Typhlitis Resulting from Treatment with Taxol and Doxorubicin in Patients with Metastatic Breast Cancer

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Background. **Typhlitis is being recognized with increasing frequency as a serious complication of aggressive chemotherapy for hematologic and solid malignancies.**

Methods. **In this report the authors describe two cases of typhlitis in patients with metastatic breast cancer treated with taxol and doxorubicin.**

Results. **Both cases occurred during the first cycle of treatment with taxol (180 mg/m^2) and doxorubicin (75 mg/m^2), being given simultaneously as 72-hour continuous intravenous infusions.**

Conclusion. **Two cases of typhlitis have occurred after combined treatment with taxol and doxorubicin, while typhlitis has not been described after treatment with either drug alone. *Cancer* 1993; 71:1797–800.**

Key words: typhlitis, taxol, doxorubicin, metastatic breast cancer.

Typhlitis (from the Greek word typhlon, or cecum) is a necrotizing inflammation of the cecum, sometimes extending into the ileum and the ascending colon. Synonyms of the syndrome include neutropenic enterocolitis, necrotizing enterocolitis, and ileocecal syndrome. The pathogenesis of typhlitis is unknown, but neutropenia and the microbiologic environment of the colon appear to be necessary conditions. The cecum seems to be especially vulnerable because it is less well vascularized than the other portions of the large intestine.

Although first and most commonly recognized in the treatment of childhood leukemia,[1] typhlitis has also been described in patients with solid tumors treated with aggressive chemotherapy.[2] Direct cytotoxicity to bowel mucosa from antitumor drugs may contribute to the development of typhlitis; however, the syndrome has also been reported in patients with cyclic neutropenia in the absence of treatment with cytotoxic drugs.[3] Typhlitis is defined clinically as fever with abdominal pain, usually in the right lower quadrant, in the setting of Grade 4 neutropenia (absolute neutrophil count below 500/μl).[1] Nausea and vomiting, abdominal distention, rebound tenderness, diarrhea, and occult blood in the stool are often present.[2] The diagnosis is usually confirmed by computed tomography (CT) scan[4] or ultrasound.[5] Management is controversial, especially with regard to the necessity and timing of surgical intervention. However, as the syndrome has become better appreciated and diagnosed earlier in its evolution, conservative management has become more acceptable, at least initially.[2]

We report two cases of typhlitis in patients with metastatic breast cancer treated on a Phase I study with the combination of taxol, doxorubicin, and granulocyte colony-stimulating factor (G-CSF). As taxol enters more widespread clinical testing in combination with other chemotherapeutic agents, this potential complication should be recognized.

Case Reports

Case 1

A 35-year-old woman had a lumpectomy and axillary dissection in August 1989 for a 3-cm, node-negative invasive ductal carcinoma of the left breast. Breast conserving surgery was followed by radiation therapy and six cycles of adjuvant cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy. In July 1991, two asymptomatic pulmonary nodules were found on chest radiograph and fine-needle aspiration revealed adenocarcinoma consistent with the breast primary. The evaluation for metastases was otherwise negative, and the patient began treatment with taxol 180 mg/m^2 and doxorubicin 75 mg/m^2 on September 17, 1991 (Day 1). On Day 5, 24 hours after the end of the 72-hour continuous

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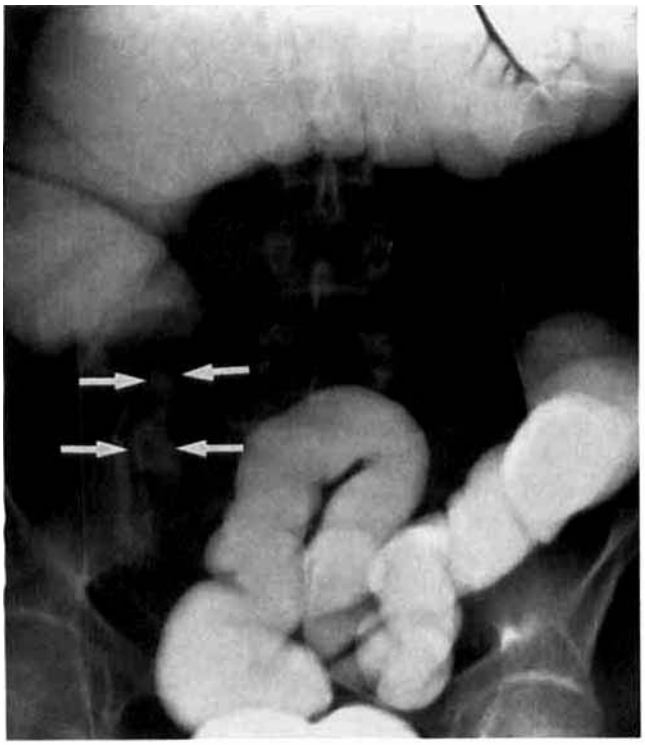
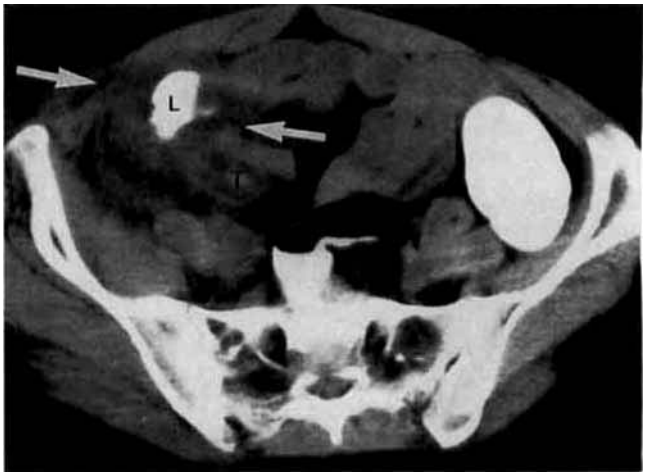
infusion, G-CSF 10 μg/kg subcutaneously (SC) daily was begun. On Day 7, the patient's absolute neutrophil count (ANC) was below 500/μl. On Day 8, the patient developed fever to 38.3°C with mild guaiac-positive diarrhea, and intravenous ceftazidime treatment was initiated. On Day 10, the patient's diarrhea suddenly ceased. On Day 11, severe cramping abdominal pain developed. Flat and upright abdominal films revealed moderate colonic and small bowel dilation but no free air. Metronidazole was added and oral intake was discontinued. In spite of nasogastric suction, the pain worsened and right lower quadrant tenderness and fullness developed. On Day 12, an abdominal CT scan obtained without oral contrast was unrevealing. Vancomycin and gentamicin were added to the antibiotic regimen. Later the same day, a meglumine diatrizoate (Gastrografin) enema and a repeat abdominal CT scan were obtained (Fig. 1) and the diagnosis of typhlitis was confirmed. The patient never became hemodynamically unstable and was managed conservatively. The patient's ANC increased to above 500/μl on Day 13 and her abdominal pain subsequently improved. The diarrhea (guaiac-positive) resumed on Day 14. The patient's temperature normalized on Day 15 and G-CSF was stopped on Day 16 for a leukocyte count of 20,500/μl. The nasogastric tube was removed on day 19 and oral intake was slowly instituted. Mild diarrhea persisted until discharge on Day 26. A follow-up abdominal CT scan with oral contrast (Fig. 1) on Day 35 showed marked improvement, but incomplete resolution of the cecal wall thickening. All microbiologic studies including repeated search for *Clostridium difficile* toxin in the patient's stools during hospitalization gave negative results.





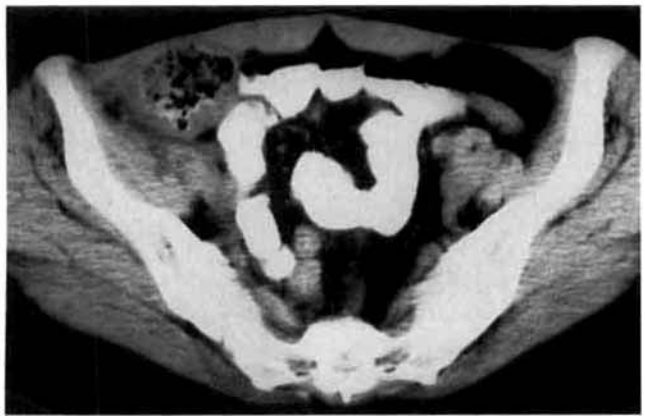


Figure 1. Radiologic studies in Case 1. (Top left) Gastrografin enema (day 13) showing normal filling up to the cecum, where the lumen abruptly narrows and only a thin irregular collection of contrast (arrows) is visualized. (Top right) Abdominal CT scan (immediately after gastrografin enema) demonstrating marked thickening of the cecal wall (arrows). L, cecal lumen. Thickening of the terminal ileum also appears (T). (Bottom) Abdominal CT scan (Day 35, with oral contrast) showing marked but incomplete resolution of cecal wall thickening.

Case 2

This 46-year-old woman was diagnosed with breast cancer in July 1991, and underwent a left modified radical mastectomy for a 4-cm, infiltrating lobular carcinoma with 10 of 10 axillary lymph nodes involved with tumor. Fine-needle aspiration of a supraclavicular node showed metastatic breast cancer. On September 23, 1991 (Day 1), treatment with taxol (180 mg/m^2) and doxorubicin (75 mg/m^2) was begun by continuous infusion over 72 hours. On Day 4, G-CSF 10 μg/kg SC daily was started. On Day 8, the neutrophil count was below 500/μl, and on Day 9, the patient was hospitalized for fevers and begun on aztreonam, gentamicin, and vancomycin. On Day 10, she developed moderate diarrhea and on Day 11 complained of right lower quadrant abdominal pain. Abdominal plain films were unremarkable, but abdominal CT scan with oral contrast (Fig. 2) showed marked cecal wall thickening suggestive of typhlitis. Oral intake was discontinued and metronidazole was added to the antibiotic regimen. By Day 15, her ANC had returned to normal and G-CSF was discontinued. Her abdominal pain had resolved, but mild guaiac-negative diarrhea persisted. An abdominal CT scan on Day 17 (Fig. 2) showed almost complete resolution of the bowel wall thickening. She remained afebrile, her diarrhea abated, and her diet was advanced. All microbiologic studies were negative, including stool *Clostridium difficile* toxin.

Discussion

We describe two patients who developed clinical typhlitis after treatment with 180 mg/m^2 of taxol and 75 mg/m^2 of doxorubicin given by simultaneous 72-hour continuous infusion. Although severe neutropenia alone may be sufficient for the development of typhlitis,[3] it is most commonly seen after treatment with aggressive chemotherapy.[1,2,4,5] It seems probable that direct mucosal damage from cytotoxic drugs is important in its pathogenesis. Typhlitis has been associated with many chemotherapeutic drugs; however, monotherapy with taxol or doxorubicin has not been reported to cause typhlitis.

Neutropenia was the dose-limiting toxicity in all Phase I solid tumor trials of taxol alone.[6] However, mucositis was the dose-limiting toxicity at a taxol dose of 375 mg/m^2 given as a 24-hour infusion to patients with leukemia.[6] Mucositis and diarrhea have also been described in the two published Phase I trials of taxol using a 5-day intermittent schedule with daily 6-hour infusions. Mild diarrhea was observed in 6 of 21 patients treated with 20 to 40 mg/m^2 daily for 5 days in one trial,[7] but not in the other.[8] Moderate mucositis occurred in two of four patients treated with 40 mg/m^2 daily for 5 days.[7] A pathologic study has described epithelial necrosis in the gastrointestinal tract (from esophagus to colon) in two patients one day after treatment with 250 mg/m^2 of taxol given as a 24-hour continuous infusion.[9] This necrosis was associated with the typical features of taxol cytotoxicity: polymerized microtubule accumulation and mitotic arrest. Taxol-related mucosal damage in the setting of neutropenia may contribute to the pathogenesis of typhlitis.

The incidence and severity of upper gastrointestinal mucositis is greater with continuous-infusion doxorubicin than with intravenous bolus therapy. Mucositis is the major dose-limiting toxicity with repeated continuous-infusion treatment.[10,11] If a 96-hour infusion of doxorubicin leads to severe mucositis, reduction in the duration of the infusion to 24 or 48 hours eliminates or

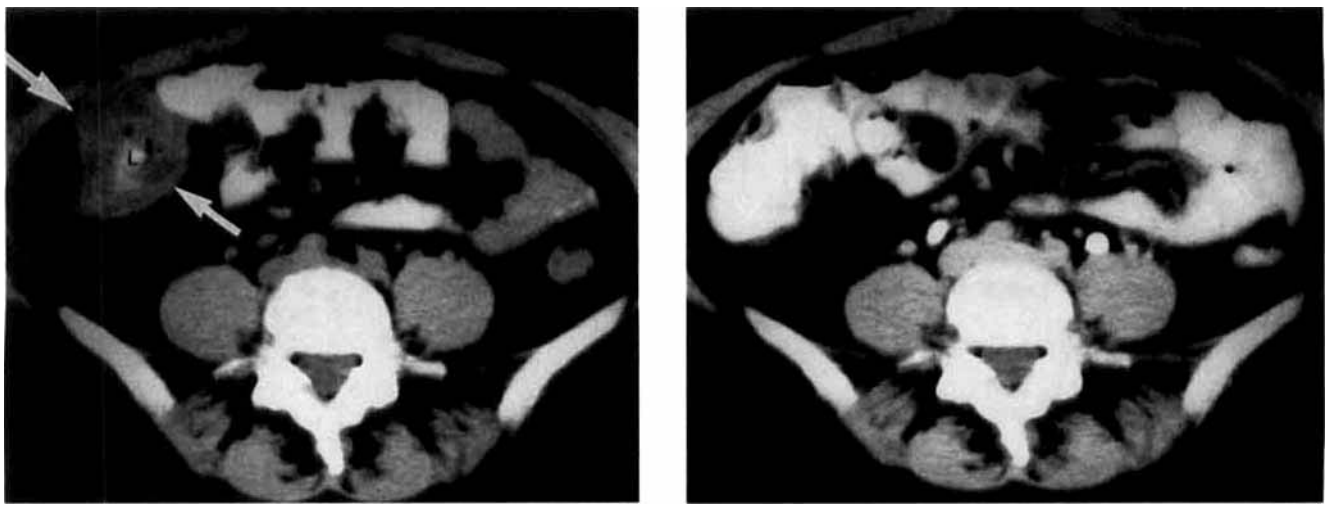


Figure 2. Radiologic studies in Case 2. (Left) Abdominal CT scan (Day 11, oral contrast) demonstrating marked thickening of the cecal wall (arrows) and narrowing of lumen (L). (Right) Abdominal CT scan (Day 17, oral contrast) showing almost complete resolution of cecal wall thickening and a lumen of normal width.

decreases this toxicity.[12] Lower gastrointestinal mucosal toxicity with diarrhea has not been reported with infusional doxorubicin, but diarrhea has been described as a consequence of bolus doxorubicin treatment.[13]

The two cases of taxol–doxorubicin–G-CSF-associated typhlitis reported here were probably the result of both severe neutropenia and direct toxicity to bowel of the antitumor agents. Both patients were retreated with taxol 160 mg/m^2 and doxorubicin 60 mg/m^2, with the same dose of G-CSF, once their diarrhea and abdominal pain had completely resolved. Both did well during Cycle 2 with no recurrence of abdominal pain. The first patient had Grade 1 diarrhea during Cycle 2. The second patient had Grade 3 diarrhea during Cycle 2 which did not recur at a doxorubicin dose of 45 mg/m^2 and taxol 160 mg/m^2 for Cycle 3. Since the development of both doxorubicin and taxol toxicities are schedule-dependent, studies of other methods of administering this combination may be warranted.

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