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Fatal Chemotherapy Associated *Clostridium Difficile* Infection – A Case Report

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ABSTRACT

***Clostridium difficile* associated diarrhoea or Pseudomembranous colitis occasionally occurs without prior antibiotic usage. While the association of chemotherapy and *Clostridium difficile* infection has previously been well recorded, the true incidence is unknown. We report a case of *Clostridium difficile* associated diarrhoea after chemotherapy for lung cancer. The fatal outcome in this case and the increasing use of chemotherapy in this country highlights the need to have a high index of suspicion in any case of unexplained diarrhoea post chemotherapy. A review of the literature is presented.**

Keywords: ***Clostridium difficile*, chemotherapy**

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INTRODUCTION

Pseudomembranous colitis is well known to be associated with prior antibiotic usage, clindamycin being one of the first agents to be implicated[1]. Bartlett and colleagues subsequently identified *Clostridium difficile* and its toxin as the cause of the disease in 1978[2]. *Clostridium difficile* colitis has occasionally not been associated with antibiotics. Diabetes mellitus, renal failure, intestinal obstruction and intestinal surgery have been noted to be associated with non-antibiotic related *Clostridium difficile* colitis[3-5]. We report a case of a patient with lung cancer and *Clostridium difficile* colitis related to chemotherapy administration.

CASE REPORT

A 73-year-old Chinese man, an ex-smoker, presented to a restructured hospital with acute shortness of breath. Chest X-ray revealed bilateral pneumonic changes. He was treated initially with a short course of empiric antibiotics with some improvement. Sputum cytology done twice was consistent with bronchioloalveolar carcinoma. He was also found to have ascites which was tapped. Cytology was also consistent with bronchioloalveolar carcinoma. He was transferred to our hospital for further oncologic management. The Karnofsky Performance Status at presentation was about 60%.

He was started on chemotherapy as for advanced bronchioloalveolar carcinoma five days after stopping antibiotics. Combination chemotherapy consisting of carboplatin and vinorelbine was administered. Two cycles of chemotherapy were given 21 days apart, with a 20% dose reduction at the second cycle for Grade 4 neutropenia at the nadir of the first cycle. The patient also experienced aesthenia and nausea after the first cycle. Dexamethasone 4 mg bid for three days was added at the second cycle for antiemetic effect. At the nadir of the second cycle, the patient was fairly well, with an absolute neutrophil count of 740 per mm^3. No antibiotics were given during the neutropenic periods as the patient did not have fever.

17 days after the second chemotherapy cycle was started, the patient developed diarrhoea with three to four watery, non-bloody stools per day. He became dehydrated, lethargic, and unable to walk. The abdomen was clinically distended with ascites again. He was admitted and started on loperamide, oral ciprofloxacin, and intravenous hydration. Stools for culture, parasites and *Clostridium difficile* toxin were sent. Admission full blood count showed a leucocytosis at 15,000/mm^3, and serum creatinine was elevated at 172 umol/L. Paracentesis was done for relief of symptoms. Four days into admission, the diarrhoea persisted and the patient developed vomiting. The abdomen became distended again and was tympanitic. Abdominal X-rays done showed dilated small bowel. The stool culture and examination for parasites was negative. However *Clostridium difficile* toxin was detected by enzyme immunoassay (Premier, Meridian diagnostics, Cincinati, USA). Blood culture was negative. Total white count was 29,000/mm^3 and creatinine had risen to 307 umol/L. Oral vancomycin and intravenous metronidazole was started. A surgical consultation was obtained. The following day the abdominal X-ray repeated showed persistent dilated small bowel.

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The patient had a sudden collapse the following morning, when he was found lying in a pool of coffee ground vomitus. Resuscitation was unsuccessful and he was signed up as *Clostridium difficile* colitis with underlying brochioloalveolar carcinoma.

DISCUSSION

The true incidence of chemotherapy associated *Clostridium difficile* colitis remains unknown. Kamthan[6] reported 70 patients who were hospitalised with diarrhoea after chemotherapy, of which one third of cases responded to empiric vancomycin or metronidazole. The true incidence may also be masked by frequent antibiotic use especially in neutropenic patients.

Clostridium difficile can be induced in animals with methotrexate or 5-fluorouracil administration. Vancomycin added to the drinking water of the animals was found to be protective[7,8].

Postulated mechanisms for chemotherapy associated *C. difficile* colitis include:

1. Alteration of gut flora by chemotherapy.
2. Chemotherapy induced gut inflammation creating an environment facilitating anaerobic growth of *Clostridium difficile*, and preventing the degradation of the toxin by host proteases.
3. Nosocomial acquisition of the organism in chemotherapy patients.
4. The added risk when antibiotics were also given[9].

In a review of 23 cases by Anand and Glatt[9], no antibiotics were administered in the preceding six weeks, and patients had clinical disease ranging from mild diarrhoea to severe hemorrhagic colitis. Onset varied between three days to five weeks after chemotherapy. Three relapses and four deaths were reported. The malignancies were diverse, and methotrexate was the most commonly implicated drug. Three patients died before therapy for *Clostridium difficile* could be initiated.

Other reports of chemotherapy associated *Clostridium difficile* infection include those by Nielson et al[10] (cisplatin, etoposide and bleomycin), Emoto et al[11] (cisplatin, adriamycin and cyclophosphamide), Paterson[12] (topotecan), Jarvis et al[13] (mitoxantrone and etoposide), and Ramos et al[14] (chlorambucil). Husain et al[15] reported 40 cases of *Clostridium difficile* colitis in a review of 624 patients who received paclitaxel-containing chemotherapy for ovarian cancer. Risk of *Clostridium difficile* colitis was as high as 20% in patients receiving a 'dose-dense' high dose protocol.

Our patient had chemotherapy associated *Clostridium difficile* diarrhoea as no antibiotics were administered for more than six weeks (43 days) prior to the onset of symptoms. *Clostridium difficile* enterotoxin was positive using an enzyme immunoassay that detects both A and B toxins. He subsequently had signs of an impending toxic-megacolon-like syndrome and could well have died from complications related to it. The abdominal X-ray showed dilatation of small bowel, a consistent radiological finding in pseudomembranous colitis[16]. Stool cultures did not grow any of the usual pathogens. Carboplatin and vinorelbine are not expected to cause severe diarrhoea, although vinorelbine neurotoxicity and loperamide administration may have contributed to bowel distension and proliferation of *Clostridium difficile*.

There is a need to have an index of suspicion in chemotherapy patients who develop diarrhoea, especially in those with a more severe course and bloody diarrhoea[6], fever[17] and recent hospitalisation[7]. The use of antimotility agents could decrease bowel transit time, promoting the anaerobic proliferation of the organism[18,19]. In suspected cases, there should be a low threshold to starting empiric treatment, eg. with oral metronidazole. Enzyme immunoassays are generally more reliable than latex-agglutination tests, although false negatives can still occur. The issue of whether the same chemotherapy can be given after an episode of *Clostridium difficile* related diarrhoea remains controversial[11,12], and should be considered on a case-by-case basis. The role of nosocomial transmission[7] and optimal enteric precautions should be clearly spelt out in health care institutions, given that *Clostridium difficile* associated diarrhoea can be a major nosocomial problem[20-22].

CONCLUSION

Clostridium difficile colitis is a known complication of chemotherapy. Although this has previously been reported locally[23], ours is the first report in Singapore of a case with fatal outcome. Medical oncologists should have a high index of suspicion in any case of unexplained diarrhoea post chemotherapy. The rising cancer incidence and increasing use of chemotherapy in our country support the need to be vigilant in the diagnosis and prompt treatment of this disease.

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