

Changing Presentation and Management of Neutropenic Enterocolitis

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Objective: To characterize the current clinical presentation and management of neutropenic enterocolitis.

Design: Retrospective review of records of oncology unit patients requiring general surgical consultation for abdominal complaints in a 1-year period.

Setting: Oncology unit of a tertiary care, university teaching hospital.

Patients and Interventions: Fourteen patients diagnosed as having neutropenic enterocolitis were managed conservatively with operation reserved for failure of conservative therapy.

Main Outcome Measures: Clinical data from patients at the time of presentation and during treatment for neutropenic enterocolitis.

Results: All 14 patients diagnosed as having neutropenic enterocolitis were receiving chemotherapy for solid tumors or leukemias. Seven patients were undergoing stem cell or autologous bone marrow transplantation. Presenting symptoms and physical examination findings were

nonspecific. All patients except one had neutropenia at the time of diagnosis. Computed tomographic scans of the abdomen were the most useful confirmatory study for the diagnosis of neutropenic enterocolitis. All patients except one had resolution of neutropenic enterocolitis with conservative therapy. One patient whose course of conservative management failed had protracted neutropenia and required operation for resection of bowel with full-thickness necrosis.

Conclusions: Neutropenic enterocolitis has evolved from a complication of patients with leukemia to a disease of patients receiving high-dose chemotherapy for many malignancies, solid as well as hematologic. Diagnosis of neutropenic enterocolitis continues to be a challenge, as patients typically present with nonspecific gastrointestinal tract symptoms. Neutropenia and computed tomographic scan findings are useful adjuncts in diagnosing neutropenic enterocolitis. Timely conservative treatment frequently allows resolution of neutropenic enterocolitis without operation.

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NEUTROPENIC enterocolitis is a necrotizing inflammation of the colon found in immunocompromised patients. Neutropenic enterocolitis was first and most commonly described in the 1970s as a complication of the treatment of childhood leukemias.¹⁻⁴ However, with the proliferation of intensive chemotherapeutic regimens for adult malignancies, it has become increasingly common in adult populations receiving treatment for solid as well as hematologic malignancies.⁵⁻⁹ The purpose of this study is to review our recent experience with neutropenic enterocolitis to characterize the current clinical presentation and management of this disease.

RESULTS

The average age of the patients in the study group was 47.3 years (age range, 24-77

years). Ten of the 14 patients were female. Leukemia was the most common primary diagnosis (5 patients), followed by breast cancer (4 cases), lymphoma (2 cases), gastrointestinal tract malignancies (2 cases), and pontine glioma (1 case).

All patients were receiving or had recently completed a cycle of chemotherapy. Chemotherapeutic regimens varied widely among patients. Alkylating agents, antitumor antibiotics, antimetabolites, steroids, and plant alkaloids were all used. Three patients with leukemia and all 4 patients with breast cancer received high-dose chemotherapy in preparation for autologous stem cell or bone marrow transplantation.

The most common presenting symptom was crampy abdominal pain that occasionally localized to the right lower quadrant. All 13 mentally alert patients complained of abdominal pain. The remaining patient had a diminished mental

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PATIENT POPULATION AND METHODS

Records of patients admitted in a 1-year period (April 1, 1996–April 1, 1997) to the Oncology Unit of the Hospital of the University of Pennsylvania, in Philadelphia, who received general surgical consultation for abdominal complaints were reviewed retrospectively. Patients with identifiable gastrointestinal tract disorders other than neutropenic enterocolitis, such as *Clostridium difficile* enterocolitis, cholecystitis, and invasive infection by opportunistic organisms such as cytomegalovirus were excluded. Fourteen patients diagnosed clinically as having neutropenic enterocolitis during the study period were identified. The hospital courses of these patients were reviewed with particular attention to clinical presentation, management, and outcome.

status related to a pontine glioma, making her presenting symptom complex and unreliable. Nausea (12 patients), vomiting (8 patients), and diarrhea (6 patients) were also common complaints. Three patients had abdominal distention and 2 had grossly bloody stools; 1 complained of constipation. All patients were febrile at the time of diagnosis with a mean temperature of 39.1°C (range, 38.0°C–40.4°C).

Physical examination findings were generally unremarkable. Twelve of the 13 mentally alert patients had mild diffuse tenderness, localizing to the lower quadrants in 3. Only 1 of the 13 mentally alert patients had peritoneal signs at the time of presentation. Three patients had abdominal distention and diminished bowel sounds. One patient had a palpable right lower quadrant mass.

A consistent pattern among patients was the onset of symptoms while their white blood cell (WBC) count was declining during or shortly after the administration of chemotherapy. Thirteen of the 14 patients diagnosed as having neutropenic enterocolitis had neutropenia. The mean WBC count at the time of diagnosis among these patients was $0.75 \times 10^9/L$. The remaining patient presented with a WBC count of $26.2 \times 10^9/L$ during a blast crisis related to chronic myelogenous leukemia and was presumed to have nonfunctioning WBCs. This patient developed abdominal complaints during a course of idarubicin hydrochloride-based chemotherapy for blast crisis and eventually developed severe neutropenia with an absolute neutrophil count of $0 \times 10^9/L$. Typically, patients' WBC counts would continue to decrease after the onset of symptoms. Only after this nadir was reached and the WBC count began to recover would patients improve. The average WBC and absolute neutrophil counts at the time of nadir were 0.45 and $0.87 \times 10^9/L$, respectively. At the time of recovery, these measurements had increased to 10.3 and $1.35 \times 10^9/L$.

Other laboratory findings were not useful in making the diagnosis of neutropenic enterocolitis except as exclusionary data. Nine patients for whom stool specimens were sent for *Clostridium difficile* toxin assay had negative results. Two patients had blood cultures positive for *Escherichia coli*.



An abdominal computed tomographic scan demonstrates diffuse pneumatosis intestinalis of the ascending colon, thickening of the bowel wall, stranding of the surrounding tissue planes, and ascites. This patient's neutropenic enterocolitis resolved after 6 days of conservative management.

Findings of plain x-ray films of the abdomen were generally normal or nonspecific. Six patients had normal findings on plain x-ray films. Abnormal findings included dilated loops of bowel (4 patients), air-fluid levels (3 patients), pneumatosis intestinalis (1 patient), thumb-printing (1 patient), and thickened bowel wall (1 patient). Computed tomographic (CT) scanning of the abdomen was performed in 8 patients and appeared to yield more sensitive and specific results. All CT scans revealed abnormal findings, which included thickened colonic wall generally localized to the right side (6 patients), ascites (5 patients), bowel distention (2 patients), pneumatosis intestinalis (1 patient), and perienteric soft tissue stranding (1 patient) (**Figure**). Three patients with normal findings on plain abdominal x-ray films subsequently underwent CT scanning of the abdomen that showed findings consistent with neutropenic enterocolitis.

Thirteen of the patients were managed initially with conservative therapy. These patients were prescribed bowel rest and broad-spectrum antibiotics with appropriate coverage for enteric organisms from the onset of their febrile illness. Typical antibiotic regimens included a combination of ceftazidime and metronidazole hydrochloride or a combination of piperacillin sodium, gentamicin sulfate, and metronidazole. Amphotericin B was added to the regimens of 2 patients because of persistent fevers. Twelve of the 13 patients managed conservatively had resolution of neutropenic enterocolitis without operation. They had resolution of symptoms and were returned to a regular diet in a mean of 6.5 days (range, 1–14 days).

In 1 patient, this initial conservative therapy failed and surgery was required on the seventh day after the onset of symptoms. This patient's course after the institution of conservative management was characterized by a prolonged period of severe neutropenia and progressive clinical deterioration mandating exploratory laparotomy. Findings at the time of operation included straw-colored ascites, a congested liver, and ischemia of the entire small bowel and right colon most severely involving the distal ileum with focal areas of transmural necrosis. Good pulses were noted throughout the bowel mesentery. The patient underwent resection of the right colon, ileum, and distal jejunum with end jejunostomy and mucous fistula. The patient recovered from the operation

but ultimately succumbed to chemotherapy-induced liver failure and died on the 46th postoperative day.

Only 1 of the 14 patients in the study was managed with immediate operation. This patient's presentation with low-grade fever, anorexia, and particularly severe right lower quadrant pain associated with peritoneal signs led to concern for appendicitis. Findings at urgent laparotomy included a normal appendix and a thickened, inflamed cecum consistent with neutropenic enterocolitis. The patient's abdomen was closed without bowel resection and the patient was treated with broad-spectrum antibiotics and bowel rest. The patient responded to this therapy with resolution of symptoms and returned to a regular diet on the sixth postoperative day.

COMMENT

The presentation of neutropenic enterocolitis has evolved considerably in the past 25 years. Neutropenic enterocolitis was originally described in 1970 in an autopsy series as a terminal complication of childhood leukemia in patients who were neutropenic as the result of chemotherapy or aplastic crisis.¹ The proliferation of myelotoxic chemotherapeutic regimens for adult leukemia has been associated with an increased incidence of neutropenic enterocolitis in adult patient populations.⁵ In the two most recently published surgical series, more than 90% of patients diagnosed as having neutropenic enterocolitis were receiving high-dose chemotherapy for hematopoietic malignancies.¹⁰⁻¹¹ At our institution, patients with leukemia continue to make up a considerable proportion of patients who require surgical consultation for neutropenic enterocolitis. Most patients in our series, however, were receiving high-dose chemotherapy for solid tumors. In particular, women with high-risk or recurrent breast cancers enrolled in protocols for chemotherapy with high-dose cyclophosphamide (Cytosan) and thiotepa prior to stem cell transplantation appear to be at high risk for the disease.

Neutropenic enterocolitis continues to be a diagnostic challenge despite our increasing awareness of its occurrence in high-risk groups. Other gastrointestinal tract complications, such as mucositis, pseudomembranous colitis, and invasive infection by opportunistic organisms are common in patients receiving chemotherapy and may lead to inappropriate management.¹² In addition, patients with neutropenia localize infection poorly and may manifest sources of intra-abdominal sepsis in an atypical fashion. Although patients in our series frequently presented with high-grade fevers, their gastrointestinal tract symptoms were generally nonspecific and limited to mild crampy abdominal pain, nausea, vomiting, and diarrhea.

The onset of neutropenic enterocolitis in all of our patients was associated with a decreasing WBC count resulting from the administration of chemotherapy. Although the severity of neutropenia at the time of diagnosis varied, the pattern of decreasing WBC count prior to the onset of symptoms was consistent throughout the series. Delay in resolution of symptoms until some improvement in neutropenia was also a consistent finding.

Radiologic tests were frequently obtained. Plain abdominal x-ray films had limited usefulness because of poor

sensitivity and findings that were frequently nonspecific. The findings from CT scans of the abdomen were more useful in confirming the diagnosis of neutropenic enterocolitis. All 8 patients for whom CT scans of the abdomen were obtained demonstrated some radiologic finding suggestive of neutropenic enterocolitis, such as pelvic fluid, cecal thickening, and mesenteric stranding (Figure). Three of these patients had previous abdominal plain films with unremarkable findings.

The management of neutropenic enterocolitis has evolved as clinical experience with the disease has grown. In its first descriptions, neutropenic enterocolitis was thought to be a terminal complication of leukemia diagnosed primarily at autopsy.^{1,2} Subsequent reports of successful treatment of neutropenic enterocolitis by surgical intervention led some surgeons to espouse aggressive surgical management of all cases, under the belief that all cases of neutropenic enterocolitis eventually lead to full-thickness necrosis of the cecum and perforation.¹³⁻¹⁵ Numerous case reports and reviews published more recently give anecdotal accounts of successful conservative as well as surgical management.¹⁶⁻²⁸ The two most recently published surgical series¹⁰⁻¹¹ advocate selective surgical management of these patients with laparotomy reserved for patients with severe presentations and traditional surgical complications such as perforation, abscess, gastrointestinal tract bleeding, and obstruction.

Our findings support this trend toward a more conservative approach in the management of patients with neutropenic enterocolitis. All patients in this study were initially managed conservatively with the exception of one who was operated on at the time of presentation for presumed appendicitis. After the diagnosis of neutropenic enterocolitis was made in this patient at the time of operation, conservative management was instituted for him as well.

In only 1 patient did conservative management fail, requiring operation on the seventh day after presentation as previously described. This patient also represents the only death in our series. The relationship between her mortality and the delay in operation is not clear as the patient died on the 46th postoperative day because of chemotherapy-induced adverse effects to the liver. Of note, this patient's clinical course prior to operation was remarkable for severe, protracted neutropenia, possibly putting her at increased risk for transmural necrosis and clinical deterioration.

The remaining patients in the study had resolution of neutropenic enterocolitis with conservative management. Success with this approach is likely multifactorial. Increasing experience with high-dose chemotherapeutic regimens on the part of medical oncologists may be limiting the period of severe neutropenia, thus allowing the milder forms of the disease to resolve without operation. It is also possible that this period of neutropenia now occurs in a more controlled environment, what with routine use of neutropenic precautions and supportive measures such as granulocyte-macrophage colony-stimulating factor. There is also a heightened awareness for the disease among both oncology and surgical services that may allow for earlier diagnosis and institution of conservative measures before irreversible changes to the bowel wall have occurred.

Neutropenic enterocolitis has become a common complication of the chemotherapeutic treatment of solid and hematologic malignancies of adults. Appropriate clinical

cal suspicion and directed laboratory and radiologic studies allow for early diagnosis and treatment of this disease. Timely conservative treatment may interrupt progressive necrosis and permit resolution of neutropenic enterocolitis. A trial of conservative management is generally warranted because in this setting neutropenic enterocolitis is self-limited.

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Homocysteine and Ischemic Heart Disease: Results of a Prospective Study With Implications Regarding Prevention

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Background: Results from prospective studies of serum homocysteine levels and ischemic heart disease (IHD) are inconclusive. We carried out a further prospective study to help clarify the position.

Methods: In the British United Provident Association (BUPA) prospective study of 21 520 men aged 35 to 64 years, we measured homocysteine levels in stored serum samples and analyzed data from 229 men without a history of IHD at study entry who subsequently died of IHD and 1126 age-matched control subjects (nested case-control design).

Results: Serum homocysteine levels were significantly higher in men who died of IHD than in men who did not (mean, 13.1 vs 11.8 $\mu\text{mol/L}$; $P < .001$). The risk of IHD among men in the highest quartile of serum homocysteine levels was 3.7 times (or 2.9 times after adjusting for other risk factors) the risk among men in the lowest quartile (95% confidence interval [CI], 1.8-4.7). There was a continuous dose-response relationship, with risk increasing by 41% (95% CI, 20%-65%) for each 5- $\mu\text{mol/L}$ increase in the serum homocysteine level. After adjustment for apolipoprotein B levels and blood pressure, this estimate was 33% (95% CI, 22%-59%). In a meta-analysis of the retrospective studies of homocysteine level and myocardial infarction, the age-adjusted association was stronger: an 84% (95% CI, 52%-123%) increase in risk for a 5- $\mu\text{mol/L}$ increase in the homocysteine level, possibly because the participants were younger; the relationship between serum homocysteine level and IHD seems to be stronger in younger persons than in older persons.

Conclusions: Our positive results help resolve the uncertainty that resulted from previous prospective studies. The epidemiological, genetic, and animal evidence together indicate that the association between serum homocysteine level and IHD is likely to be causal. A general increase in consumption of the vitamin folic acid (which reduces serum homocysteine levels) would, therefore, be expected to reduce mortality from IHD. (1998;158:862-867)

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