

# Neutropenic Enterocolitis Associated with Docetaxel Therapy in a Patient with Breast Cancer

Kenneth V. I. Rolston, MD

Department of Infectious Diseases, Infection Control and Employee Health,  
The University of Texas, M. D. Anderson Cancer Center, Houston, Texas

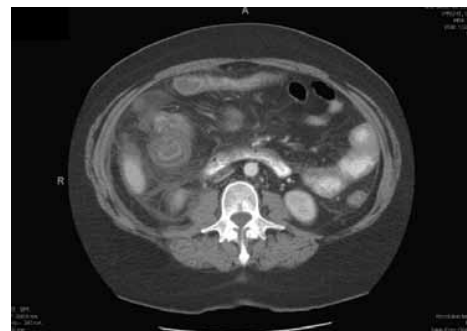
A 53-year-old woman with a diagnosis of inflammatory carcinoma of the right breast received 5 courses of standard FAC (5-fluorouracil, doxorubicin, cyclophosphamide) chemotherapy between June and September of 2007 with no adverse events or complications. In October 2007, she underwent modified mastectomy of the right breast, again with no complications. The following month, she was started on docetaxel and presented 3 days later to our emergency center with a 24-hour history of explosive diarrhea (8 times), fever (38.9°C), and severe/diffuse abdominal pain, which was most prominent in the lower quadrants. On physical examination, she appeared fatigued, but “non-toxic”, with a temperature of 38.7°C, respiratory rate of 24, heart rate of 112 beats per minute, and blood pressure of 142/70 mm Hg. Significant findings on physical examination included moderate abdominal distention, diffuse abdominal tenderness without rigidity or rebound tenderness, and diminished bowel sounds in all quadrants. The white blood cell (WBC) count was  $0.4 \times 10^9/L$  with an absolute neutrophil count of zero. Computed tomography (CT) scan of the abdomen/pelvis showed the presence of ascites, some small bowel thickening in jejunal loops, and thickening of the walls of the ascending, transverse, and descending colons (Figure 1). The patient was admitted and received parenteral meropenem and ciprofloxacin, and other supportive measures such as intravenous (IV) fluids and bowel rest. The patient was discharged after 14 days. She was afebrile, no longer neutropenic, and had no abdominal symptoms. All microbiologic cultures and *Clostridium difficile* toxin assays were negative. The patient was instructed to return to the breast outpatient clinic for a follow-up visit in a week.

Six days later, she returned to the clinic with increasing lower quadrant abdominal pain, nausea, vomiting, and general “deconditioning”. She was afebrile (36.1°C) and had stable vital signs. Abdominal examination revealed distension and diffuse tenderness with rebound. The WBC count was  $14.4 \times 10^9/L$ . CT scan showed the presence of a fluid collection with gas and some contrast in the

mesentery consistent with perforation in the region of the right colon. The patient received supportive measures and piperacillin/tazobactam plus moxifloxacin. She underwent exploratory laparectomy with right hemicolectomy and primary anastomosis, lysis of massive adhesions, and right ureteral stent placement. Blood cultures were positive for *Pseudomonas aeruginosa*, which was susceptible to meropenem, piperacillin/tazobactam, and ciprofloxacin. Ciprofloxacin was substituted for moxifloxacin. The patient had an uneventful postoperative course, was discharged in stable condition after 4 weeks of hospitalization, and has remained stable after 1 year of follow-up.

## Discussion

Neutropenic enterocolitis (NEC), sometimes referred to as typhlitis, is an uncommon but often life-threatening complication of intensive cytotoxic chemotherapy (eg, cytosine, arabinoside plus idarubicin) in patients with leukemia.<sup>1</sup> It has been reported in patients with other neoplastic disorders, including lymphoma and certain solid tumors, and may also occur in patients with aplastic anemia or cyclic neutropenia who have not received any cytotoxic agents. Some recent reports have documented an association between NEC and taxanes (docetaxel, paclitaxel) and vinorelbine, which are used to treat a variety of solid tumors including breast, lung, and ovarian cancers.<sup>2-6</sup> Increased awareness of this association can be critical in the early recognition of NEC, as the initial



**Figure 1.** Abdominal computed tomography scan showing bowel wall thickening (jejunal loops, ascending and proximal transverse colon) and ascites

Address correspondence to:

Kenneth Rolston, MD, The University of Texas, M. D. Anderson Cancer Center, Department of Infectious Diseases, Infection Control and Employee Health, 1515 Holcombe Blvd. (Unit 1460), Houston, Texas 77030; Phone: 713-792-6830; Fax: 713-794-4351; E-mail: krolston@mdanderson.org

manifestations may be attributed to routine adverse events associated with these agents.

The usual clinical features of fever, abdominal pain, and diarrhea are not specific and may suggest other abdominal diseases.<sup>7,8</sup> In fact, some authorities have questioned the very existence of NEC based on the lack of specific or uniformly accepted clinical and diagnostic criteria.<sup>9</sup> A recent systematic analysis of NEC in adults has examined the quality of evidence of all relevant published reports and has attempted to resolve this controversy by proposing a definition based on a combination of clinical and radiologic criteria.<sup>10</sup> The criteria included in this definition are fever, abdominal pain, and any bowel wall thickening (BWT) greater than 4 mm detected by ultrasonography or CT. A recent study reinforced this definition by demonstrating that BWT is not a feature of chemotherapy-induced mucositis, and when present, should be considered a sign of NEC/infectious colitis.<sup>11</sup> BWT has also been demonstrated to be a prognostic sign with mural thickness of more than 10 mm being associated with poorer outcomes in patients with NEC.<sup>12</sup>

The most common pathogens recovered from blood cultures of patients with NEC are the enteric gram-negative bacilli—*Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella* spp.<sup>1,8,10</sup> Other bacteria include viridans group streptococci, *Enterococcus* spp. and anaerobes such as *Bacteroides* spp., and *Clostridium* spp. (excluding *Clostridium difficile*). There is increasing evidence that fungi, particularly *Candida* spp., also play an important but secondary role compared to bacterial pathogens.<sup>7,13</sup>

The pathogenic mechanisms that result in NEC are probably multifactorial with neutropenia itself being a contributing factor. Other factors include a) destruction of normal mucosal architecture with possible coexistence of leukemic or lymphomatous bowel infiltrates,<sup>14</sup> b) intramural hemorrhage due to severe thrombocytopenia, and c) a shift in the normal gastrointestinal flora due to antibiotics, antifungals, and acquisition of pathogenic hospital flora.<sup>1</sup> Microscopic findings include edematous and thickened bowel walls with varying degrees of ulceration, submucosal edema, hemorrhage, and necrosis with few inflammatory cells due to the existence of neutropenia in most cases.

There is no uniform management strategy for all cases of NEC.<sup>1</sup> Most patients receive and respond to conservative medical measures such as IV fluids, bowel rest, and total parenteral nutrition, if necessary.<sup>15</sup> Antimicrobial therapy consists of monotherapy with broad spectrum agents (eg, the carbapenems, piperacillin/tazobactam) with activity against gram-positive, gram-negative, and anaerobic bacteria, or a combination of these agents with an aminoglycoside or a quinolone.<sup>1</sup> Initial antifungal coverage is not recommended.<sup>10</sup> The most common complications include ileus, lower gastrointestinal bleeding, and bowel perforation, which

occurs in approximately 5–10% of cases.<sup>1,8,10</sup> As seen in our patient, some of these complications can occur late in the course of the infection, and even after resolution of neutropenia. Consequently, close monitoring for the development of these complications is essential, particularly since prompt recognition and appropriate surgical intervention is often life-saving.<sup>8</sup>

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## Review

### Neutropenic Enterocolitis: Challenges in Diagnosis and Treatment

Nicole M.A. Blijlevens, MD

*Department of Haematology, Radboud University Medical Centre Nijmegen, The Netherlands.*

Rolston<sup>1</sup> reports a case of neutropenic enterocolitis (NEC) in a woman treated with docetaxel for breast cancer. Her initial presentation did not seem too dramatic;

Address Correspondence to: Nicole M.A. Blijlevens, Radboud University Medical Centre Nijmegen, Department of Haematology, P.O. Box 9101, NL-6500 HB Nijmegen, The Netherlands; Phone: 31-24-361-47-62; Fax: 31-24-354-20-80; E-mail: n.blijlevens@hemat.umcn.nl

it entailed primary diarrhea, mild abdominal discomfort, and bowel wall edema (observed with computed tomography [CT] scan), and resolved after conservative therapy. Unfortunately, after the recovery of her neutrophils, she presented with general malaise and increasing abdominal complaints due to a bowel wall perforation seen on CT scan with bacteremia due to *Pseudomonas aeruginosa*. She underwent surgery, was given antimicrobial therapy, and recovered completely.

Over the past decade, the number and variety of patients who are being treated for cancer with chemotherapy, radiation therapy, or targeted therapy continues to grow. In order to improve survival, better recognition of intestinal complications, such as NEC, and proper management is warranted.

Although NEC has been reported in patients suffering from aplastic anemia or AIDS, the current term NEC is used to describe an inflammatory process involving the colon (mainly the cecum) with or without involving adjacent areas of the small intestine in the context of chemotherapy-induced neutropenia. NEC can potentially result in life-threatening complications such as ischemia, necrosis, hemorrhage, bacteremia, and perforation, as in the case presented by Rolston.

Mortality rates vary from 50 to 100%.<sup>2</sup> A systematic review of 21 studies (mainly case reports and reviews) reported a pooled incidence of 5.3% (266/5058) among adults treated for hematologic malignancies, solid tumors, or aplastic anemia.<sup>3</sup> One of the few prospective surveys reported a 17.7% overall incidence of abdominal infections and a 6.5% incidence of NEC among adults treated for acute leukemia.<sup>4</sup> Robust epidemiologic data on NEC are scarce because of the heterogeneity of the various patient groups studied, the fact that most studies were retrospective, the variability in follow-up, and the lack of uniformly applied diagnostic criteria.

The common clinical manifestations of NEC, as in the initial presentation of the case, are fever, abdominal pain, and diarrhea. The pain is often localized to the right lower quadrant with or without rebound tenderness, but can be accompanied by diarrhea (92%), nausea (75%), vomiting (67%), decreased bowel sounds (62%), and abdominal distension or lower gastrointestinal tract bleeding.<sup>5</sup> These symptoms are neither specific nor pathognomonic for NEC and must be differentiated from other potential causes of abdominal complications such as appendicitis, pseudo-membranous colitis, ischemic colitis, obstruction, and intussusceptions. Typically, NEC occurs between 10 and 30 days after starting cytotoxic treatment, so the case reported by Rolston presented quite early. A recently published cohort study reported an overall incidence of diarrhea of 18.6% in 317 neutropenic episodes of 215 patients treated for hematologic malignancies.<sup>6</sup> NEC was diagnosed during 11 episodes (incidence rate 3.5%). In

72.7% of these episodes, patients suffered abdominal pain, which in a minority of the cases was localized to the right lower quadrant. Furthermore, there were no significant differences in vital signs or laboratory measurements between patients suffering from diarrhea, regardless of whether it was associated with NEC. Hence, additional tools are needed to diagnose NEC.

Plain abdominal radiography is of limited utility, but can show bowel wall distension and thickening, obstruction, and even pneumatosis intestinalis (air within the bowel wall). Ultrasound sonography (US) or CT appears more valuable in the diagnosis and monitoring of suspected NEC. The normal thickness of the bowel wall estimated by US is less than 2 mm, and thickening of more than 5 mm is considered abnormal or at least matching NEC. Bowel wall thickening (BWT) between 2–5 mm is more difficult to interpret.<sup>7</sup> Most reports concerning NEC adopt the principle that a BWT of more than 3 mm is abnormal, and either matches or supports a diagnosis of NEC. The characteristic sonographic features of NEC are echogenic asymmetric thickening of the mucosal wall with a transmural inflammatory reaction, areas of different echogenicity caused by edema, and necrosis with or without hemorrhage. Additional signs of pericolic fluid and intramural or abdominal free air can be seen and might indicate perforation. The typical 5-layer morphology of the ileum and colon seen only by US is called the “gut-signature”, leading some to proclaim US to be more accurate than CT in measuring BWT.<sup>8</sup> CT tends to overestimate BWT because intraluminal contents impair identification of the mucosa, and inflammatory changes in the surrounding mesentery may inhibit serosal surface identification. Both US and CT were used to diagnose 99 episodes of NEC in a cohort of 92 children treated for cancer over a 10-year period.<sup>9</sup> The mean bowel wall thickness measured by CT (1.4 cm) was significantly larger than that measured by US (0.65 cm), but in contrast to the US measurements, the CT measurements did not correlate with the duration of NEC-related symptoms. US therefore would be the preferred way of measuring bowel wall thickness.<sup>10</sup> The fact that US does not expose the patient to ionizing radiation, and its ease of use at the bed-side of ill patients, especially children, makes it very attractive, assuming there are competent sonographers available. However, the main advantage of CT is its ability to differentiate NEC from other intestinal complications in neutropenic patients. For instance, the highest mean BWT (12 mm) was seen in *Clostridium difficile*-related colitis in an analysis of 76 neutropenic patients with various gastrointestinal disorders. On the other hand, *pneumatosis intestinalis* was very suggestive of NEC, though the small intestines are seldom thickened without involvement of the cecum.<sup>11</sup> US findings of BWT of more than 10 mm were associated with a significantly higher

mortality rate (60%) than was found for those with a bowel thickness of 10 mm or less (4.2%).<sup>12</sup> Positron-emission tomography scanning might provide more information, as diffuse bowel fluorodeoxyglucose uptake would indicate gut inflammation.<sup>13</sup>

Our understanding of the pathobiology of chemotherapy-induced mucosal injury, of which NEC is the most extreme example, has advanced in the last few years. A 5-phase model was developed to explain the pathobiology of oral mucositis, but can also be extended to the rest of the injured alimentary tract.<sup>14</sup> The hallmark of this process is the induction of inflammation and subsequent disintegration of the mucous layer. Microorganisms and their cell wall products, particularly peptidoglycan and lipopolysaccharide, can translocate across the damaged physical barrier more easily and are able to activate tissue macrophages to produce more pro-inflammatory cytokines that in turn amplify local tissue damage.<sup>15</sup> As mentioned before, deaths are mostly due to perforation and sepsis.

Bacteremia due to *Staphylococcus aureus*, *Pseudomonas aeruginosa* (as in this case), *Clostridium* species, and *Candida* species are clearly associated with neutropenic enterocolitis.<sup>16</sup> Indeed, bacteremia due to certain species of *Clostridium* (eg, *Clostridium tertium* and *Clostridium septicum*) are considered pathognomonic in the setting of NEC. Presumably, prolonged exposure to antibiotics results in a marked shift in the gut microflora toward toxin-producing bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Clostridium septicum*. Mucosal or transmural necrosis and hemorrhage of the mucosal surface of the ileocecal region probably provides a favorable environment for the spores of *Clostridium* species to germinate and may be their portal of entry into the bloodstream.<sup>17</sup> The predilection for the cecum may be related to the naturally limited blood supply, although there are no clinical data to support this argument. The pathogenesis of NEC seems to require various elements to be present simultaneously, namely, cytotoxic therapy-induced mucosal damage, a perturbed resident microflora, and profound neutropenia. The recovery of neutrophils usually resolves the clinical problem of NEC, but might have been initially deleterious to the patient's condition, as tissue infiltration of neutrophils in an inflamed bowel wall containing micro-organisms could have resulted in perforation in this case.

Because there is no uniform treatment strategy available for patients suffering from NEC in general, it is recommended to act conservatively and avoid unnecessary surgery, as no published prospective randomized trials have ever showed a better treatment regimen. Patients presenting without significant complications of NEC need supportive care consisting of bowel rest, nasogastric suction, total parenteral nutrition, and if indicated, broad-spectrum antimicrobial therapy to cover *Candida* species and *Clostridium* species.<sup>18</sup>

The use of granulocyte colony stimulating factor to hasten neutrophil count or function is still under debate. However, treatment with keratinocyte growth factor (or fibroblast growth factor family-7) might be worth pursuing, as it is exclusively synthesized by mesenchymal cells, particularly fibroblasts, and plays a key role in maintaining the barrier function of epithelial tissues by its trophic and cytoprotective effects.<sup>19</sup> Recombinant human keratinocyte growth factor-1 (rHuKGF; palifermin) is indicated for the prevention of severe oral mucositis in hematopoietic stem cell transplant patients, and clearly supports healing of inflamed epithelial tissue. Hence, its potential in the treatment of NEC deserves further exploration.<sup>20</sup>

In case of sudden clinical deterioration due to massive bleeding or perforation, emergency surgery is essential for survival, though resections should not be too aggressively pursued as extensive mucosal necrosis may be present.

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