
Neutropenic Enterocolitis in a Woman Treated with 5-Fluorouracil and Leucovorin for Colon Carcinoma

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Patients who become neutropenic after getting combined chemotherapy are at special risk of developing neutropenic enterocolitis (also called typhlitis), a necrotizing inflammation of the cecum.¹⁻¹⁰ In 1970, Wagner et al¹¹ first described neutropenic enterocolitis in children with hematologic malignancies or aplastic anemia, but since then many adult cases have been reported.^{1,3-4,7-10,12} The condition has been detected in 10-46% of patients with acute leukemia,¹³⁻¹⁴ and in other diseases like acquired immunodeficiency syndrome (AIDS) that lead to profound neutropenia.^{10,15-16,17} In fact, it is a potential complication of any hematologic or solid malignancy treated with aggressive chemotherapy,^{6,10,12,15-16,25} especially combined therapy (taxol and doxorubicin,⁶ cytosine-arabinoside and hydroxydaunorubicin,⁷ etoposide and amsacrine,⁸ etoposide and high-dose cytosine-arabinoside⁹).

Diarrhea is a side effect of 5-fluorouracil therapy because, particularly when combined with leucovorin, it can damage gut mucosa.¹⁵ However, two cases of neutropenic enterocolitis have been associated with 5-fluorouracil treatment; one in a patient with laryngeal carcinoma who received 5-fluorouracil and cisplatin, and the other in a patient with colorectal carcinoma who received 5-fluorouracil and leucovorin.^{15,25} We describe here another typical case, with a good outcome.

Our Patient

A 57-year-old woman with colon cancer came to the emergency department of a community hospital complaining of lower abdominal pain, nausea, vomiting, and diarrhea for five days. She had been diagnosed with Dukes' class C colon

carcinoma approximately two months earlier, and undergone right hemicolectomy. She had completed a second cycle of 5-fluorouracil and leucovorin five days before the onset of illness.

She was febrile and had direct but not rebound tenderness in the right lower abdomen. Contrast-enhanced computed tomographic (CT) scan of the abdomen and pelvis showed no evidence of acute or inflammatory process (no distended bowel segments, no sites of bowel wall thickening). There were post-operative changes consistent with hemicolectomy, and multiple, low-density areas in the liver consistent with hemangiomas that had been noted two months earlier.

She was neutropenic, and so was admitted for treatment with broad-spectrum intravenous antibiotics. Filgrastim was given for the neutropenia. She continued to have fever and her abdominal pain worsened. Over three days she developed thrombocytopenia and became confused. She was transferred to our facility for further management.

She complained of continuing nausea, vomiting, and diarrhea, but abdominal pain had lessened from its peak. Abdominal radiographs revealed multiple, dilated loops of small bowel with air fluid levels. Contrast-enhanced CT scan confirmed the marked dilatation of small and large bowel; there was minimal thickening of the transverse colon wall (Figure). The largest area of dilatation, thought to be a high-grade ileus or a very distal obstruction of the ascending colon, measured 8-9 cm in transverse diameter and extended to the level of the hepatic flexure.

The patient was awake and oriented but slightly confused. She was febrile. Bowel sounds were decreased, and she was tender in the right lower abdomen with no rebound

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tenderness. Neutropenia and thrombocytopenia were still present, but she was also found to have disseminated intravascular coagulation (schistocytes on peripheral smear, elevated partial thromboplastin and prothrombin time, elevated fibrinogen, and elevated levels of circulating fibrinogen D-dimers). She was hypokalemic, hypocalcemic, hypocapnic, hypophosphatemic, and hypomagnesemic.

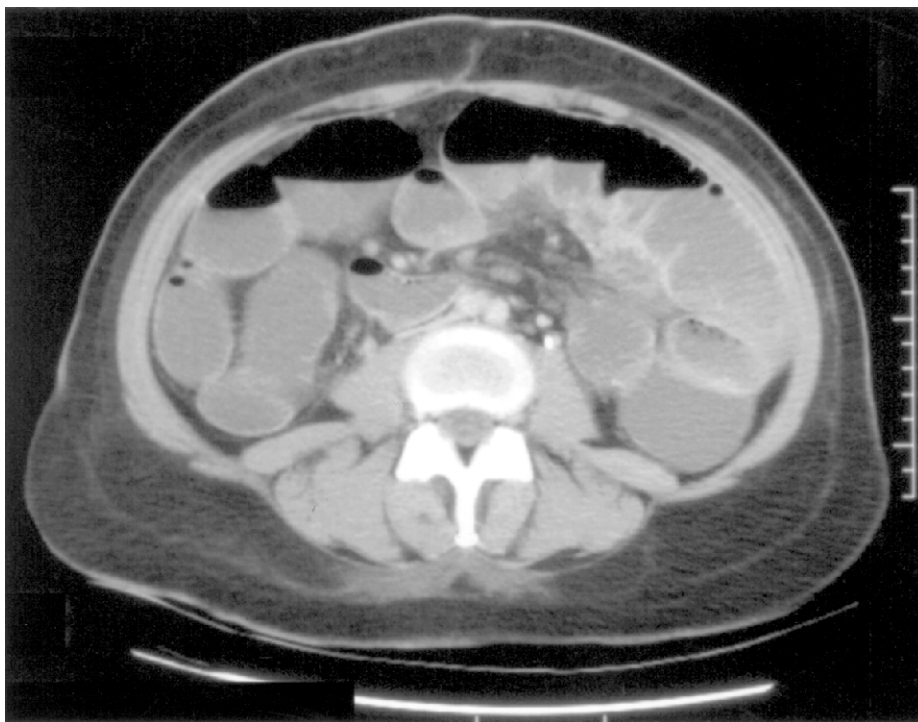
Neutropenic enterocolitis was diagnosed on the basis of clinical findings, laboratory results, and the CT scan showing dilated loops of small and large bowel with minimal bowel wall thickening of the transverse colon. Initial management consisted of stopping oral intake, replacing electrolytes appropriately, and giving broad-spectrum intravenous antibiotics. The coagulopathy was closely monitored but not actively treated.

The patient responded quickly. Two days after transfer abdominal pain, nausea, and vomiting resolved, and she began eating. The intravenous antibiotics were replaced with oral antibiotics four days into her hospitalization. Electrolyte abnormalities corrected, neutropenia and coagulation abnormalities resolved completely, and thrombocytopenia improved. She was discharged home five days after transfer to our facility, to complete a ten-day course of antibiotic therapy; diarrhea was still present, but two days later she had completely recovered.

Discussion

The cecum is the blind pouch found below the ileocecal valve at the juncture of the small and large intestines. The upper end of the cecum is continuous with the colon; the lower end bears the vermiform appendix. When immunosuppression occurs, the cecum is prone to neutropenic enterocolitis because of its poor arterial perfusion and its exposure to the abundant colon bacteria.¹ Besides the cecum, neutropenic enterocolitis can involve the ileum, ascending colon, appendix, and small intestine (terminal ileitis).^{3,4,9,16}

The typical setting is as follows: a patient with a hematologic malignancy, who has had a recent course of chemotherapy and antibiotic therapy and who has neutropenia and thrombocytopenia,⁴ develops diarrhea, high fever, and right



Contrast-enhanced computed tomographic (CT) scan of the abdomen and pelvis showing marked dilatation of the small and large bowel with minimal wall thickening of the transverse colon.

lower quadrant abdominal pain.^{1-4,6-10,15} Radiographic findings vary and are usually nonspecific, but they may show some characteristic features (ileus with focal dilation of scattered small bowel loops; loss of bowel gas in the right lower quadrant; distention of surrounding small bowel; fluid-filled and dilated colon that may show thumbprinting of the mucosa^{5,9,11-12,18}). The small bowel may be obstructed at the ileocecal valve from edema of the adjacent colon wall.¹² A contrast enema may clarify the diagnosis,¹⁹ but it must be done carefully to prevent perforating the bowel.²⁰ Noninvasive studies (CT or ultrasound scans) may demonstrate severe transmural inflammation and bowel wall thickening.^{12,21-22}

Treatment consists of intravenous fluids, electrolyte replacement, and antibiotics if the disease process has been detected promptly; chemotherapy should be postponed until symptoms have completely resolved.²³ Surgical drainage may be needed in patients with one of the following: (1) persistent gastrointestinal bleeding after resolution of neutropenia and thrombocytopenia and correction of clotting abnormalities, (2) evidence of intestinal perforation (free intraperitoneal air), (3) uncontrolled sepsis (suggested by clinical deterioration requiring vasopressors or large volumes of fluid), and (4) signs of an intra-abdominal abscess.^{2-5,7,15-16,24}

Our patient's symptoms and clinical presentation along with the laboratory and radiographic findings suggested neutropenic enterocolitis. She responded quickly to conservative therapy (intravenous fluids, electrolyte replacement,

and appropriate antibiotics). Her case illustrates the previously reported observation of neutropenic enterocolitis after 5-fluorouracil and leucovorin therapy.

Failure to recognize neutropenic enterocolitis is a problem because, though it is still a rare disease, we can expect its incidence to rise as chemotherapy becomes increasingly aggressive and as survival of adult and pediatric patients with immunosuppression is prolonged. It is important that doctors consider the possibility of this rapidly progressive and potentially fatal disease in any neutropenic patient with diarrhea, fever, and abdominal pain because increased awareness leads to accurate diagnosis and the prompt treatment that can decrease morbidity and mortality.

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