

CASE REPORT

Sequential use of Antibiotics and Adjuvant Chemotherapy Leading to a Fatal Pseudomembranous Colitis

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INTRODUCTION

Pseudomembranous colitis (PMC) was first described in 1893 by Finney as a post-operative complication of gastrojejunostomy for an obstructive peptic ulcer (1). It is a clinicopathological diagnosis based on diarrhea and exudative raised plaques with skipped areas of hyperemic colonic mucosa (2). These plaques may enlarge and coalesce over large segments of intestine. The primary cause in the last thirty years has been antibiotics, while other causes have included surgery, uremia, heavy metal poisoning and ischemic heart disease (3,4).

Antibiotic-associated PMC is caused by toxins produced by the bacterium *Clostridium difficile*. The use of antibiotics alters the normal bacterial flora to allow *C. difficile* to proliferate. PMC usually becomes symptomatic 4-10 days after the initiation of antibiotic therapy but approximately 15-25 % of patients develop symptoms only after discontinuation of therapy, usually within 4-6 weeks (4). Some patients may have resolution of PMC without stopping the causative drug, while others have diarrhea continuing up to 8 weeks. Although stopping the offending agent in some patients prevents further diarrhea, many cases will need oral vancomycin and metronidazole. The relapse rate is around 9 % and for these resistant cases, rifampin is suggested (2). Complications of PMC include toxic megacolon and perforation and, for severely ill patients, the mortality rate is as high as 30 % (2).

Chemotherapeutic agents have also been implicated as causative factors in the pathogenesis of PMC, with 15 reported cases of chemotherapy-associated PMC unrelated to antibiotic use. Responsible agents have

included cytarabine (5), methotrexate (6), 5-fluorouracil (7,8), ChIVPP (9), CVB (10), CMF (11) and CAP (12). Cases of PMC in patients receiving both chemotherapy and antibiotics have also previously been reported in ovarian cancer patients (12) and in one series of leukemic patients, all five of whom died from secondary complications of PMC (13).

In recent years, it has been shown that adjuvant chemotherapy is beneficial in prolonging disease-free survival in several forms of cancer, most notably colon and breast (14,15). As these patients are essentially asymptomatic from their disease, it is important that the risks of such potentially useful therapy be kept to a minimum. However, it is likely that with the increasing utilization of chemotherapy, the incidence of complications, sometimes severe and tragic, will also rise, forcing a greater care in its administration and perhaps a more informed and critical appraisal of its advantages. With this in mind, the current authors describe a fatal case of severe PMC with features of toxic megacolon related to both previous antibiotic therapy and adjuvant chemotherapy.

THE CASE

A 49 year old postmenopausal white female presented with a stage II adenocarcinoma of the left breast. Two years earlier, she had had a total abdominal hysterectomy and bilateral salpingo-oophorectomy, followed by radiotherapy, for a stage IB, grade III endometrial adenocarcinoma. She underwent a segmental mastectomy and axial dissection. Pathology revealed a high-grade infiltrating ductal carcinoma with three of eleven lymph nodes positive for tumor. Her post-operative course was complicated by a wound infection treated by a seven day course of oral clindamycin. Two weeks later, she was started on

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adjuvant chemotherapy consisting of cyclophosphamide and 5-fluorouracil. On the seventh day of the first cycle, she developed increased frequency of bowel movements, changing over the course of a few days to explosive, watery, bloodless diarrhea.

At the time of admission, she looked unwell with a temperature of 38.8 °C and a blood pressure of 100 / 70. Abdominal examination revealed a soft, diffusely tender abdomen without guarding or rebound tenderness. The total white blood cell count was 3 800 / mm³. Stool cultures were taken and the patient was treated with piperacillin and tobramycin. Three days later, the stool assay was positive for *C. difficile* toxin and antibiotics were changed to vancomycin and metronidazole. Her clinical condition rapidly deteriorated over the next 48 hours, with increasing abdominal pain and dilation of the colon to 12 cm, as seen on plain films of the abdomen, and culminating in septic shock. She was admitted to the intensive care unit where her blood pressure was stabilized with fluids and dopamine. She then went into acute oliguric renal failure and required dialysis.

Several days later it was decided to perform a subtotal colectomy because of failure of the patient to improve on vancomycin, metronidazole, intravenous solumedrol and infusion of dopamine. The clinical diagnosis was a persistent PMC not responsive to medical treatment.

Over the next eight weeks, the patient's condition remained very poor with severe weakness, renal failure still requiring dialysis, a rapid onset of jaundice and respiratory failure leading to death. The cause of death was attributed to multi-organ failure. At autopsy, findings included bilateral pneumonia, diffuse liver and renal atrophy and diffuse ischemic colitis compatible with PMC.

DISCUSSION

The susceptibility to chemotherapy-associated PMC is probably multifactorial. Suppression of normal bowel flora may lead to overgrowth of toxigenic *C. difficile*. Local host defense may be altered through the cytotoxic effect on bowel mucosa and the depression of the systemic immune response may both contribute to mucosal damage leading to the symptoms of cramps, pain and diarrhea. So-called Toxins A and B from *C. difficile* have been extensively studied and shown to be responsible for PMC (2).

In this case, PMC occurred after the first cycle of chemotherapy had been administered. The diagnosis was made based on the history of antibiotic use and presence of *C. difficile* toxin in the stool (16,17). The absence of neutropenia in this patient suggests that local effects of the chemotherapy may have been more important in the pathogenesis of the PMC than systemic effects related to myelosuppression. Neutropenia has also

been associated with a different form of colitis known as agranulocytic colitis, neutopenic colitis or typhillitis, which often only involves the cecum (18).

The patient's rapid deterioration was perhaps due to an amplification of antibiotic-induced changes in intestinal flora by the chemotherapeutic agent's local gastrointestinal toxicity or systemic immunosuppression. It may also be possible that surgery was delayed, thus enabling the ongoing septicemia to lead to multiple organ failure and the patient's demise. Recent studies have, in fact, pointed to the need for rapid surgical intervention in order to decrease the high mortality of PMC-associated toxic megacolon (11).

In an autopsy series of 26 patients who had been receiving both antibiotics and chemotherapy, Dosik (19) found that necrotizing colitis was more often due to PMC (69%) than to agranulocytic colitis (19%) or ischemic colitis (12%). Compared with the paucity of reports of PMC associated with chemotherapy alone, one may conclude that most cases of life-threatening chemotherapy-associated PMC occur in association with antibiotics, with both agents combining to increase the severity of PMC.

Even more rarely, anti-neoplastic chemotherapy CEF (20) and methorexate (21) have been reported to be associated with toxic megacolon, but in only one case has PMC been implicated as the responsible pathogenic mechanism. The agents used in this report by Velanovich et al. were vincristine, chlorambucil, procarbazine and prednisone for Hodgkin's disease (9).

Adjuvant therapy is now known to be advantageous for node positive as well as many node negative breast cancer patients and also for stage C colon cancer patients (14,15). Information about the timing of post-operative chemotherapy is available but inconclusive. Brooks reported an improved disease-free survival for stage II breast cancer patients with 1-3 positive nodes receiving adjuvant adriamycin and cyclophosphamide four weeks post-operatively compared to those receiving it after four weeks (22). Pronzato reported improved survival in CMF-treated breast cancer patients receiving chemotherapy within 35 days of surgery compared to those receiving it more than 35 days (23). Several groups are now investigating the use of peri-operative chemotherapy in breast cancer patients with inconsistent results (24). Recent NSABP protocols required the administration of adjuvant chemotherapy within 2-5 weeks of surgery (25). Meanwhile, the incidence of wound infection after breast surgery ranges from 4 to 18% (26).

The administration of peri- or post-operative chemotherapy to those patients who received peri- or post-operative antibiotics would mean giving potentially PMC-inducing treatment to patients already at increased risk for PMC. Although managing post-

operative infections with antibiotics may not always be required, if they are needed, it would be wise to avoid antibiotics such as clindamycin or ampicillin, so as to minimize the risk of a more severe form of PMC.

In conclusion, the decision to administer post-operative antibiotics and the choice of the specific agent to be used in patients scheduled for chemotherapy shortly thereafter, has to take into account the possibility of such a disastrous complication as occurred in this patient, and thus cannot be made lightly. The rapidly increasing number of such patients therefore requires a high degree of awareness of the possible interaction between chemotherapeutic agents and antibiotics.

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