

Unusual Case of Bowel Infarction with Invasive Aspergillus in an Immunocompromised Patient

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Abstract

Introduction: We report a patient with bowel infarction due to invasive Aspergillus infection as a result of prolonged chemotherapy-induced neutropenia. **Clinical Picture:** The patient was given neoadjuvant chemotherapy with doxorubicin, docetaxel, and capecitabine for a breast tumour. She developed prolonged neutropenia, Escherichia coli and Candida krusei sepsis, acute arterial thrombosis of the left lower limb, and invasive aspergillus infection. **Treatment:** She underwent a subtotal colectomy, small intestine resection and an above-knee amputation. **Outcome:** The hospitalisation was complicated with methicillin-resistant Staphylococcus aureus pneumonia and short gut syndrome. She subsequently underwent simple mastectomy with axillary clearance and received adjuvant chemotherapy and radiation without complication. **Conclusion:** Chemotherapy should be protocol-directed. In a non-trial situation, protocol must have a sound basis, proven safety, and efficacy. Aspergillus infection is uncommon in patients with solid tumours; prompt treatment must be started on high suspicion.

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Introduction

The role of neoadjuvant chemotherapy for locally advanced breast cancer has been established and there has been a growing interest in its role in early and operable breast cancer.¹ Most neoadjuvant chemotherapeutic regimens contain an anthracycline and are usually combined with cyclophosphamide, with or without 5-fluorouracil. Novel chemotherapeutic regimens using docetaxel, capecitabine and doxorubicin have not been studied in any clinical trials to date.

We report a case of a patient with early operable breast cancer, who experienced a severe and prolonged neutropenia complicated by unsuspected disseminated aspergillus infection after undergoing such a regimen. This is not commonly seen in patients with solid tumours who have received conventional chemotherapy.

Case Report

In April 2000, a 57-year-old woman of Bangladeshi extraction presented with a right breast lump. Mammography and ultrasonography subsequently confirmed a 2.5 × 1.6-cm mass in the upper and outer quadrant. Cytology from a fine needle aspirate confirmed ductal cell carcinoma. Clinical examination did not reveal any other significant mass. No further metastatic work-up was performed. She consulted a clinical oncologist in her country who started her on neoadjuvant chemotherapy, consisting of 14 days of capecitabine (2500 mg/m² in two divided doses), doxorubicin (35 mg/m²), and docetaxel (60 mg/m²) given on the eighth day of capecitabine treatment. The patient tolerated the treatment well until the fourth day after the onset of intravenous chemotherapy when she developed severe mucositis, diarrhoea and

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vomitting. At that point, her hemogram was unremarkable. She was treated with ciprofloxacin 500 mg twice a day. Three days later, she was admitted into the hospital with a fever of 39°C and grade 4 mucositis (World Health Organization classification). Her neutrophil count at that time was $14 \times 10^6/L$. Intravenous ceftriaxone therapy was commenced at 1 g twice a day, which was subsequently changed 3 days later to ceftazidime 1 g 8-hourly, vancomycin 1 g 12-hourly, and netilmycin 150 mg twice a day, when a swab culture from the oral cavity grew *Pseudomonas aeruginosa*. Throughout this period, she was given blood product support as well as a course of granulocyte colony stimulating growth factor (G-CSF). Her condition did not improve and she was transferred to our centre for further management, 14 days after docetaxel and doxorubicin were started. Following the transfer, she remained neutropenic for another 6 days despite the use of growth factors, and thrombocytopenic for another 8 days with a platelet nadir of $3 \times 10^{12}/L$. At this point, she developed *Escherichia coli* septicæmic shock, paroxysmal atrial fibrillation, *Candida krusei* fungaemia, and acute thrombosis of the right popliteal artery. The infections were controlled with intravenous injections of meropenem 1 g twice a day, amikacin 750 mg once a day, vancomycin 750 mg twice a day, and amphotericin B 50 mg per day. In view of the grade 4 thrombocytopenia and severe mucositis with frequent bowel motion, the acute left leg thrombosis was treated conservatively. Thrombolytic intervention with urokinase on the acutely thrombosed leg was attempted 2 days later when the platelet count reached $90 \times 10^{12}/L$. This was abandoned when she bled from the central line and her oral cavity.

Two days later, the patient developed abdominal distension with signs consistent with an acute abdomen. An urgent computer tomographic scan of the abdomen revealed free intra-abdominal gas, distension of the small bowel, and inflammatory stranding on the right side (Fig. 1). Emergency laparotomy was performed on the same day, revealing severe soilage of the peritoneal cavity with melaenic and faeculant material. Massive dilatation of small bowel with multiple centimetre-long perforations in the jejunum and ileum were seen; the terminal ileum was ischaemic, and the caecum, proximal ascending colon, and apex of the sigmoid colon were not viable. A subtotal colectomy and small intestinal resection was performed, leaving 1.5 m of the small bowel behind. The histopathological report of the resected gut described multiple foci of ulceration and perforation associated with recent infarction involving both small and large bowel. Intramural blood vessels within the infarcted areas contained abundant branching septate fungi characteristic of *Aspergillus*. The mesentery and omentum also showed patchy haemorrhagic necrosis and associated venous thrombi containing *Aspergillus* organisms (Fig. 2).

The patient was transferred to the intensive care unit. The intra-abdominal infection was well controlled with meropenem 1 g twice a day, vancomycin 1 g twice a day, and amphotericin B (accumulated dose of 1.6 g). Unfortunately, the thrombosed left leg became gangrenous, necessitating amputation within the next 24 days.

She experienced transient short gut syndrome for the next 2 months following her gut resection. In addition, she developed methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia which resolved subsequently with a course of vancomycin.

After a period of rehabilitation, she was discharged from the hospital and was readmitted 2 months later for elective

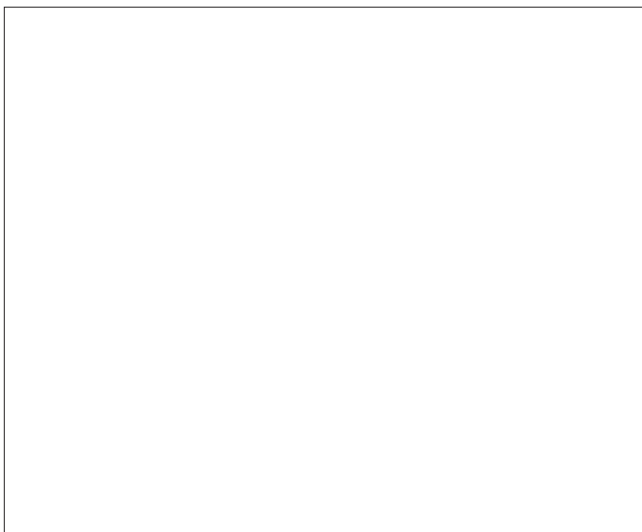


Fig. 1. Free communication between the small bowel and the peritoneal cavity.

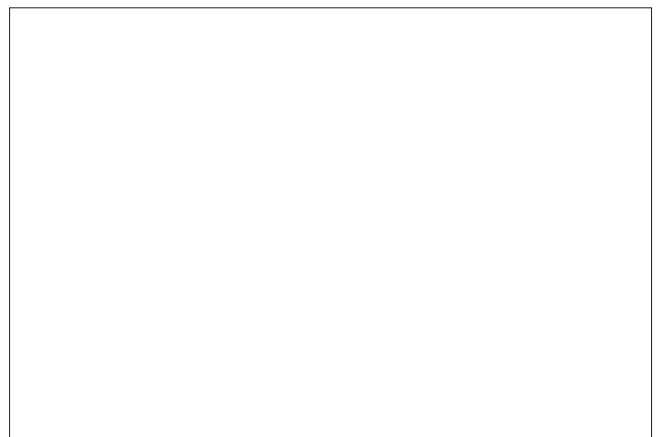


Fig. 2. Septate branching hyphae of *aspergillus* are present within a mesenteric blood vessel and surrounding fat. (Silver methanamine stain, $\times 72$)

simple mastectomy with axillary clearance. Ten of the 13 axillary nodes sampled were positive for tumour. The oestrogen and progesterone receptors were negative. She was commenced on adjuvant chemotherapy and radiotherapy. Six cycles of doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) were given with G-CSF support. In view of the previous disseminated *Aspergillus* infection, itraconazole was prophylactically given to prevent reactivation or reinfection. Radiotherapy was given after completing chemotherapy. This was uneventful, and the patient was well after the adjuvant treatment.

Discussion

Aspergillus is an ubiquitous fungus that grows well in decaying vegetation, compost, cereal grains, wool and hay. There are many strains but only *Aspergillus fumigatus* and *Aspergillus flavus* produce disease in humans. Host factors, including structural or immunologic defects, determine the types of disease that evolve. The syndromes that develop with infection may follow tissue invasion, significant colonisation or antigenic stimulation with resultant reactions. Invasive aspergillosis is a devastating infection that usually develops only in hosts with defects in cellular and humoral immunity and is more frequently reported in haematological malignancies for which treatment is more intense than solid tumours with consequent longer period of neutropenia.²⁻⁴ Though uncommon, invasive aspergillosis can be expected to increase with the advent of new and possibly more intense chemotherapeutic regimes developed for solid tumours.

The toxicity profile in any combination regime is usually more pronounced than with single-agent regimes. This patient was given a triple chemotherapeutic combination comprising docetaxel, doxorubicin and capecitabine outside a clinical trial. The safety and efficacy of this triplet combination of docetaxel, doxorubicin and capecitabine have yet to be reported. However, the doublet combination of docetaxel and doxorubicin in breast cancer was recently reported.⁵ In this phase II study, 150 Asian patients with metastatic breast cancer were treated with docetaxel and doxorubicin, given at 50 mg/m² and 60 mg/m², respectively once every 3 weeks. Ninety-five percent of the patients were reported to have grade 3 and 4 neutropenia, and neutropenic fever occurred in 32% despite the use of G-CSF in 35% of the patients. There have also been reports of typhilitis or even necrotising enterocolitis with the use of docetaxel or capecitabine.⁵ Our patient developed severe neutropenia for 13 days with grade 4 mucositis following the triplet chemotherapy. Despite empiric treatment with broad spectrum antibiotics, her condition still deteriorated when invasive *Aspergillus* infection developed, resulting in gut perforation and arterial thrombosis of the right leg.

Hence, novel combination chemotherapy can be a hazardous experience unless it is given in a clinical trial setting with previous phase I and II information.

Review of published literature showed that gastrointestinal aspergillosis is rarely recognised antemortem and diagnosis would require aggressive diagnostic procedures such as a biopsy of the involved organ. Fungal cultures are occasionally useful, but are often worthless in the absence of a clinical syndrome. Serologic tests are also not helpful for invasive disease, except for the diagnosis of aspergilloma or allergic bronchopulmonary aspergillosis.⁶ In one series of 91 patients with invasive *Aspergillus* infection by Young and colleagues,⁷ 21 patients had evidence of gastrointestinal aspergillosis. The oesophagus, colon, jejunum, stomach, tongue, ileum, soft palate and hypopharynx are affected most frequently in descending order.

In another study with 93 patients, only 9 had gastrointestinal involvement; only 1 patient with a possible antemortem diagnosis of gastrointestinal aspergillosis has been reported.⁸ The diagnosis was based on clinical features of abdominal pain, ileus and a positive stool culture for *Aspergillus niger* in a neutropenic patient with acute myeloid leukaemia.

How *Aspergillus* invades the gastrointestinal system is unknown, but it would seem feasible through the filtering of the conidia by the nose and swallowing of the nasopharyngeal mucus. This might be the mechanism of infection in this patient as there was no established infection in the more common sites such as the lungs.

Diagnosis of invasive aspergillosis confers a very poor prognosis. The mainstay of treatment for the infection is amphotericin B with a response of 37% reported in well-characterised patients.⁹ No thorough prospective studies have been done relating to outcome, and recommendations as to the dosage are based purely on the ability to tolerate the drugs.¹⁰ In their article, Fisher and associates¹¹ described that the duration of amphotericin B was not significantly longer; neither was the dose greater in the 10 survivors than the 19 patients who died, suggesting that amphotericin B does not greatly influence the course of aspergillosis and that the outcome is more related to granulocytopenia and the underlying disease process. Our patient received a total of 1600 mg of amphotericin B before treatment was stopped. She has been well since then without evidence of reinfection. However, we cannot exclude the possibility that the infection may recur. In view of her high risk for recurrent breast cancer and high lymph node status, our patient received 6 cycles of adjuvant chemotherapy with itraconazole given prophylactically during the period of highest risk for neutropenia. She has done well without

reinfection despite having transient neutropenia after the first cycle of the adjuvant chemotherapy.

Conclusion

Chemotherapy is not without its risks. Neutropenic fever is a known and serious adverse effect, particularly from combination chemotherapy. Novel combinations may potentially yield promising result, but their use is fraught with danger in the absence of proper dose-finding phase I and phase II clinical trials. Invasive aspergillosis is highly lethal in the immunocompromised host, even following treatment. We must be cognizant of its possible existence even among patients with solid tumours. Work-up must be prompt, and aggressive therapy may need to be initiated upon suspicion of diagnosis, and prior to diagnostic confirmation.

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