrane formation.

Glutaraldehyde has long been used to sanitize endoscopes because of its broad antimicrobial activity. Nevertheless, if the disinfecting solution is not adequately rinsed off the endoscope, direct contact with colonic mucosa can produce an allergic and a chemical reaction, resulting in an acute self-limited colitis with pseudomembrane formation.⁴

Chemotherapeutic and antiproliferative agents can be toxic to the bowel, generally through production of free radicals and up-regulation of inflammatory cytokines. The colonic epithelium is then more susceptible to ulceration and mucosal necrosis with pseudomembrane development. Cisplatin, cyclosporine A, docetaxel, and 5-fluorouracil are prominent examples.⁵⁻⁸

Nonsteroidal anti-inflammatory drugs can damage the mucosa at all levels of the gastrointestinal tract. Although gastric ulcerations are more typical (from nonselective cyclooxygenase inhibition), colonic ulcerations and colitis can occur.⁹ These drugs, particularly diclofenac and indomethacin, have been associated with non-*C difficile* pseudomembranous colitis when used by themselves or in conjunction with other agents such as cyclosporine A.^{8,10,11}

Infections

C difficile is the organism most commonly linked to pseudomembranous colitis, but other bacterial, viral, and parasitic pathogens have also been implicated.

Staphylococcus aureus was believed to be responsible for enterocolitis in a series of 155 surgical patients between 1958 and 1962 receiving antibiotic therapy. All had a positive stool culture for *S aureus*, and nine were found to have pseudomembranes at autopsy.¹²

Although this finding has been disputed as a misdiagnosis, since *C difficile* infection was not widely recognized until the 1970s, there is evidence that *S aureus* may indeed be a cause of non-*C difficile* pseudomembranous colitis. In a review of 36 cases of methicillin-resistant *S aureus* bacteremia in Japan, four patients were documented to have intestinal pseudo-

membranes either by endoscopy or autopsy. In two of these patients, biopsies of the pseudomembranes were positive for methicillin-resistant *S aureus*.¹³

***Escherichia coli* O157:H7.** Pseudomembranes have been seen endoscopically in several adults and children with enterohemorrhagic *E coli* O157:H7 infection.^{14,15} This invasive gram-negative rod normally resides in the gastrointestinal tract of cattle, sheep, and other animals and can be pathogenic to people who eat undercooked beef. The organism attaches to and effaces intestinal epithelial cells, and bacterial proteins and the Shiga toxin then damage the vasculature, precipitating bloody diarrhea. Colonic damage can range from mild hemorrhagic colitis to severe colitis with ischemic changes. In patients with enterohemorrhagic *E coli* O157:H7 infection, pseudomembrane formation results from colon ischemia due to microvascular thrombosis or from destructive effects of bacterial enterotoxin.^{1,15}

Cytomegalovirus is a ubiquitous human herpes virus that can affect nearly all organ systems. Infection is often reported in immunocompromised patients, eg, those with acquired immunodeficiency syndrome, chronic corticosteroid use, inflammatory bowel disease, malignancy, or solid-organ transplants. Gastrointestinal manifestations can be nonspecific and range from abdominal discomfort to diarrhea to tenesmus. Pseudomembranous colitis can be a presenting feature of cytomegalovirus involvement.^{16,17} Ulcerative lesions in the colonic mucosa are a frequent accompanying finding on endoscopy.^{18,19}

Other rarer infectious causes of pseudomembranous colitis identified in case reports include *Clostridium ramosum*, *Entamoeba histolytica*, *Klebsiella oxytoca*, *Plesiomonas shigelloides*, *Schistosomiasis mansoni*, and *Salmonella* and *Shigella* species.^{20–26} Additionally, there have been two reports of *Strongyloides stercoralis* hyperinfection manifesting as pseudomembranous colitis.^{27,28}

Ischemia

Colon ischemia usually affects elderly or debilitated patients who have multiple comorbidities. Known risk factors include aortoiliac surgery, cardiovascular disease, diabetes mel-



FIGURE 1. Pseudomembranes (arrow) seen on flexible sigmoidoscopy in a patient with *Clostridium difficile* infection.

litus, hemodialysis, and pulmonary disease. The ischemia can be related to an occlusive arterial or venous thromboembolism, but hypoperfusion without occlusion of the mesenteric or internal iliac arteries is the primary mechanism. Low blood flow states such as atherosclerosis and septic shock can affect the watershed areas, typically the splenic flexure and rectosigmoid junction.

We reported a case of a patient with vascular disease who was incorrectly diagnosed and treated as having refractory *C difficile* infection when pseudomembranes were seen on flexible sigmoidoscopy. Further investigation revealed ischemic colitis secondary to a high-grade inferior mesenteric artery stenosis as the true cause.²⁹

Microvascular thrombosis is the likely mechanism in a number of non-*C difficile* causes of pseudomembranous colitis. For example, in most patients with enterohemorrhagic *E coli* O157:H7 infection, histologic review of colonic mucosal biopsies has revealed fibrin and platelet thrombi in the capillaries, suggesting microvascular thrombosis.^{15,30}

Cocaine has been associated with pseudomembranes in the setting of ischemia in the cecum and ascending colon. Cocaine can cause vasoconstriction after stimulation of alpha-adrenergic receptors and hence intesti-

Cocaine can cause vasoconstriction, thrombosis, and ischemia in the colon

nal ischemia, thrombosis of vessels in the large and small intestines, and direct toxic effects.³¹

Inflammatory conditions

Collagenous colitis is an inflammatory disease that often affects middle-aged women and presents with copious watery diarrhea. It is a type of microscopic colitis—the endoscopic appearance is often normal, while the histologic appearance is abnormal and characterized by collagen deposition in the lamina propria. Medications that have been implicated in microscopic colitis include acid-suppressive agents (eg, histamine receptor antagonists, proton pump inhibitors) and nonsteroidal anti-inflammatory drugs.

An increasing number of cases of pseudomembranous changes are being reported in patients diagnosed with collagenous colitis.^{32–36} Although the pathophysiologic mechanism is unknown, some authors have suggested that pseudomembrane formation is actually part of the presenting spectrum of collagenous colitis.³⁶

Inflammatory bowel disease. Crohn disease and ulcerative colitis have been associated with pseudomembranous colitis. Pseudomembranes can be found on endoscopy in patients with inflammatory bowel disease during a disease exacerbation with or without *C difficile*.^{37,38} In patients with inflammatory bowel disease and *C difficile* infection, pseudomembranes can be found endoscopically in up to 13% of cases.³⁹ Pseudomembranous colitis has been reported in a patient with ulcerative colitis exacerbation in association with cytomegalovirus colitis.⁴⁰

Behçet disease is a rare, immune-mediated small-vessel systemic vasculitis. It usually presents with mucous membrane ulcerations and ocular disease but can affect any organ.⁴¹ Pseudomembranous colitis can occur in Behçet disease in the absence of *C difficile* infection or any infectious colitis. Treatment includes corticosteroids and immunosuppressants such as azathioprine and anti-tumor necrosis factor agents.⁴¹

■ INITIAL EVALUATION

The initial evaluation of a patient with suspected or confirmed pseudomembranous colitis should include a comprehensive medical history with information on recent hospitalizations or procedures, antibiotic use, infec-

tions, exposure to sick contacts, recent travel, and medications taken.

Testing for *C difficile*

As most patients with pseudomembranous colitis have *C difficile* infection, it should be excluded first. Empiric anti-*C difficile* treatment is recommended in seriously ill-appearing patients, ideally starting after a stool sample is obtained.

Diagnosis of *C difficile* infection requires laboratory demonstration of the toxin or detection of toxigenic organisms. The gold standard test is the cell culture cytotoxicity assay, but it is labor- and time-intensive.⁴² More widely available tests are polymerase chain reaction for the toxin gene or genes, enzyme immunoassay, and stool evaluation for glutamate dehydrogenase, which can yield results readily within hours.

Polymerase chain reaction has a sensitivity of 97% and a specificity of 93%. Results can be falsely positive if empiric treatment is started before specimen collection, in which case *C difficile* DNA may still be present and detectable, but not the organism itself.⁴³

Enzyme immunoassay for toxins A and B carries a sensitivity of 75% and a specificity of 99%, but 100 to 1,000 pg of toxin must be present for a positive result.^{44,45}

If the initial enzyme immunoassay or polymerase chain reaction result is negative, current guidelines do not recommend repeat testing, which has limited value.^{44,46} Repeat testing after a negative result is positive in less than 5% of samples and greatly increases the chances of false-positive results.^{44,46} Nevertheless, if a laboratory's enzyme immunoassay test has a low sensitivity, repeating negative tests may improve its sensitivity.

Glutamate dehydrogenase is an enzyme produced by both toxigenic and nontoxigenic strains of *C difficile*. As a result, stool testing for glutamate dehydrogenase is sensitive but not specific for *C difficile* infection, although multistep testing sequences (glutamate dehydrogenase followed by polymerase chain reaction) have proven to be useful screening tools.⁴⁴

Treatment for *C difficile* infection

If testing for *C difficile* is positive, treatment is generally based on the severity and the complications of the illness⁴⁶:

- **Mild or moderate *C difficile* infection** should be treated with oral metronidazole 500 mg three times per day for 10 to 14 days.
- **Severe infection**, which is defined as a white blood cell count of $15.0 \times 10^9/L$ or higher or a serum creatinine level greater than or equal to 1.5 times the premorbid level, should be treated with oral vancomycin 125 mg four times per day for 10 to 14 days.
- **Severe *C difficile* infection complicated by hypotension, shock, ileus, or megacolon** should be treated with a combination of high-dose oral vancomycin (and possibly rectal vancomycin as well) at 500 mg four times per day plus intravenous metronidazole.

Additional treatment recommendations for individualized situations, recurrent *C difficile* infection, and comorbid conditions are discussed elsewhere.⁴⁶

■ ENDOSCOPIC EVALUATION

Colonoscopy or flexible sigmoidoscopy is the primary means by which pseudomembranous colitis is diagnosed. Lower endoscopy should be pursued as an adjunctive tool when *C difficile* infection remains strongly suspected despite negative testing, when presumed *C difficile* infection does not respond to medical therapy, and when non-*C difficile* diagnoses are considered. If pseudomembranes are demonstrated on lower endoscopy, obtaining biopsy samples of normal- and abnormal-appearing mucosa is recommended. Pseudomembranes are suggestive but not diagnostic of *C difficile* infection, and microscopic evaluation of the mucosa is warranted to explore causes of pseudomembranous colitis not related to *C difficile*.

The pattern and distribution of pseudomembranes may provide clues to the etiology and the degree of mucosal injury. In intestinal ischemia, for example, a localized segment of the bowel is typically involved, and mucosal

changes are often well delineated from normal mucosa. On endoscopic examination, mild ischemia is characterized by granular mucosa with decreased vascularity, whereas friable, edematous, ulcerated, and at times necrotic mucosa is evident in severe cases. Punctate pseudomembrane formation is seen in early ischemia, but as injury progresses, the pseudomembranes may grow and merge. In fact, diffuse involvement of the mucosal surface of the biopsy specimen by pseudomembranes has been shown to be more closely associated with ischemic colitis than *C difficile* infection.⁴⁷

■ MICROSCOPIC EVALUATION

Histologic study can differentiate the various causes of pseudomembranous colitis.

In *C difficile* infection and drug reaction, there is acute crypt injury and dilation. The upper lamina propria is usually involved, and affected crypts are filled with an exudate similar to that found in pseudomembranes.¹ However, in drug reaction, there is also prominent apoptosis and increased intraepithelial lymphocytosis.⁹

In colon ischemia, hyalinization of the lamina propria is a sensitive and specific marker.⁴⁷ This has been shown in a study comparing histologic characteristics of colonic biopsies in patients with pseudomembranous colitis due to either known colon ischemia or *C difficile* infection.⁴⁷ Crypt atrophy, lamina propria hemorrhage, full-thickness mucosal necrosis, and layering of pseudomembranes would further favor the diagnosis.

In collagenous colitis, a thickened subepithelial collagen band and intraepithelial lymphocytosis are often seen.

In inflammatory bowel disease, even with secondary pseudomembranes, ulcerative colitis and Crohn disease retain the characteristics of inflammatory bowel disease with crypt architectural distortion and focal or diffuse basal lymphoplasmacytosis on microscopy.⁴⁸ ■

Polymerase chain reaction can be falsely positive if empiric treatment is started before specimen collection

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