Neutropenic Enterocolitis: Current Issues in Diagnosis and Management

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Neutropenic enterocolitis or typhlitis (from the Greek word typhlon, meaning cecum) is a clinical syndrome that occurs in the setting of disease or chemotherapy-induced neutropenia. The disease is characterized by an inflammatory process involving colon and/or small bowel, and it can result in ischemia, necrosis, bacteremia, hemorrhage, and perforation. The classic clinical features include fever and abdominal pain. The diagnosis is supported by the findings of bowel wall thickening on ultrasonography or CT imaging. The management of neutropenic enterocolitis is controversial. Neither prospective nor high-quality retrospective studies concerning medical or surgical therapies are available. Most authors will recommend initial conservative management with bowel rest, intravenous fluids, total parenteral nutrition, broad-spectrum antibiotics and normalization of neutrophil counts. Surgical intervention is recommended in the setting of obstruction, perforation, persistent gastrointestinal bleeding despite correction of thrombocytopenia and coagulopathy, and clinical deterioration.

Introduction

Neutropenic enterocolitis is a clinical syndrome in neutropenic patients characterized by fever, abdominal pain, and diarrhea. This highly life-threatening abdominal infection is the most important entity in neutropenic patients. Early recognition and treatment are essential for survival. Neutropenic enterocolitis was originally described in children following induction chemotherapy for acute leukemia [1]. Subsequently, it has been reported in adults with hematologic malignancies who are yet to receive chemotherapy, patients with granulocytopenias from other causes, patients with AIDS, and patients following immunosuppressive therapy for solid malignancies and transplants [2,3].

The true incidence of neutropenic enterocolitis is unknown. Postmortem studies in leukemics, mostly from the pediatric literature, report incidence rates ranging from 12% to 46% [2,4]. In a recent systematic review of 21 studies, the reported pooled incidence rate was 5.3% (266/5058; 95% CI, 4.7%–5.9%) in adult patients hospitalized for the treatment of hematologic malignancies, high-dose chemotherapy in solid tumors, or aplastic anemia [5••]. In a prospective study of abdominal infections in adults with acute leukemia, the reported incidence of neutropenic enterocolitis was 6.5% per neutropenic episode [6]. The mortality rate varies from 50% to 100% [7,8], with most deaths due to bowel perforation and uncontrolled sepsis. More recently, early recognition and progress in management have probably reduced mortality; however, no large series have been published on the subject.

Neutropenic enterocolitis has been traditionally associated with chemotherapeutic agents used in the treatment of leukemias and lymphomas, particularly cytosine arabinoside (ara-C), vincristine, doxorubicin, methotrexate, cyclophosphamide, etoposide (VP-16), daunomycin, and prednisone [1,2,7]. Recently, agents used for the treatment of ovarian, lung, colon, and breast cancer have also been implicated in the development of this syndrome, including vinorelbine, docetaxel, paclitaxel, carboplatin, gemcitabine, and 5-fluorouracil [9–16].

Clinical Presentation

Patients with neutropenic enterocolitis may present with fever and abdominal pain (often localized to the right lower quadrant), with or without rebound tenderness. Other presenting signs and symptoms include abdominal distension, nausea, vomiting, watery or bloody diarrhea, and right lower quadrant fullness or mass. In a retrospective study of children treated for cancer at St. Jude's Children's Hospital over a period of 30 years, 24 cases of neutropenic enterocolitis were identified. All of the patients had fever and abdominal pain. The most frequently associated signs or symptoms reported were diarrhea (in 92% of

patients), nausea (75%), vomiting (67%), decreased bowel sounds (62%), and rebound or guarding (58%) [1]. Lower gastrointestinal bleeding is also common in neutropenic enterocolitis. In a retrospective study of 291 patients with hematologic malignancies, 32 cases of overt gastrointestinal hemorrhage were observed: 25 of them were classified as upper and seven as lower in origin. Neutropenic enterocolitis was the underlying cause in all seven patients with lower gastrointestinal bleeding [17].

Symptoms usually occur within 30 days following initiation of cytotoxic chemotherapy [2,7]. This entity can also present with the same frequency during induction therapy, remission, or relapse [1,18]. Since the symptoms and clinical findings of neutropenic enterocolitis can be nonspecific, one must consider other entities in the differential diagnosis, including pseudomembranous colitis, acute appendicitis, ischemic colitis, colonic pseudo-obstruction, infectious colitis, and inflammatory bowel disease. Physicians should also be aware that two disease entities might coexist in the same patient. There have been numerous reports of *Clostridium difficile* colitis and other bacterial stool pathogens present in the setting of neutropenic enterocolitis [1,19].

Recurrence may occur, particularly in patients requiring further chemotherapy in the setting of leukemia or lymphoma. In a study of 33 children with neutropenic enterocolitis, five patients (15%) had recurrence. All of them were receiving treatment for Burkitt's lymphoma with cytosine arabinoside (ara-C) and VP-16 [20]. In a study of 16 leukemic adults with neutropenic enterocolitis, five developed recurrence when they received further chemotherapy with high-dose ara-C and daunorubicin. Three of them died, two after surgery [18].

Pathogenesis

The pathogenesis of neutropenic enterocolitis is poorly understood. A number of factors may play a role including mucosal injury by cytotoxic drugs, neutropenia, and impaired host defense to intestinal organisms [3]. The initial insult appears to be disruption of the integrity of the bowel mucosa due to the cytotoxic effect of chemotherapy or the presence of leukemic infiltrates. This is followed by bacterial invasion of the bowel wall, facilitated by a decreased defense due to the neutropenia. Bacterial endotoxins are produced, leading to necrosis and hemorrhage. On autopsy or surgical pathology specimens, the gross appearance of the bowel demonstrates a dilated, edematous, and frequently hemorrhagic external appearance [2]. Microscopically, there is edema of the mucosa or the entire intestinal wall, mucosal ulcerations, focal hemorrhage, and mucosal or transmural necrosis. Fungal organisms are often seen in the superficial necrotic tissue. In deeper portions of the bowel wall, there may be small blood vessels surrounded and infiltrated by bacteria, generally gram-negative rods [2]. Rarely are leukemic or acute inflammatory infiltrates identified [3]. The cecum is almost always affected, but the disease may also involve small bowel and right and left colon [2]. The predilection for the cecum may be related to its distensibility and limited blood supply.

Multiple organisms have been identified in surgical specimens and peritoneal fluid, including gram-negative rods, gram-positive cocci, enterococci, *Clostridium septicum*, *Candida*, and cytomegalovirus [3]. Bacteremia and fungemia are frequently reported. In the study by Katz et al. [2], at premortem, 84% of patients had bacterial organisms cultured from blood. *Pseudomonas* spp were the most frequent bacterial isolates, whereas *Escherichia coli*, *Klebsiella* spp, *Staphylococcus aureus*, and alpha streptococci were prevalent. Sixteen percent of patients had fungal organisms isolated in blood, with *Candida* being the most common fungal isolate. Postmortem blood cultures differed strikingly as fungal pathogens, *Candida* and *Aspergillus* spp represented 53% of organisms identified [2].

In a systematic analysis of the literature, Gorschlüter et al. [21] reviewed 186 relevant papers and found 29 reports describing 53 patients with neutropenic enterocolitis and invasive fungal infection, defined by a positive blood or ascitic fluid cultures. The pooled frequency of fungal infection was 6.2% (53/860; 95% CI, 4.7%–8%). In 94% of the patients, *Candida* sp was the organism involved. Fungal infection was associated with high mortality. In nine of the 53 patients, it was unclear whether they survived or died in the course of the infection. In the remaining 44 patients, 36 died with a pooled mortality rate of 81.8% (95% CI, 68%–91%).

Diagnosis

The diagnosis of neutropenic enterocolitis needs to be supported by radiologic imaging. In fact, bowel wall thickening (BWT) as demonstrated by CT or ultrasonography is one of the main proposed criteria to establish the diagnosis (Fig. 1) [5••].

CT imaging and ultrasonography are more sensitive than radiography or barium studies in demonstrating thickening of the bowel wall [1]; furthermore, they may help differentiate neutropenic enterocolitis from other potential diagnoses. Other pertinent findings on CT and ultrasonography include a fluid-filled dilated cecum, a right lower quadrant inflammatory mass, and pericecal fluid or inflammatory changes in the pericecal soft tissues. Findings on plain films of the abdomen may be nonspecific, but occasionally, a distended cecum is noted with dilated adjacent small bowel loops, thumbprinting, or localized pneumatosis intestinalis [4]. Barium enema and colonoscopy may be risky and contraindicated, as they can precipitate perforation.

In the only prospective study using ultrasonography to evaluate leukemic patients after chemotherapy, significant BWT (> 4 mm) was seen only in those patients who

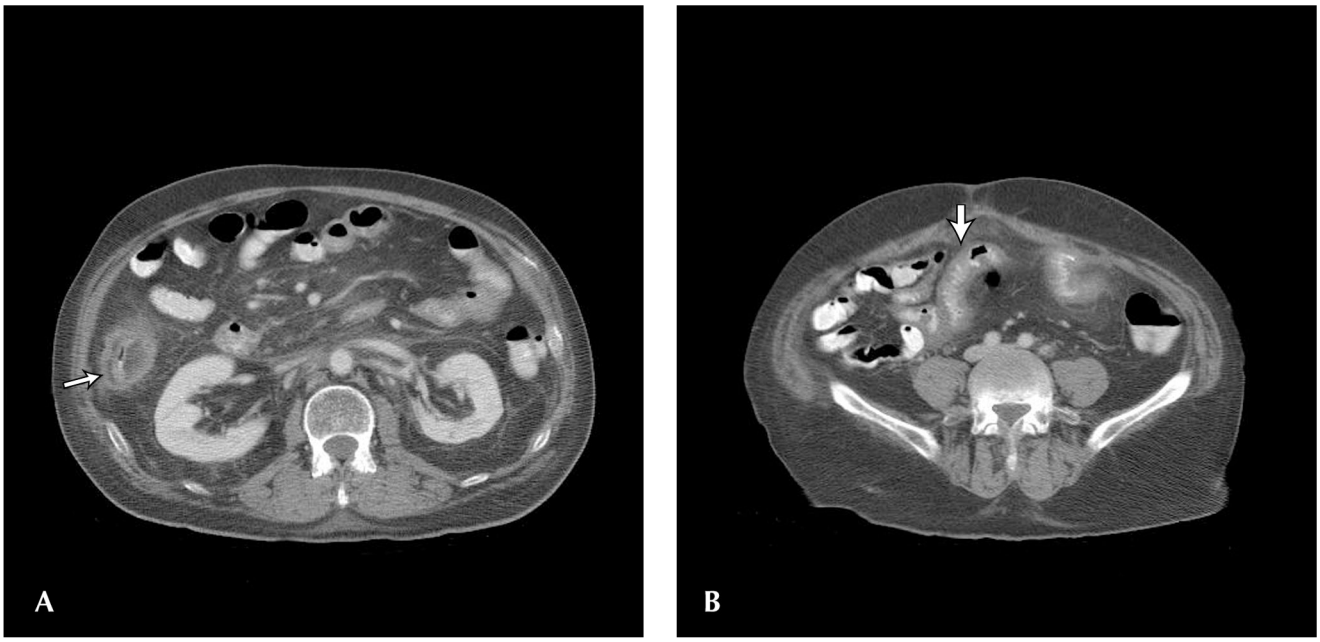

Figure 1. Abdominal CT of a patient with neutropenic enterocolitis showing thickening of the ascending colon (**A,** *arrow*), and small bowel (**B,** *arrow*).

fulfilled symptom criteria for neutropenic enterocolitis. It was not seen in those patients with mucositis alone, those with documented bacterial infectious colitis, or those who remained asymptomatic [6]. Furthermore, ultrasonographic evidence of BWT can be used as a prognostic factor to determine patient outcome. In a retrospective study, Cartoni et al. [22] reviewed the ultrasonographic findings in 88 neutropenic patients with fever, abdominal pain, and diarrhea. A thickness of greater than 5 mm was considered abnormal and diagnostic of neutropenic enterocolitis. The study revealed that the mean duration of symptoms was significantly longer among patients with sonographically detected BWT (7.9 days) than among patients without mural thickening (3.8 days), and the related mortality rate was higher (29.5% vs 0%). Moreover, 60% of patients with BWT greater than 10 mm died from neutropenic enterocolitis compared with only 4.2% of those with mural thickness of 10 mm or less [22]. In a similar study, BWT more than 10 mm was associated with significant likelihood of mortality [23].

Despite the encouraging results of ultrasonography in the recognition of this disease, other studies have reported significant overlap in BWT measurements among neutropenic patients with a variety of gastrointestinal disorders. In a retrospective study comparing CT findings in patients with neutropenic enterocolitis, *C. difficile* colitis, graft-versus-host disease, cytomegalovirus colitis, and ischemic colitis, BWT was significantly more prominent in patients with *C. difficile* colitis compared to the other groups [24]. Pneumatosis intestinalis was a much more specific finding, seen only in those with neutropenic enterocolitis and ischemia. The location of wall thickening was also helpful, with combined involvement of the small and large bowel pointing more toward the diagnosis of neutropenic enterocolitis [24].

In summary, the value of BWT in the diagnosis of neutropenic enterocolitis remains a matter of debate. A systematic study validating the sensitivity and specificity of radiologically detected BWT is lacking. Nevertheless, some authors argue that the diagnostic accuracy for neutropenic enterocolitis can be increased when radiologic findings are added to symptoms and physical signs. Therefore, some have recommended the following criteria for the diagnosis of neutropenic enterocolitis: fever, abdominal pain, and demonstration of BWT of more than 4 mm (transverse scan) over more than 30 mm (longitudinal scan) in any segment by ultrasound or CT scanning [5••]. These criteria await validation by well-designed, prospective studies.

Management

Treatment for neutropenic enterocolitis remains controversial because prospective randomized trials on the subject have never been published. Treatment recommendations are based mostly on descriptive or retrospective studies, clinical experience, and opinions of respected authorities. In patients presenting without significant complications such as peritonitis, perforation, or massive bleeding, nonsurgical management should be the initial approach. Medical treatment consists of bowel rest, intravenous fluids, total parenteral nutrition, and broad-spectrum antibiotics [1,3,4,5••]. Antibiotic coverage for *C. difficile* infection should be added if pseudomembranous colitis has not been excluded. Antifungal treatment to cover *Candida* should be strongly considered [21].

The Infectious Diseases Society of America has published guidelines for the use of antimicrobial agents in neutropenic patients with cancer and in patients with complicated intra-abdominal infections [25,26]. These 2003 guidelines suggest expanded spectrum of coverage in the setting of immunosuppression, including the use of meropenem, imipenem/cilastatin, piperacillin/tazobactam, ciprofloxacin plus metronidazole, or a third or fourth generation cephalosporin plus metronidazole [26]. Although the use of antibiotics has been prospectively evaluated in a number of randomized trials in febrile, neutropenic patients, no studies have looked specifically to a population of patients with neutropenic enterocolitis. Until better evidence is available, an intensive combination antibiotic regimen might be best for these patients. Antimicrobial therapy should be continued until resolution of clinical signs of infection occurs, including normalization of temperature and white cell count and return of gastrointestinal function.

In neutropenic enterocolitis, normalization of the leukocyte count is essential for healing and recovery. Although granulocyte colony-stimulating factor (G-CSF) has been used to hasten recovery, no prospective or retrospective studies have been conducted regarding its use in this disease. The recommendation from expert opinion is to apply the current American Society of Clinical Oncology guidelines [27]. The guidelines recommend the use of G-CSF in patients with fever and neutropenia who are at high risk for infection-associated complications and have prognostic factors predictive of poor clinical outcome. Neutropenic enterocolitis carries a very poor prognosis and the conclusion from expert opinion is that G-CSF should be strongly considered in this setting [5••].

Surgery has been recommended for patients with gastrointestinal bleeding that persists despite correction of cytopenias and coagulopathy, for those with free intra-abdominal perforation or clinical deterioration during medical therapy, and to differentiate from other acute abdominal diseases for which surgery is indicated [4,28]. The type of surgical procedure that should be performed is controversial. Perforated or necrotic bowel must be resected. A primary bowel anastomosis should not be attempted in the face of ongoing leukopenia [29,30]. Resection and diversion are recommended instead [4]. In patients with edematous and thickened bowel in the absence of perforation, either aggressive resection or diversion of the fecal stream should be performed [8,18]. A surgeon must exert caution when dealing with edematous bowel without apparent gangrene, since mucosal necrosis may be present below very unimpressive serosal inflammation.

Conclusions

In summary, neutropenic enterocolitis is a life-threatening complication of chemotherapy or disease-induced neutropenia. Diagnostic criteria should include three basic elements: fever, abdominal pain, and BWT greater than 4 mm as determined by ultrasound or CT. Most patients can be managed conservatively with bowel rest, total parenteral nutrition, intravenous fluids, broad-spectrum antibiotics, antifungals, and recombinant G-CSF to hasten return of neutrophils. Surgery should be reserved for patients with significant clinical deterioration, massive bleeding, and perforation. Mortality remains high, and prompt intervention is essential for the survival of these patients.

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