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CASE REPORT

# Typhlitis in breast cancer patient using Docetaxel-based chemotherapy: case report

*Tiflite em paciente com câncer de mama em uso de quimioterapia com Docetaxel: relato de caso*

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**Descritores**

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**Keywords**

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## ABSTRACT

The authors report a case of neutropenic enterocolitis (typhlitis) secondary to the use of adjuvant chemotherapy for breast cancer treatment. A 46-year-old woman received the diagnosis of typhlitis and underwent a right hemicolectomy.

## RESUMO

*Os autores relatam um caso raro de enterocolite neutropênica (tiflite) secundária ao uso de quimioterapia adjuvante para tratamento de câncer de mama. Uma mulher de 46 anos de idade foi diagnosticada com tiflite, sendo realizada hemicolectomia direita.*

## Introduction

Typhlitis or neutropenic enterocolitis refers to necrotizing colitis with inflammation of the cecum and adjacent tissues. It represents the most common gastrointestinal complication in leukemia patients[1]. The pathogenesis of typhlitis is unknown. However, neutropenia and colon microbial environment seem to be essential contributory factors. The cecum appears to be especially vulnerable, since it is less vascularized than other portions of the large bowel[2]. Although this condition occurs mainly in severely immunosuppressed or myelosuppressed patients with leukemia, it has also been seen in individuals with other advanced malignancies receiving immunosuppressant chemotherapy[1-4].

It is uncommon to find this clinical presentation in breast cancer patients. The period of neutropenia related to chemotherapy is usually of short duration in these patients. Methotrexate has been implicated in the development of typhlitis. However, in recent years, the condition has been reported in patients undergoing taxane-based chemotherapy. It is well-known that these agents have a great potential to cause extensive inflammatory changes in the colonic mucosa. Furthermore, these drugs create a favorable environment for proliferation of *Clostridium difficile* that produces and releases an inflammatory exotoxin[4].

Typhlitis has a high mortality rate due to hemorrhage, perforation or septicemia[5]. Early diagnosis and treatment are fundamental for the reduction in mortality. To the best of our knowledge, only 36 cases of typhlitis in breast cancer patients on taxane-based chemotherapy have been published in the literature.

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## Case report

A 46-year old female patient presented with invasive ductal carcinoma of the right breast. She underwent segmental breast excision and level I and II axillary lymphadenectomy. The largest diameter of the tumor measured 1.5 cm and tumor differentiation was grade G3. There was no evidence of circulatory and lymphatic invasion and two out of 19 excised axillary lymph nodes were affected. Final pathological stage was T1cN1M0 breast cancer. Immunohistochemical study revealed a triple negative tumor. Following surgery, a chemotherapy protocol of intravenous doxorubicin (60 mg/m$^2$) and cyclophosphamide (600 mg/m$^2$) was started on day 1, every 21 days through a totally implantable portacath. The patient had episodes of febrile neutropenia in the first two cycles of chemotherapy and was treated with empiric antibiotic therapy. After the third cycle of adjuvant chemotherapy, associated with filgrastim support (300 mcg/day for 5 days) for febrile neutropenia, the patient presented with lumbar and abdominal pain diagnosed as renal colic. She was afebrile and neutropenic on day 10 of chemotherapy. Despite improvement in pain, she progressed with complaints of diarrhea, early satiety and right pleuritic pain. Chest radiograph was normal and abdominal ultrasound revealed a right renal pelvic calculi measuring 0.4 cm without urinary obstruction.

At day 21 of the third cycle, the patient presented fever and chills. A right flank mass appeared, with no peritoneal reaction. Hemoglobin was 8.2 g/dL, white blood cell count 5,660/mm$^3$ and platelets 375,000/mm$^3$ at the time. Computed tomography was performed, demonstrating segmental parietal wall thickening of the ascending and transverse colon (Figure 1). A diagnosis of typhlitis was made and antibiotic therapy began with the administration of ampicillin and sulbactam. After 48 hours of treatment, the fever persisted and antibiotic therapy was changed to cefepime and metronidazole. Surgical treatment was indicated, although the patient was stable. She presented with a flaccid abdomen and only an inflammatory mass was palpable.

During the intraoperative period, the right colon was intensely walled off and apparently there was wall thickening of the mesenterium and retroperitoneum. The right colon showed a confined perforation (Figure 2). A right hemicolectomy with end-to-end ileocolic anastomosis was carried out. Histopathology revealed chronic typhlitis with acute episodes and foci of epithelial erosion, in addition to organized steatonecrosis. The clinical course of the patient was uneventful, and she received hospital discharge 10 days after surgery. Six out of eight cycles of the scheduled chemotherapy were performed and she underwent radiation therapy targeting the breast and homolateral supraclavicular fossa. Thirty-six months after breast cancer treatment, the patient still has no evidence of active disease.

## Discussion

Of the 36 cases of typhlitis reported in the literature, 16 occurred with Docetaxel. The main clinical presentation and treatment are shown in Chart 1.

The disease has been increasingly recognized and reported. It is believed to be caused by the proliferation of myelotoxic chemotherapeutic regimens in adult leukemia and the use of combined chemotherapy in solid tumors. It also occurs in immunocompromised patients due to organ transplantation[6,7].

Typhlitis is a complication of taxane-based chemotherapy but its mechanism is still unknown. Chemotherapeutic agents exert systemic toxicity on tissues with the highest turnover rate, including the gastrointestinal tract mucosa. These drugs act by binding the β-subunit of tubulin and forming stable, nonfunctional microtubule bundles that interfere with cell mitosis. Furthermore, it has been postulated that these drugs have a direct cytotoxic effect on the bowel mucosa. More recent evidence suggests that taxanes may also

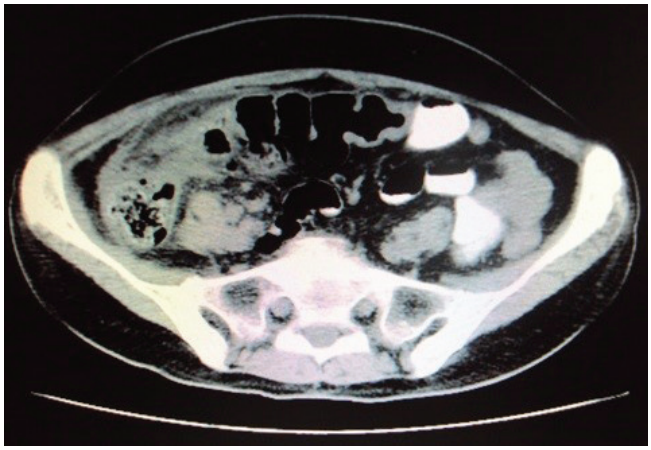

**Figure 1.** Contrast-enhanced computed tomography of the abdomen, showing segmental parietal wall thickening of the ascending and transverse colon

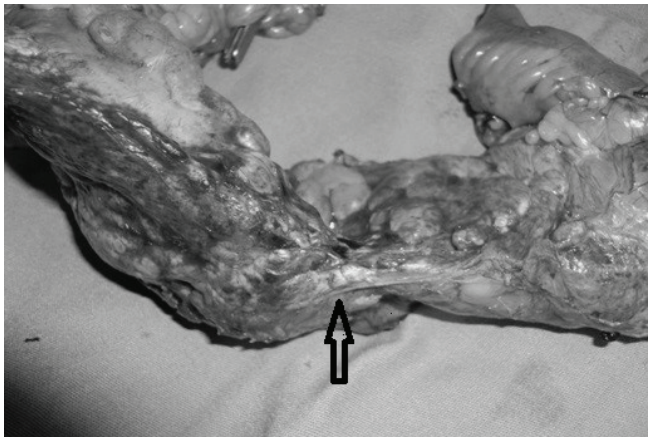

**Figure 2.** Macroscopic aspect of typhlitis of the ileocecal junction, showing the right colon with a confined bowel perforation (arrow)

induce apoptosis. Antitumor drugs damage the bowel mucosa by direct cytotoxicity, facilitating bacterial invasion of the bowel wall during a period of neutropenia. As a result, typhlitis may occur. The administration of broad-spectrum antibiotics can also contribute to the development of typhlitis due to alteration in the intestinal microbiota. The most common pathogenic organism implicated in typhlitis is *Clostridium difficile*. However, other microorganisms such as species of *Pseudomonas* and *E. Coli*, among other bacteria, fungi and viruses, have also been reported. Predilection for the cecum is possibly related to its unique properties, including greater distensibility, lower vascular perfusion, and increased lymphatic drainage[3-12].

Clinical manifestations of typhlitis include abdominal pain, in general localized in the right lower quadrant, fever and severe neutropenia (absolute blood neutrophil count <500/dL). Nausea and vomiting, abdominal distension, increased abdominal rebound tenderness on palpation, diarrhea and fecal occult blood are frequently found. Signs of peritoneal irritation and shock suggest a possible bowel wall perforation. Symptoms usually occur within 10 to 15 days after the beginning of chemotherapy[4,5,8,10,13].

The key to diagnosis is the rapid recognition of clinical features. Patients at higher risk are those who develop fever and an absolute blood neutrophil count <500/dL.

CT scan is the diagnostic modality of choice, since its false-negative rates of diagnosis (15%) are lower than ultrasound (23%) or abdominal radiographs (48%). Ultrasound may reveal an enlarged cecum with characteristic echogenic mucosal thickening, with or without fluid collection[1].

**Chart 1.** Symptoms, treatment and outcome of cases of reported typhlitis

| Symptoms | Treatment | Death |
|---|---|---|
| Fever and abdominal pain | Laparotomy | No |
| Malaise and diffuse pain abadominal | Laparotomy | Yes |
| Fever, abdominal pain and bloody diarrhea | Laparotomy | Yes |
| Abdominal pain, fever and diarrhea | Conservative | Yes |
| Abdominal pain, fever and diarrhea | Conservative | Yes |
| Fever | Conservative | Yes |
| Abdominal pain, fever and vomiting | Conservative | Yes |
| Abdominal pain and vomiting | Conservative | No |
| Diarrhea, abdominal pain and fever | Laparotomy | No |
| Generalized abdominal pain, fever and vomiting | Laparotomy | No |
| Diffuse abdominal pain | Conservative | Yes |
| Diarrhea, nausea and vomiting | Conservative | No |
| Diffuse abdominal pain, fever, bloody diarrhea | Conservative | No |
| Abdominal pain and bloody diarrhea | Conservative | No |
| Abdominal pain and bloody diarrhea | Laparotomy | No |
| Abdominal pain and fever | Laparotomy | No |

In the current report, renal colic was initially suspected. However, a change in the clinical presentation, with pain and a palpable mass in the right iliac fossa, led to the suspicion of typhlitis, which was confirmed on abdominal CT scan.

Management of typhlitis remains controversial. Treatment options range from a conservative approach to early surgical intervention. Aggressive medical management and the increase in white blood cell count are essential for patient survival. Prolonged leukopenia may allow continuous bacterial invasion of the bowel wall with persistence of intestinal injury, accompanied by necrosis and perforation[8].

Of the 36 cases reported in the literature, death occurred in 35% of patients receiving conservative treatment and 25% undergoing surgery. The general consensus on conservative medical management is that broad-spectrum antibiotics, bowel rest, abdominal decompression and support with total parenteral nutrition are fundamental. Frequent imaging studies are required to monitor treatment progress and detect possible perforations or other conditions requiring surgical intervention. CT is the diagnostic modality of choice. Guidelines also suggest the advantage of using granulocyte colony-stimulating factor (G-CSF) in neutropenic patients with sepsis or shock[13,14].

A colectomy with ileostomy and mucosa fistula is usually carried out, if surgical intervention is deemed necessary. In a very select group of patients, primary anastomosis may be performed, as in our hemodynamically stable patient who developed a confined bowel perforation[5,8].

## Conclusion

The mortality rate of typhlitis is elevated, ranging from 10 to 40%. Death is due to transmural intestinal necrosis, perforation, hemorrhage and sepsis[5,6]. However, the timely decision to indicate surgical treatment is fundamental for patient survival, as observed in the present case.

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