ATYPICAL PRESENTATIONS OF *CLOSTRIDIUM DIFFICILE*

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When *C. difficile* infection has atypical features, the diagnosis may be missed and hospital stay prolonged. But how prevalent are atypical manifestations among veterans, and does atypical symptomology affect outcome?

Each year in the United States, *Clostridium difficile* causes between 300,000 and 3,000,000 cases of diarrhea and colitis.[1] This gram-positive, spore-forming, anaerobic bacillus is the most common infectious cause of nosocomial diarrhea.[2] In fact, in one epidemiologic study of 428 hospitalized patients, 29 (7%) had positive cultures at admission and 83 (21%) of the 399 patients who had negative cultures at admission acquired *C. difficile* during the course of their hospitalization.[3] *C. difficile* infection is known to increase hospital length of stay.[4] And when *C. difficile*-associated diarrhea (CDAD) has atypical features, it lengthens hospitalization by an average of four days.[5]

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In order to promote the early recognition of atypical CDAD, we in the gastroenterology section of the Dayton VA Medical Center in Dayton, OH—in conjunction with colleagues from Wright State University, also in Dayton—undertook a retrospective medical record review and analysis of patients who had been diagnosed with CDAD within our facility over the course of a year. Our study's primary goals were to determine the prevalence of atypical CDAD manifestations within our patient population and, possibly, to establish whether atypical symptomology has an impact on patient outcome. In this article, we describe our study methodology and present our findings.

STUDY DESIGN

The first step in our retrospective study was to review the medical records of all the patients at the Dayton VA Medical Center who had been diagnosed with CDAD during the 1999 calendar year. This included patients whose stool study was positive for *C. difficile* toxin or whose colonoscopy or flexible sigmoidoscopy had revealed evidence of pseudomembranous colitis. In addition to patient demographics, we recorded the following: whether the patients had received any antibiotics or chemotherapeutic agents in the three months prior to the onset of diarrhea, serum albumin level, total white blood cell count, presence or absence of abdominal distension, presence or absence of small intestine involvement, and death during the same hospital admission or within three months of diagnosis. Based on data from our previous study[6] and a review of medical literature, we defined atypical presentations of CDAD as being characterized by one or more of the following: no antibiotic or chemotherapeutic therapy in the three months preceding admission, drop in serum albumin to 3 g/dL or lower, presence of gaseous distension of the abdomen (ileus or megacolon), small intestine involvement, and marked leukocytosis (white blood cell count greater than 25,000/mm^3). Univariate and multivariate analysis using Cox regression was performed

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to determine any significant differences between typical and atypical groups.

SURPRISING RESULTS

Between January 1, 1999 and December 31, 1999, 67 patients were diagnosed with CDAD during the course of hospitalization. Twenty-three (34%) of these patients had typical presentations with recent antibiotic use preceding the onset of diarrhea and none of the atypical features mentioned previously; 44 (66%) had unusual features. In the latter group, 32 (73%) of the patients had an acute drop in serum albumin (to 3 g/dL or less), 23 (52%) had marked leukocytosis (white blood cell count greater than 25,000/mm^3), 10 (23%) had no antibiotic or chemotherapeutic therapy within three months of hospital admission, four (9%) had abdominal distension, and one (2%) had evidence of small intestine involvement. Eight patients who had low serum albumin prior to admission were not included in the atypical group. In both groups, patients' mean age was similar (71 years).

Twenty-five (57%) of the patients with atypical features died within three months of diagnosis. Of these patients, 13 (52%) died during the same hospital admission and 12 (48%) died after discharge within three months of diagnosis. Eleven (48%) of the patients with typical presentations died within three months of diagnosis; none of the deaths occurred during the same hospital admission.

Univariate analysis revealed a nonsignificant association between risk of death within three months of diagnosis and two baseline characteristics: low albumin (P = 0.143) and no use of antibiotic or chemotherapeutic agents in the three months prior to hospital admission (P = 0.138). Multiple logistic regression analysis did not reveal any independent risk factors.

WHEN TO CONSIDER THE DIAGNOSIS

Among patients with atypical presentations in our study, the two most common features were: a sharp drop in serum albumin (to 3 g/dL or less), which occurred in 32 (73%) of patients with atypical presentations; and marked leukocytosis (white blood cells below 25,000/mm^3), which occurred in 25 (52%) of patients with atypical presentations (Table). Others included: no prior use of antibiotic or chemotherapeutic agents, which occurred in 10 (23%) of patients with atypical presentations; and toxic megacolon, which occurred in 4 (9%) of patients with atypical presentations. In only one (2%) of the patients with atypical presentations was the small intestine involved.

According to classic studies, only 15% of stool specimens submitted for *C. difficile* toxin detection are positive for *C. difficile*.[7,8] Some cases of *C. difficile* are detected relatively late in the course of the disease requiring surgical intervention, and the delay in diagnosis is due mainly to atypical presentations. We recommend considering a diagnosis of CDAD in patients who have diarrhea and either a high white blood cell count or low serum albumin with or without recent use of antibiotics.

The marked peripheral leukocytosis is an inflammatory response of the colon secondary to toxin A release by *C. difficile*.[9] The usual peripheral leukocyte count in patients with CDAD is 12,000 to 20,000/mm^3.[1] Bulusu and colleagues have described three different patterns of leukocytosis secondary to CDAD: leukocytosis coinciding with the onset of diarrhea, unexplained leukocytosis preceding the onset of diarrhea and serving as a harbinger of CDAD, and a worsening of existing leukocytosis serving as a surrogate marker of CDAD.[10] Knowledge of these three patterns of leukocytosis may aid in the prompt diagnosis of unusual cases of CDAD.

Ramaswamy and colleagues showed that a serum albumin of less than 2.5 mg/dL upon hospital admission was indicative of increased mortality.[11] Hypoalbuminemia (serum albumin below 3 g/dL) may be caused by increased catabolism or by severe mucosal injury resulting in protein-losing enteropathy. Rybolt and colleagues reported that protein-losing enteropathy (confirmed by stool alpha-1-antitrypsin assay) was present in all cases of pseudomembranous colitis, in 43% of CDAD cases without pseudomembranes, and in none of the healthy controls.[12]

It's been established that as many as 20% of patients with CDAD do not develop symptoms for six to eight weeks after discontinuation of antibiotic therapy.[13] In our study, however, a subset of patients was found to have not used antibiotic or chemotherapeutic agents within the three-month period preceding onset.

Even absence of diarrhea should not preclude the diagnosis of pseudomembranous colitis, as it was found in five of 12 patients in one study.[14] This might represent colitis localized to the right side of the colon or the terminal ileum. Fever and pain or tenderness in the right lower abdominal quadrant may be the only clues to this type

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Table. Comparison of typical and atypical *Clostridium difficile*-associated diarrhea

Parameter of comparison	Typical presentations (n = 23)	Atypical presentations (n = 44)
Selected atypical feature		
Hypoalbuminemia (albumin < 3 g/dL)	0	32 (73%)
Marked leukocytosis (white blood cell count > 25,000)	0	23 (52%)
No recent history of antibiotic treatment or chemotherapy	0	10 (23%)
Abdominal distension	0	4 (9%)
Small intestine involvement	0	1 (2%)
Outcome		
Mortality	11 (48%)	25 (57%)

of presentation. This condition can progress rapidly to toxic megacolon or colonic perforation requiring emergent colectomy.[14]

The atypical group in our study had a higher mortality rate within three months of diagnosis, compared to the typical cases. The in-hospital mortality in atypical cases may be due to colonic ischemia, marked dehydration, and sepsis due to release of bacterial toxins. We were surprised to find that a majority of CDAD cases in our series had more than one atypical feature. That might also explain the higher mortality observed in such cases of CDAD.

ATYPICAL SIGNS OR MARKERS OF SEVERITY?

It's probable that marked leukocytosis and an acute drop in serum albumin in CDAD are consistent with an advanced stage or severe case of *C. difficile* infection, rather than simply an atypical presentation of CDAD. Although, initially, we considered these features—which we observed in many of the patients in our study—atypical characteristics of CDAD, after analyzing our findings and conducting a literature search, we concluded that these are markers of severe CDAD and may account for the higher mortality associated with such cases. Even in the absence of diarrhea, when hospitalized patients have these characteristics, *C. difficile* colitis should be considered in the differential diagnosis.

The opinions expressed herein are those of the authors and do not necessarily reflect those of Federal Practitioner, *Quadrant HealthCom Inc., the U.S. government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.*

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