

Pseudomembranous Colitis in a Patient Treated with Paclitaxel for Carcinoma of the Breast: A Case Report

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Introduction: The concomitant antimicrobial properties of antineoplastic agents may play a role in causing pseudomembranous colitis, which has been documented for cisplatin, cyclophosphamide and 5-fluorouracil. **Clinical Picture:** We describe the first case reported in the English literature of severe pseudomembranous colitis occurring in a patient given paclitaxel as adjuvant chemotherapy for breast cancer. There was no prior antibiotic therapy. Stool culture confirmed *Clostridium difficile*. **Treatment:** Oral vancomycin, metronidazole and cholestyramine led to prompt improvement of intestinal symptoms, which resolved in two weeks. **Outcome:** Repeat colonoscopy performed 3 months later showed total resolution of the colitis. **Conclusions:** Awareness of pseudomembranous colitis after paclitaxel chemotherapy can avert life-threatening complications.

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Introduction

Paclitaxel was discovered in 1963 as a crude extract from the bark of the pacific yew *Taxus brevifolia*. Since its development, a range of anticancer activity has been demonstrated. It was initially approved for the treatment of women with epithelial ovarian cancer. However, other trials have demonstrated its activity in breast, lung, head and neck as well as testicular, bladder and oesophageal cancers.¹ Following the significant activity seen in metastatic disease, trials exploring the use of paclitaxel in the adjuvant setting in breast cancer showed that it conferred an improvement in disease-free and overall survival in patients with node-positive breast cancer.² With its widespread use, major toxicities documented include neutropenia, hypersensitivity, peripheral neuropathy and cardiac rhythm disturbances.¹ There is one report of typhlitis resulting from high doses of paclitaxel in combination with doxorubicin and cyclophosphamide.³ *Clostridium difficile* has also been isolated in the stools of patients presenting with diarrhoea after paclitaxel chemotherapy. However, pseudomembranous colitis has not been reported.

Case Report

Madam G, a 51-year-old postmenopausal Indian lady

presented with a left breast lump in January 1998. This was diagnosed to be an invasive ductal carcinoma of the breast for which she received wide excision and axillary clearance as primary treatment. There was evidence of lymphovascular invasion and 5 of 15 lymph nodes were positive. Oestrogen and progesterone receptors were negative. Staging investigations with chest X-ray, ultrasound of the liver and Tc-99m radionuclide bone scan were negative for metastases. She underwent postoperative adjuvant radiotherapy to the conserved breast, which she completed in May 1998.

Adjuvant chemotherapy was planned with 4 cycles of doxorubicin and cyclophosphamide followed by 4 cycles of paclitaxel. The first cycle of chemotherapy was started 4 months post resection, with doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m². The doxorubicin was given as a 72-hour infusion via central line. She underwent 4 cycles of treatment without any dose attenuation or serious toxicity and had the last cycle of doxorubicin and cyclophosphamide on 11 August 1998. She was given the first cycle of paclitaxel (Taxol® Bristol-Myers Squibb) at 175 mg/m² on 4 September 1998. Premedication was given with oral dexamethasone 20 mg given 6 and 12 hours before the chemotherapy as well as intravenous

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diphenhydramine 25 mg, cimetidine 300 mg and ondansetron 8 mg given 30 minutes before paclitaxel. The paclitaxel infusion was delivered over 3 hours.

She made an unscheduled visit 3 days later complaining of severe myalgia over the whole body and tingling sensation in the fingers. She was not toxic and did not report any fever or abdominal symptoms then. She was treated symptomatically with codeine phosphate, 60 mg tds, ibuprofen 400 mg tds, amitriptyline 10 mg bid and midazolam 15 mg on.

On the sixteenth day post paclitaxel infusion, she attended the emergency with a 4-day history of severe profuse diarrhoea, colicky abdominal pain and vomiting. She sought advice from her family doctor but took only the anti-diarrhoea medication while omitting the antibiotics prescribed.

On examination, she had diffuse tenderness in the abdomen on deep palpation but no guarding or rebound. She was afebrile initially, but subsequently developed a low grade temperature. Plain abdominal and chest X-rays were unremarkable. The result of her full blood count done on admission is shown in Table I. She was treated with anti-diarrhoea medication and intravenous fluid rehydration. She continued to purge more than 15 times a day, even when she was not taking orally. Oral ciprofloxacin was started empirically and anti-diarrhoea medications stopped. Her stool examination revealed leukocytes but culture for salmonella, shigella, vibrio and campylobacter were negative. Blood cultures for aerobic and anaerobic bacteria were negative.

A CT scan of the abdomen revealed colonic wall thickening, especially of the caecum, ascending colon and transverse colon. There was thickening and inflammatory changes of the peritoneum in the region of the right paracolic gutter. The rest of the abdominal organs were normal. The findings suggested colitis.

Colonoscopy revealed severe pancolitis with ulcers and typical pseudomembranes (Fig. 1a). Histology confirmed pseudomembranous colitis with the mucosa in the superficial crypts lined by cells with foamy and bubbly cytoplasm with enlarged hyperchromatic nuclei suggestive of chemotherapy

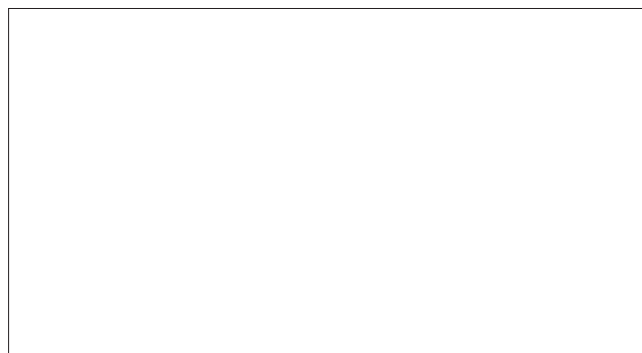


Fig. 1a

Fig. 1a. (left) Colonoscopy showing severe pancolitis with ulcers and typical pseudomembranes.

Fig. 1b.

Fig. 1b. (right) Resolution of colitis after treatment.

related changes. A repeat stool examination for *C. difficile* was positive but attempted isolation of the cytotoxin was negative on two occasions. She was started on oral vancomycin, metronidazole, ciprofloxacin and cholestyramine. Clinical improvement was noted 2 days after starting the antibiotics with abatement of diarrhoea and abdominal pain by 5 days. Her fever settled soon after. She was on 14 days of vancomycin and ciprofloxacin, and 21 days of metronidazole and cholestyramine.

A repeat colonoscopy done 3 months after the onset of the illness showed some mucosa oedema but otherwise complete resolution of the colitis (Fig. 1b).

Discussion

C. difficile infection is classically associated with the use of broad spectrum antibiotics. It is a common nosocomial commensal and had been identified in the stools of healthy neonates. Initially thought to be a commensal, it was identified later in 1978 to be an aetiological agent producing antibiotic-associated diarrhoea and pseudomembranous colitis. *C. difficile* is responsible for 95% to 100% of all cases of pseudomembranous colitis and can be isolated in up to 20% of antibiotic-associated diarrhoea without colitis.⁴ The clinical manifestation of *C. difficile* infection ranges from an asymptomatic carrier to severe toxic megacolon and fatality. The majority have mild to moderate diarrhoea with occasional abdominal cramps. Prior antibiotic use remains the most important risk factor, although in recent years, antineoplastic chemotherapy has been increasingly linked to *C. difficile* infection. The exact mechanism of developing pseudomembranous colitis remains elusive. Damage to the intestinal mucosa does occur with chemotherapy. There can be loss of intestinal epithelium, superficial necrosis and inflammation of the bowel wall.^{5,6} Presumably, a higher rate of gastrointestinal colonisation must play a part in the pathogenesis. Sporulation by clostridia enables the organism to survive in adverse conditions. It is not surprising that this ubiquitous organism should replicate

TABLE I: FULL BLOOD COUNT DONE ON ADMISSION

Haematology	Units	Range
Total white	13.03 x 10 ⁹ /L	4.0-10.0
Neutrophils	94.7%	40-75
Lymphocytes	3.6%	15-41
Monocytes	1.5%	2-10
Eosinophils	0.2%	0-6
Haemoglobin	11.3g/dL	14.0-18.0
Platelets	159 x 10 ⁹ /L	140-440

to the vegetative forms and elaborate its toxin when the intestinal mucosa barrier is damaged by chemotherapy.

Diarrhoea can be common following chemotherapy. In patients on chemotherapy, *C. difficile* can be present as a commensal or be pathological. Husain et al⁷ retrospectively reviewed 624 patients who were treated with paclitaxel-containing chemotherapy for advance ovarian cancer and found 40 cases with *C. difficile*-associated diarrhoea, with 24 of the patients receiving paclitaxel within the prior 4 weeks. None of the patients were reported to have pseudomembranous colitis. Trevisani et al⁸ reported a case of 5-fluorouracil induced pseudomembranous colitis given for treatment of colon cancer and Lincoln et al⁹ reported a postmortem showing pseudomembranous colitis in a patient with ovarian cancer who perished one week after being given cyclophosphamide and cisplatin chemotherapy. In treating chemotherapy-induced diarrhoea, initial pharmacologic management is oral anti-diarrhoea medication aimed at decreasing the frequency and volume of stools.¹⁰ For patients with pseudomembranous colitis, this can be detrimental. Isolation of the organism from the stools is not always indicative of pseudomembranous colitis. Colonoscopy is not routinely recommended for the evaluation of diarrhoea following chemotherapy either. This dilemma facing the practicing clinician requires him to have a high index of suspicion, awareness of the diagnostic pitfalls and good clinical acumen to diagnose a potentially life-threatening condition.

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