Nonantibiotic-Associated Pseudomembranous Colitis: A Case Report and Review of the Literature
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Abstract

Almost all cases of pseudomembranous colitis reported during the past 3 decades have been associated with antimicrobial use. We report a case of nonantibiotic-associated pseudomembranous colitis and review similar cases in the literature that suggest the need for increased clinical awareness of this condition.

A 77-year-old white female presented with a history of watery diarrhea, abdominal cramping, and a 30-lb weight loss during the past 6 weeks. She denied recent antibiotic use, which was confirmed by contacting her pharmacist. Colonoscopy revealed severe focal ulceration of the colonic mucosa and adherent yellow plaques in the rectum and sigmoid colon, pathologic features consistent with pseudomembranous colitis. The result of a stool cytotoxin assay was positive for Clostridium difficile. The patient was treated with oral vancomycin and exhibited rapid improvement. In a review of the literature, we found 9 well-documented cases of nonantibiotic-associated pseudomembranous colitis in patients without predisposing factors. Most of those patients were elderly women who presented with diarrhea and abdominal pain. The diagnosis of pseudomembranous colitis was confirmed by colonoscopy, by the identification of C difficile in stool culture, or by cytotoxicity assay. Treatment usually was initiated with oral vancomycin and dosages differed. In the 9 cases reviewed, the mortality rate was 11% and the rate of relapse, 33%.

(Aadv Stud Med. 2003;3(10):571-574)
abdominal cramping, and a 30-lb weight loss. Her medical history included a myocardial infarction 4 years prior to admission and a 10-year history of osteoarthritis, for which she had recently begun treatment with diclofenac 50 mg twice daily. The patient’s other medications included diltiazem 120 mg once daily and transdermal nitroglycerin 0.4 mg/hour for 12 hours daily. She denied recent antibiotic use, which was confirmed by contacting her pharmacist. Physical examination revealed an elderly white female with orthostatic hypotension, decreased skin turgor, and dry mucous membranes. Her abdomen was mildly distended with left lower quadrant tenderness. Rectal examination revealed no masses and the presence of loose dark stools that were negative for fecal occult blood. Colonoscopy revealed severe focal ulceration of the colonic mucosa with adherent yellow plaques in the rectum and sigmoid colon, pathologic features consistent with PMC (Figure). The stool cytotoxin assay was positive for C. difficile. Treatment with oral vancomycin produced rapid improvement.

**Literature**

In a review of the literature from 1966 to 1999, we found 9 well-documented cases of nonantibiotic-associated PMC in patients without predisposing factors (Table). Most patients were elderly (mean age, 69 years). There was a striking predominance of females (89%) among the cases reported. The most common clinical features reported included diarrhea (in all patients), abdominal pain (3 patients), weight loss (2 patients), and anorexia (1 patient). The mean duration of symptoms prior to diagnosis was 26 days. The diagnosis of PMC was confirmed by colonoscopy in 7 of the patients and by the results of both stool culture and cytotoxicity assay for C difficile in 6 patients. Treatment was most commonly initiated with oral vancomycin at varying doses. In the 9 cases reviewed, 1 patient died and 3 patients relapsed.

**Discussion**

Earlier teaching about the pathogenesis of PMC centered on the overgrowth of C difficile caused by antibiotic suppression of the normal bowel microflora, which appears to be the major risk factor for the development of PMC. However, the mechanism of disease is probably more complex, because many of the antibiotics that cause PMC are active against C difficile and other bowel microflora, and because diarrhea does not develop in many patients who become colonized with C difficile. Although C difficile can be detected in the stool of only 2% to 3% of healthy adults in the United States, retrieval of C difficile from stool occurs in 20% of asymptomatic adults who have recently been treated with antibiotics. PMC was reported before the antibiotic era; Finney’s original description of the disease preceded the advent of antimicrobial therapy by more than 40 years. Thus, factors other than antimicrobial therapy must account for the disturbance in bowel microflora and the enhanced toxin production, both of which predispose patients to PMC. The role of other medications in this disease is not known. PMC has been reported during gold therapy and during treatment with diclofenac, an anti-inflammatory agent that inhibits cyclooxygenase and reduces intracellular concentrations of free arachidonate in leukocytes. Gentric and Pennec reported a case of diclofenac-induced PMC in 1992. That article presents the second reported case of PMC associated with diclofenac use.

The complex interaction among the normal microflora of the intestine, antibiotics and other drugs that affect the microbial environment, and procedures that alter motility may contribute to the proliferation of pathogens. In the absence of antimicrobial treatment, PMC may occur after surgery and in patients with chronic, debilitating illnesses. Other risk factors for
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PMC include spinal fracture, intestinal obstruction, carcinoma, leukemia, chemotherapy for cancer, severe burns, uremia, intestinal obstruction, and heavy-metal poisoning. PM C is also a recognized complication of Hirschsprung’s disease unrelated to antibiotic use. It has been suggested that bowel ischemia may cause nonantibiotic-associated PMC. Antibiotic-associated susceptibility to C difficile appears to increase with age, and mesenteric ischemia occurs at a higher rate in elderly patients with diffuse vascular disease. Elderly patients with mesenteric ischemia may be at higher risk for the overgrowth of C difficile and for PMC. Additional studies are needed to address the quan-

Table. Nonantibiotic-Associated Pseudomembranous Colitis: Features, Diagnosis, Treatment, and Outcome

<table>
<thead>
<tr>
<th>Patient Age (y), Gender</th>
<th>Clinical Features</th>
<th>Stool Culture Positive for C difficile</th>
<th>Stool Culture Positive for C difficile Toxin</th>
<th>Endoscopy</th>
<th>Treatment</th>
<th>O utcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>80, F 10</td>
<td>Diarrhea for 8 d, weight loss of 6 lb</td>
<td>N o</td>
<td>N o</td>
<td>Yes</td>
<td>Vancomycin 500 mg po qd</td>
<td>Improvement</td>
</tr>
<tr>
<td>92, F 11</td>
<td>Diarrhea for 2 wk</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Vancomycin 250 mg po tid for 3 d</td>
<td>Improvement</td>
</tr>
<tr>
<td>78, F 11</td>
<td>Diarrhea for 1 d</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Vancomycin 250 mg po tid for 3 d</td>
<td>Improvement</td>
</tr>
<tr>
<td>74, F 11</td>
<td>Abdominal pain, diarrhea for 5 d</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Vancomycin 250 mg po tid for 10 d</td>
<td>Initial improvement; disease recurred, and patient underwent urgent colectomy</td>
</tr>
<tr>
<td>69, F 12</td>
<td>Diarrhea for 3 mo</td>
<td>N o</td>
<td>N o</td>
<td>Yes</td>
<td>Metronidazole 15 g qd for 7 d</td>
<td>Improvement</td>
</tr>
<tr>
<td>57, F 13</td>
<td>Anorexia, abdominal pain, diarrhea for 2 mo; weight loss of 10 lb</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Vancomycin 500 mg po q 6 h for 1 wk</td>
<td>Initial improvement; patient required second course of vancomycin for recurrent disease, was readmitted with a colonic perforation, and died after surgery</td>
</tr>
<tr>
<td>22, M 14</td>
<td>Abdominal pain, diarrhea for 4 wk</td>
<td>Yes</td>
<td>N o</td>
<td>Yes</td>
<td>Vancomycin 250 mg po q 8 h</td>
<td>Rapid improvement</td>
</tr>
<tr>
<td>67, F 15</td>
<td>Diarrhea for 3 d</td>
<td>N o</td>
<td>Yes</td>
<td>Yes</td>
<td>Vancomycin 1 g po bid for 10 d</td>
<td>Partial improvement</td>
</tr>
<tr>
<td>82, F 16</td>
<td>Diarrhea, weakness, confusion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Vancomycin 500 mg po qid</td>
<td>Initial improvement but disease recurred 2 wk later; no response to metronidazole 750 mg po tid for 8 d, after which patient improved with vancomycin 500 mg po qid and was discharged with treatment of vancomycin 125 mg po bid for prophylaxis</td>
</tr>
</tbody>
</table>

F = female; qd = daily; po = by mouth; M = male; bid = twice daily; qid = 4 times daily; tid = 3 times daily.
quantitative or qualitative changes that occur in the bowel microflora in patients with sustained hypoxemia and bowel ischemia.

CONCLUSION

PMC caused by C. difficile may occur without prior antibiotic therapy, surgery, or overt systemic illness. The occurrence of nonantibiotic-associated PMC underscores the importance of obtaining a stool cytotoxicity assay for C. difficile and of considering sigmoidoscopy in the evaluation of patients with acute and persistent diarrhea. Patients who have an acute diarrheal illness associated with fecal leukocytes often have been exposed to an infectious agent or have underlying inflammatory bowel disease. When more common causes of acute enteritis and colitis have been ruled out, PMC should be considered in patients who develop persistent diarrhea, even those without a history of antibiotic use. This case report and review of the literature demonstrate that PMC may occur in patients who have no underlying illness and have not received recent antibiotic therapy.

REFERENCES