Cholestatic jaundice and pseudomembranous colitis following combination therapy with doxorubicin and docetaxel

S. Sundar[a] and S.Y. Chan[b]

We report a case of cholestatic jaundice and pseudomembranous colitis (PMC) following combination therapy with docetaxel and doxorubicin. This clinical syndrome has not been previously reported with this combination. In particular, this is the first report of non-*Clostridium difficile*-associated PMC with docetaxel-based chemotherapy. Docetaxel is principally metabolized by the hepatic cytochrome P450 mixed-function oxidases, in particular by the isoform CYP3A. This patient was on long-term erythromycin prophylaxis following splenectomy. Erythromycin is a known inhibitor of CYP3A. We postulate that erythromycin probably contributed to the observed clinical syndrome. Clinicians should be aware of potential drug interactions, when unusual toxicities occur with novel combinations of chemotherapeutic agents. *Anti-Cancer Drugs* 14:327–329 © 2003 Lippincott Williams & Wilkins.

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[a]Department of Oncology, Leicester Royal Infirmary, Leicester, UK and [b]Department of Clinical Oncology, Nottingham City Hospital, Nottingham, UK.

Correspondence to S. Sundar, Department of Oncology, Osborne Building, Leicester Royal Infirmary, Leicester LE1 5WW, UK.
Tel: +44 7980 737938; fax: +1 44 116 2585942;
e-mail: sundar@oncology.org

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Introduction

Doxorubicin and docetaxel (A & T) are highly active cytotoxics now widely used in the treatment of metastatic breast cancer [1]. We report a case presenting with cholestatic jaundice and non-*Clostridium difficil*e (non-CD) pseudomembranous colitis (PMC) following combination treatment with doxorubicin (50 mg/m^2) and docetaxel (75 mg/m^2) in a phase III trial for metastatic breast cancer.

Case report

A 45-year-old woman, who presented with loco-regional recurrence of breast cancer along with bone metastasis, was given A & T chemotherapy. The patient did not have any liver or peritoneal metastasis. The patient's pretreatment liver function tests, abdominal ultrasound and CAT scan of the abdomen were normal. The chemotherapy schedule included granisetron and dexamethasone as antiemetics, and premedication with dexamethasone. Other concurrent medications were omeprazole, morphine sulfate, ibuprofen and metoclopramide. She was also on long-term prophylactic erythromycin following the splenectomy in 1995.

Six days after the first cycle of A & T chemotherapy, the patient developed an erythematous maculopapular rash on the face followed by neutropenic fever, vomiting and watery diarrhea. Blood cultures and stool cultures were negative, Liver enzymes were normal and CD cytotoxin (CD-toxin) was not detectable in stools. Diarrhea improved with symptomatic management.

Four days after the second cycle of A & T chemotherapy (given 3 weeks after first cycle), the patient was admitted again with vomiting, watery diarrhea, abdominal pain and distension, and febrile neutropenia. There was no clinical response to broad-spectrum antibiotics (i.v. ceftazidime and gentamicin). As the diarrhea worsened, antibiotic-induced diarrhea was suspected and the antibiotics were stopped. Metronidazole was started and later oral vancomycin was added. On the 15th day, the patient developed mouth ulcers followed by worsening of abdominal distension and the diarrhea turned bloody. Subsequently, the patient also had episodes of hematemesis. Abdominal X-ray showed dilated gas-filled loops of the bowel with widespread mucosal irregularity suggestive of extensive colitis. Sigmoidoscopy showed inflamed rectal mucosa covered with pseudo membranes. Colonic biopsy specimens showed 'volcano' lesions typical of PMC (Fig. 1). However, the stool cultures were negative and CD-toxin was not found in the stools. Moreover, the diarrhea did not respond to vancomycin and metronidazole, thereby suggesting an alternate pathological process.

During the same period the liver function tests became abnormal (normal range in brackets): alanine transaminase 35 (5–40) U/l, γ-glutamyltransferase 497 (10–50) U/l, bilirubin 82 (0–17 μmol/l, albumin 18 (30–52) g/l and alkaline phosphatase 2212 (80–280) U/l (Fig. 2).

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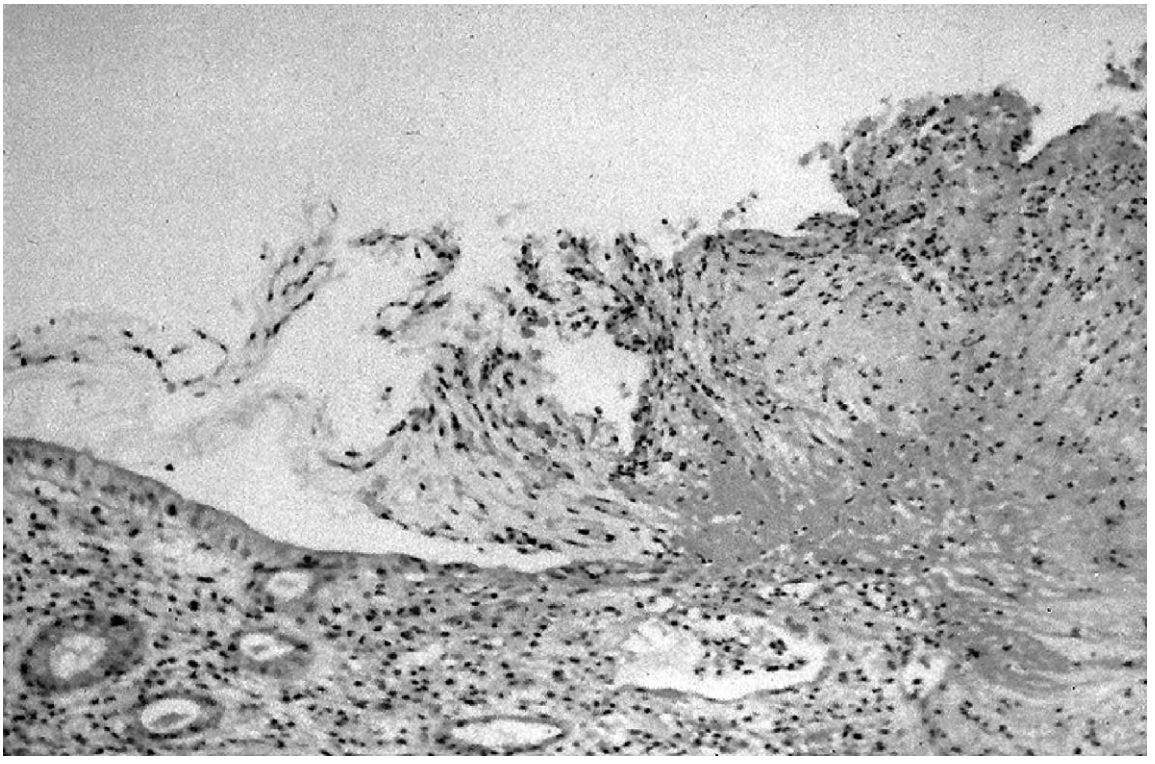
Fig. 1



Colonic biopsy showing 'volcano' lesions typical of PMC.

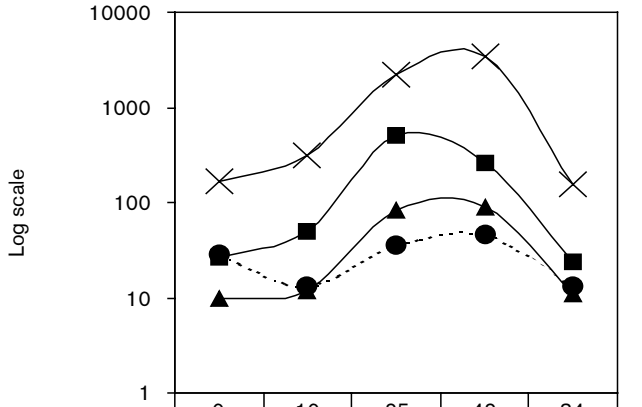
Fractionated alkaline phosphatase showed liver and biliary isoenzymes, thereby ruling out bone metastasis as a potential source of the enzymes. Ultrasound examination showed normal liver and thickened gall bladder wall, but there was no biliary calculi or bile duct dilatation, which could have been responsible for the cholestatic picture. Serological examination for Hepatitis A, B and C virus, and cytomegalovirus were negative.

Over the next 6 weeks, the patient was hemodynamically unstable, but eventually with aggressive supportive management the diarrhea resolved and liver enzymes improved. Repeat blood cultures and stool cultures for *Salmonella*, *Shigella*, *Campylobacter* and CD-toxin assay of stools were negative. The patient was finally discharged after about 12 weeks of hospitalization.

Discussion

Doxorubicin and docetaxel either alone or in combination has not been reported to cause cholestatic jaundice or a colitis mimicking CD-associated colitis. Docetaxel is known to cause neutropenic enterocolitis and doxorubicin in combination with 6-mercaptopurine was reported to have caused cholestatic jaundice [2–4].

Fig. 2



	0	10	25	42	84
ALT	29	13	35	46	13
GGT	27	49	497	261	24
Bilirubin	10	12	82	90	11
ALP	169	311	2212	3436	159

Days after chemotherapy

Temporal profile of liver enzymes.

PMC is a pathological diagnosis, now used synonymously with antibiotic-associated colitis caused by CD. Rarely certain conditions such as cytomegalovirus colitis, ischemic colitis and others have been reported to histopathologically mimic CD-associated colitis [5–8].

In our patient CD cannot be implicated because the test for CD-toxin done twice by using 'the gold standard' Vero cells cytotoxicity assay was negative [9]. Cytomegalovirus colitis was ruled out after a histological search for cytomegalovirus inclusions by immunostaining was negative. Our patient's age, sex, lack of risk factors, extent of colonic involvement and clinical course ruled out ischemic colitis.

Similarly, there was no obvious cause for the observed cholestatic jaundice. Radiological investigations ruled out any intrinsic as well as extrinsic biliary tract obstruction. Serological examination ruled out viral hepatitis as a cause of jaundice. The temporal relationship strongly suggests that the combination of docetaxel and doxorubicin is the most likely cause.

Six months later, when the patient died of cerebral metastasis, post-mortem examination showed no evidence of any underlying liver or bowel pathology. Hence, the most probable cause of colitis and cholestasis in our patient is the combination chemotherapy of docetaxel and doxorubicin.

This is the first report of a PMC (non-CD associated) occurring with docetaxel-based combination chemotherapy. PMC (non-CD associated) has been previously reported with cancer chemotherapy, but in many of those reports the gold standard CD-toxin assays were not used and in some cases the transport medium was defective [10]. This is also the first report of cholestatic jaundice occurring with the combination of doxorubicin and docetaxel.

Doxorubicin can inhibit docetaxel metabolism in human hepatocytes, but *in vitro* and clinical experience indicate that it is unlikely to be the causative factor for the observed syndrome [11,12]. We postulate that the long-term prophylactic erythromycin usage in our patient is the probable contributing factor for the observed syndrome in our patient. Our hypothesis is based on the fact that docetaxel is primarily metabolized by the hepatic cytochrome P450 mixed-function oxidases, in particular by isoform CYP3A, and erythromycin is a known inhibitor of CYP3A [11,13]. In fact, erythromycin breath tests are being evaluated as a tool in predictive dosing of docetaxel [13,14]. Moreover the concurrent administration of omeprazole, which is also an inhibitor of CYP3A, might have potentially influenced the patient's clinical syndrome [15].

In conclusion, cholestatic jaundice and PMC (non-CD associated) is a rare and severe complication of docetaxel-based combination chemotherapy. As the combination of docetaxel and doxorubicin enters into more widespread clinical use, potential drug interactions should be borne in mind by the clinicians.

Acknowledgments

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References

1 Chan S, Friedrichs K, Noel D, Pinter T, Van Belle S, Vorobiof D, *et al.* Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. The 303 Study Group. *J Clin Oncol* 1999; **17**:2341–2354.
2 Cardenal F, Montes A, Llort G, Segui J, Mesia R. Typhlitis associated with docetaxel treatment. *J Natl Cancer Inst* 1996; **88**:1078–1079.
3 Minow RA, Stern MH, Casey JH, Rodriguez V, Luna MA. Clinico-pathologic correlation of liver damage in patients treated with 6-mercaptopurine and Adriamycin. *Cancer* 1976; **38**:1524–1528.
4 Kreis W, Petrylak D, Savarese D, Budman D. Colitis and docetaxel-based chemotherapy. *Lancet* 2000; **355**:2164.
5 Beaugerie L, Ngo Y, Goujard F, Gharakhanian S, Carbonnel F, Luboinski J, *et al.* Etiology and management of toxic megacolon in patients with human immunodeficiency virus infection. *Gastroenterology* 1994; **107**:858–863.
6 Dignan CR, Greenson JK. Can ischemic colitis be differentiated from C difficile colitis in biopsy specimens? *Am J Surg Pathol* 1997; **21**:706–710.
7 Dickinson RJ, Rampling A, Wight DG. Spontaneous pseudomembranous colitis not associated with *Clostridium difficile*. *J Infect* 1985; **10**:252–255.
8 Phillips RK, Glazer G, Borriello SP. Non-*Clostridium difficile* pseudomembranous colitis responding to both vancomycin and metronidazole?. *Br Med J (Clin Res Ed)* 1981; **283**:823.
9 Fekety R, Shah AB. Diagnosis and treatment of *Clostridium difficile* colitis. *J Am Med Ass* 1993; **269**:71–75.
10 Yokoyama T, Kondo H, Yokota T, Tokue Y, Saito D, Shimada Y, Sugihara, *et al.* Colonoscopy for frank bloody stools associated with cancer chemotherapy. *Jpn J Clin Oncol* 1997; **27**:111–114.
11 Marre F, Sanderink GJ, de Sousa G, Gaillard C, Martinet M, Rahmani R. Hepatic biotransformation of docetaxel (Taxotere) *in vitro*: involvement of the CYP3A subfamily in humans. *Cancer Res* 1996; **56**:1296–1302.
12 Royer I, Monsarrat B, Sonnier M, Wright M, Cresteil T, *et al.* Metabolism of docetaxel by human cytochromes P450: interactions with paclitaxel and other antineoplastic drugs. *Cancer Res* 1996; **56**:58–65.
13 Hirth J, Watkins PB, Strawderman M, Schott A, Bruno R, Baker L. The effect of an individual's cytochrome CYP3A4 activity on docetaxel clearance. *Clin Cancer Res* 2000; **6**:1255–1258.
14 Rivory LP, Slaviero K, Seale JP, Hoskins J, Boyer MJ, Beale PJ, *et al.* Optimizing the erythromycin breath test for use in cancer patients. *Clin Cancer Res* 2000; **6**:3480–3485.
15 Ko JW, Sukhova N, Thacker D, Chen P, Flockhart DA. Evaluation of omeprazole and lansoprazole as inhibitors of cytochrome P450 isoforms. *Drug Metab Dispos* 1997; **25**:853–862.