Digestive Diseases and Sciences, Vol. 50, No. 2 (February 2005), pp. 215–220 (© 2005)
DOI: 10.1007/s10620-005-1585-1

REVIEW

Neutropenic Enterocolitis in Adults: Case Series and Review of the Literature

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Necrotizing enterocolitis in adults is a rare disease and, in the past, has been associated with nearly uniform mortality. In recent years, necrotizing enterocolitis, now termed *neutropenic enterocolitis*, in adults has become more prevalent as a complication of aggressive systemic chemotherapy. In this report, we discuss two cases of neutropenic enterocolitis secondary to the administration of systemic chemotherapy in adult cancer patients: one with lung carcinoma, the other with leukemia. Both patients were successfully treated with early surgical intervention for resection of all necrotizing enteric lesions, and subsequent aggressive critical care support. Our experience suggests that early surgical intervention in adult patients with intestinal necrosis due to chemotherapy is essential to avoid mortality from this condition. Given the widespread, aggressive use of systemic chemotherapy in the neoadjuvant setting, patients at risk for this potentially lethal complication of neutropenic enterocolitis are increasingly common.

KEY WORDS: neutropenic enterocolitis; necrotizing enterocolitis; chemotherapy; intestinal complication.

Necrotizing enterocolitis (NEC) is common in the pediatric age group, but is rare in adults (1). In 1962, Amromin and Salomon reported NEC in adults, describing 69 patients with leukemia or lymphoma with necrotizing enteric lesions identified at autopsy over a 5-year period, 1956–1961 (2). Characteristically, these patients developed the necrotizing enteric lesions during or immediately after receiving chemotherapy and were apparently having an excellent therapeutic response. Common clinical features included leukopenia (secondary to chemotherapy or neoplastic marrow infiltration), gastrointestinal mucosal ulcerations with necrotic foci, and histologic evidence of mucosal and submucosal intestinal invasion by enteric organisms. The clinical course was that of hemodynamic collapse and the findings of intestinal necrosis at autopsy. Operation was performed in only 4 of these 69 patients, and no patient survived after the development of necrotizing enterocolitis.

Subsequent to this initial report, an additional 69 adult cases of NEC associated with malignancy and the administration of systemic chemotherapy were reported (3–10). The majority of these patients were treated medically, without surgical intervention, and almost all died.

In this report, we present two cases of adult patients who developed necrotizing enterocolitis after chemotherapy and were treated successfully by rapid surgical intervention and subsequent aggressive critical care management.

CASE REPORTS

Case 1. A 76-year-old black male underwent a right lower lobectomy for presumed squamous cell carcinoma of the lung. Final pathology revealed a small-cell carcinoma (Stage 1). Two weeks after his third chemotherapy session (etoposide, following cisplatin induction), the patient presented with acute abdominal pain. Abdominal examination revealed distension and diffuse tenderness. White blood cell count was 1000 cells/μL. Admission chest and abdominal x-rays documented pneumoperitoneum and dilated small and large intestine (Figure 1).

Manuscript received July 16, 2004; accepted July 26, 2004.
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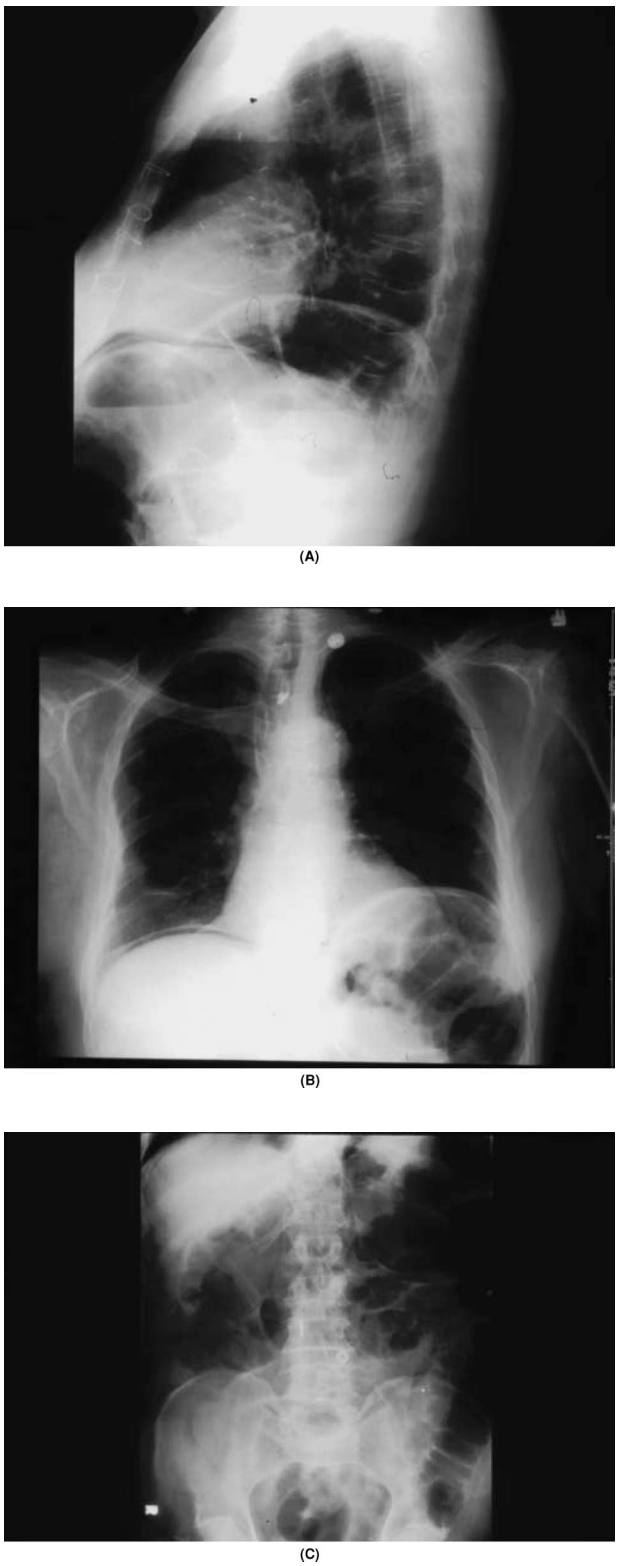


Fig 1. Anteroposterior (A) and lateral (B) chest radiographs and supine abdominal radiograph (C) from Case 1, documenting pneumoperitoneum and markedly dilated bowel with air/fluid levels.

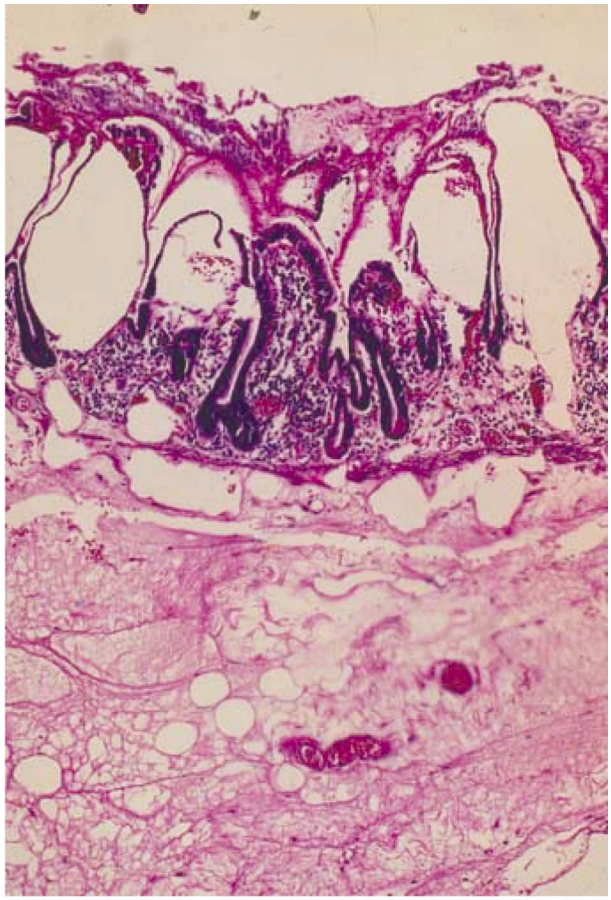
Emergent laparotomy revealed segmental jejunal, ileal, transverse, and right colon severe necrotizing enterocolitis, with emphysema of the bowel wall and adjacent mesentery. No macroperforations were identified. Extensive distal enterectomy and extended right hemicolectomy were performed, with creation of an end-jejunostomy and distal transverse colon mucous fistula. The remaining viable small bowel measured approximately 165 cm. Pathologic findings of the resected intestine revealed marked ischemic changes, with submucosal and mucosal edema, hemorrhage, epithelial erosions, and focal necrosis of the muscularis propria (Fig. 2). The jejunal and transverse colon margins of resection were confirmed to be viable on histologic examination.

The postoperative course was complicated by severe adult respiratory distress syndrome (ARDS), profound neutropenia requiring administration of granulocyte-colony stimulating factor, renal and hepatic insufficiency, and short-bowel syndrome. The patient remained hospitalized for 6 months for management of these life-threatening complications and spent an additional 4 months in a chronic care facility. He had a slow weight increase over the ensuing months with aggressive enteral nutritional support and his bone marrow function slowly recovered. He underwent closure of his jejunostomy with jejuno–descending colon anastomosis approximately 14 months after his initial surgical intervention for necrotizing enterocolitis and recovered uneventfully. He is tolerating a regular diet and has approximately three to five bowel movements daily. He has no evidence of malignant disease.

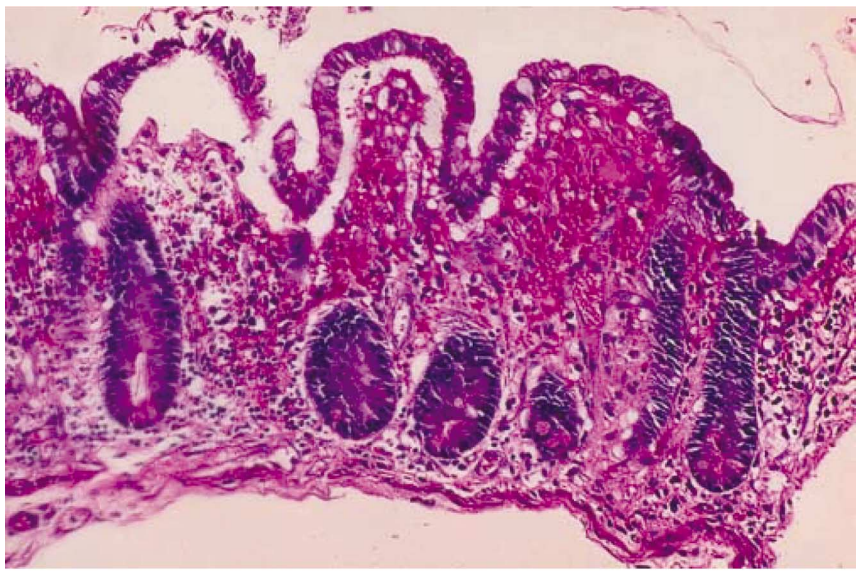
Case 2. A 46-year-old black male with erythroleukemia being treated with daunorubicin and Ara-C complained of abdominal pain, nausea, and vomiting suddenly after the last chemotherapy session. He developed acute severe septic shock and required emergent intubation and mechanical ventilation for acute respiratory failure and pressor support for hemodynamic instability. Abdominal physical examination revealed diffuse abdominal distention and tenderness. Abdominal x-rays confirmed pneumatosis and a computed tomography (CT) scan of the abdomen and pelvis (Figure 3) showed evidence of bowel induration, edema, and pneumatosis but no pneumoperitoneum. Laboratory evaluation revealed a white blood cell count of 2900 cells/μL, 26,000 platelets/μL, and a hematocrit of 20%. Emergent laparotomy for an acute abdomen revealed necrotizing enterocolitis which was diffuse but restricted to the small bowel. No macroperforations were identified. Necrotic distal jejunum (30 cm) was resected. Multiple areas of patchy ischemia were not resected at the initial laparotomy since the patient was hemodynamically unstable intraoperatively, despite the aggressive administration of fluids and pressors. Systemic broad-spectrum antibiotics and antifungal therapy were administered, and blood cultures were positive for *Candida* species.

A second-look laparotomy was performed the following day. Patchy areas of ischemia on the antimesenteric border of the midjejunum had progressed, necessitating additional jejunal resection, leaving approximately 120 cm of proximal jejunum and 110 cm of distal ileum, and a primary jejunoileal anastomosis was performed. A total of 230 cm of viable small bowel remained. Pathologic findings of the resected intestine showed areas of marked edema, acute and chronic inflammation, and focal necrosis. The surgical margins of the resected small intestine appeared viable.

Postoperatively the patient was critically ill in severe septic shock. He developed severe ARDS, cardiac failure, pancytopenia, coagulopathy, and acute tubular necrosis requiring

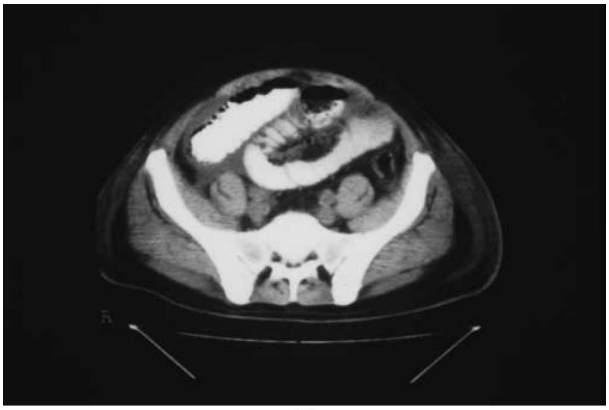


(A)

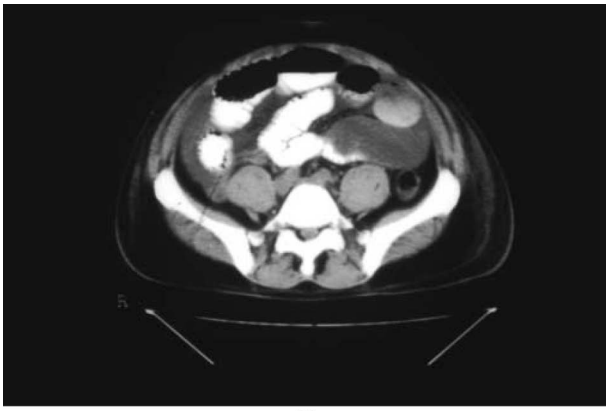


(B)

Fig 2. Histology of the resected intestine: Case 1. Jejunum and ileum with marked ischemic changes, including submucosal and mucosal edema and hemorrhage (A), and epithelial erosions, villous sloughing, and focal necrosis of the epithelium and muscularis propria (B).



(A)



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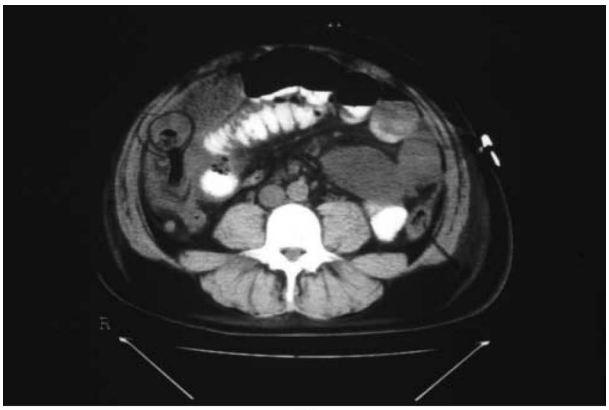

(C)

Fig 3. CT scan of the abdomen confirming intestinal pneumatosis (A and B), and bowel wall induration and edema (C): Case 2.

hemodialysis. He required mechanical ventilation for 2 weeks and continued vasopressor infusion for 8 days for treatment of septic shock. The patient improved steadily over the next month, and upon his discharge to a rehabilitation facility, laboratory studies were improved, with a white blood cell count of 9300 cells/μL, hematocrit of 24.2%, and platelet count of 116,000 platelets/μL. His renal function also recovered, allowing discontinuation of hemodialysis. The patient was tolerating a regular oral diet in small quantities, receiving supplemental enteral nutrition via the transgastric jejunostomy and having normal bowel movements.

DISCUSSION

Neutropenic enterocolitis has been referred to as typhlitis, ileocecal syndrome, and, more commonly, necrotizing enterocolitis. This potentially lethal complication of anticancer therapy has been reported to occur with a variety of solid tissue (5, 11–15) and hematologic tumors before (16–19) and after treatment with a variety of chemotherapeutic regimens (20, 21).

The toxicity of systemic chemotherapeutic agents is exerted on rapidly dividing tissues, including the gastrointestinal mucosa. Direct cytotoxicity to bowel mucosa from antitumor drugs, followed by microbial invasion of the injured mucosa in the face of immunosuppression and ileus, may lead to the development of necrotizing enterocolitis (3, 4, 20). The administration of broad-spectrum antibiotics may also contribute to the development of NEC by alteration of the endogenous microflora of the gut (4, 22).

Pestalozzi and colleagues (5) reported two cases of taxol/doxorubicin-associated typhlitis, and the authors concluded that the typhlitis was the result of both severe neutropenia and direct toxicity to the intestinal mucosa from the antitumor agents. Amromin and Solomon (2) reported a 17% incidence of "necrotizing enteric lesions" in autopsies of leukemia and lymphoma patients who died between 1956 and 1961. Prolla and Kirsner (8) reported a 5% incidence of "neutropenic colitis" during this same period. Hersh *et al.* (23) found a 1% incidence of enterocolitis in leukemia patients from 1954 to 1963. In 1975, Moir and Bale (24) reported on 50 consecutive autopsies of patients with childhood leukemia, and colitis was present in 46% of those cases and was probably a major cause of death in 38% of the patients.

In 1979 Varki *et al.* (7) reported the first successful treatment for typhlitis in a 48-year-old female with acute lymphoblastic leukemia by early surgical intervention. This patient developed fever and right lower quadrant abdominal tenderness 10 days after induction chemotherapy. The patient was started on broad-spectrum antibiotics but, 2 hr later, developed point-tenderness in the right iliac fossa associated with tachycardia, tachypnea, and a metabolic acidosis. Laparotomy revealed gross evidence of cecal ischemia, and a right hemicolectomy and ileocolic anastamosis were performed. Pathologic examination revealed transmural necrosis of the cecal wall, with dense growth of gram-positive cocci. The patient recovered without sequelae and remained in remission.

Prior to this report by Varki *et al*. (7), there were only four previous surgical interventions reported for acute enterocolitis associated with malignancies, and all patients died. Varki and colleagues state, "The survival of our patient could be attributed to early clinical diagnosis and surgical intervention. The absence of bacteria from the peritoneal cavity in the presence of clinical signs of peritoneal irritation suggested that bacterial invasion was imminent, but was averted by immediate removal of the necrotic cecum."

Since that first successful surgical treatment of necrotizing enterocolitis, there have been several series and reviews supporting operative (25–27) and nonoperative (28–31) management of these patients. Review of the literature, however, reveals that the predominant view among surgeons and nonsurgeons is that treatment must be individualized on a case-by-case basis (15, 20, 32–35). The two cases presented herein support the necessity of early clinical diagnosis and aggressive surgical intervention for optimal management and improved survival of necrotizing enterocolitis. In cases of nonnecrotizing neutropenic colitis, however, nonoperative management is more likely to be successful, and those are likely the cases comprising the reports of successful nonoperative management of patients for whom no pathology or autopsy is reported. In this regard, Kouroussis *et al*. (29) report a series of patients for whom nonoperative treatment of neutropenic enterocolitis complicating taxane-based chemotherapy was successful, but because there was no pathologic specimen for any patient, and because all patients recovered, it is unlikely that there was any necrotic element to their enterocolitis.

The clinical diagnosis of necrotizing enterocolitis may be exceedingly difficult to establish in a neutropenic host. The onset of infection in patients with neutropenia differs from that in patients with normal polymorphonuclear leukocyte counts, and an acute surgical abdomen is particularly difficult to identify due to the lack of a significant intraperitoneal inflammatory response. CT findings such as pneumatosis support the diagnosis but have been shown not to be specific for any process requiring operation (36). The manifestation of neutropenic enterocolitis can rapidly progress from mild abdominal pain and low-grade fever to life-threatening septic shock. For this reason, a low threshold for operative management might well be considered more conservative than nonoperative observation.

With the increasing use of new toxic drugs and multiple drug chemotherapeutic techniques, it becomes increasingly important to be alert to life-threatening complications of these therapies. Clinicians should be acutely aware of the association of necrotizing enterocolitis and chemotherapy, since early surgical intervention can enhance the chances of successful treatment.

REFERENCES

1. Sherman NJ, Wooley MM: The ileocecal syndrome in acute childhood leukemia. Arch Surg 107:39–42, 1973
2. Amromin GD, Solomon RD: Necrotizing enteropathy. A complication of treated leukemia or lymphoma patients. JAMA 182(1):23–29, 1962
3. Kies MS, Luedke DW, Boyd JF, McCue MJ: Neutropenic enterocolitis. Two case reports of long-term survival following surgery. Cancer 43:730–734, 1979
4. Alt B, Glass NR, Sollinger H. Neutropenic enterocolitis in adults: Review of the literature and assessment of surgical intervention. Am Journal Surg 149:405–408, 1985
5. Pestalozzi BC, Sotos GA, Choyke PL, Fisherman JS, Cowan KH, O'Shaughnessy JA: Typhlitis resulting from treatment with taxol and doxorubicin in patients with metastatic breast cancer. Cancer 71:1797–1800, 1993
6. Kingry RL, Holeson RW, Muir RW: Cecal necrosis and perforation with systemic chemotherapy. Am Surg 39:129–133, 1973
7. Varki AP, Armitage JO, Feagler JR: Typhlitis in acute leukemia. Successful treatment by early surgical intervention. Cancer 43:695–697, 1979
8. Prolla JC, Kirsner JB: The gastrointestinal lesions and complications of the leukemias. Ann Intern Med 61:1084–1103, 1964
9. Steinberg D, Gold J, Brodin A: Necrotizing enterocolitis in leukemia. Arch Intern Med 131:538–544, 1973
10. Del Fava RL, Cronin TG: Typhlitis complicating leukemia in an adult: Barium enema findings. Am J Roent 129:347–348, 1977
11. Kronawitter U, Kemeny NE, Blumgart L: Neutropenic enterocolitis in a patient with colorectal carcinoma: Unusual course after treatment with 5-Fluorouricil and Leucovorin—A case report. Cancer 80(4):656–660, 1997
12. Hayes D, Leonardo JM: Neutropenic enterocolitis in a woman treated with 5-Fluorouricil and Leucovorin for colon carcinoma. NC Med J 63(3):132–134, 2002
13. Clemons M, Valle J, Harris M, *et al*.: *Citrobacter freundii* and fatal neutropenic enterocolitis following adjuvant chemotherapy or breast cancer. Ann Oncol 8:405, 1997
14. Stein M, Zalik M, Drumea K, *et al*.: Fatal neutropenic colitis complicating successful chemotherapy for small cell lung cancer: A case report. Isr J Med Sci 31:194–196, 1995
15. Avigan D, Richardson P, Elias A, *et al*.: Neutropenic enterocolitis as a complication of high dose chemotherapy with stem cell rescue in patients with solid tumors: A case series and review of the literature. Cancer 83(3):409–414, 1998
16. Quigley MM, Bethel K, Nowacki, *et al*.: Neutropenic enterocolitis: A rare presenting complication of acute leukemia. Am J Hematol 66:213–219, 2001
17. Ahsan N, Sun CC, Di John D: Acute ileotyphlitis as presenting manifestation of acute myelogenous leukemia. Am J Clin Pathol 89:407–409, 1988
18. Kaste SC, Flynn PM, Furman WL: Acute lymphoblastic leukemia presenting with typhlitis. Med Pediatr Oncol 28:209–212, 1997
19. Paulino AF. Kenney, Forman EN, Medeiros LJ: Typhlitis is a patient with acute lymphoblastic leukemia prior to the administration of chemotherapy. Am J Pediatr Hematol 16:348–351, 1994

20. Bavaro MF: Neutropenic enterocolitis. Curr Gastroent Rep 4:297–301, 2002
21. Ferrazzi E, Toso S, Zanotti M, Guiliano G: Typhlitis (neutropenic enterocolitis) after a single dose of vinorelbine. Cancer Chemother Pharmacol 47:277–279, 2001
22. Deitch EA: Role of bacterial translocation in necrotizing enterocolitis. Acta Paediatr Suppl 396:33–32, 1994
23. Hersh EM, Bodey GP, Nies BA, Freireich EJ: Causes of death in acute leukemia. JAMA 193(2):99–103, 1965
24. Moir DM, Bale PM: Necropsy findings in childhood leukaemia, emphasizing neutropenic enterocolitis and cerebral calcification. Pathology 8:247–258, 1976
25. Moir CR, Scudamore CH, Benny WB: Typhlitis: Selective surgical management. Am J Surg 151:563–566, 1986
26. Kunkle JM, Rosenthal D: Management of the ileocecal syndrome. Dis Colon Rectum 29(3):196–199, 1986
27. Koea AB, Shaw JHF: Surgical management of neutropenic enterocolitis. Br J Surg 76:821–824, 1989
28. Gomez L, Martino R, Rolston KV: Neutropenic enterocolitis: Spectrum of the disease and comparison of definite and possible cases. Clin Infect Dis 27:695–699, 1998
29. Kouroussis C, Samonis G, Androulakis N, *et al*.: Successful conservative treatment of neutropenic enterocolitis complicating taxane-based chemotherapy: A report of five cases. Am J Clin Oncol 23(3):309–313, 2000
30. Song HK, Kreisel D, Canter R, *et al*.: Changing presentation and management of neutropenic enterocolitis. Arch Surg 133:979–982, 1998
31. O'Connor K, Dijkstra B, Kelly L, *et al*.: Successful conservative management of neutropenic enterocolitis: A report of two cases and review of the literature. ANZ J Surg 73(6):463–465, 2003
32. Wade DS, Nava HR, Douglass HO: Neutropenic enterocolitis. Cancer 69(1):17–23, 1993
33. Büyükaşik Y, Özcebe OĪ, Haznedaroğlu ĪC: Neutropenic enterocolitis in adult leukemias. Int J Hematology 66:47–55, 1997
34. Abbasoglu O, Cakmakei M: Neutropoenic enterocolitis in patients without leukemia. Surgery 113:113–116, 1993
35. Kulaylat M, Doerr R, Ambrus J: A case presentation and review of neutropenic enterocolotis. J Med 28:1–19, 1997
36. Kernagis LY, Levine MS, Jacobs JE: Pneumotosis intestinalis: Correlation of CT findings with viability of the bowel. Am J Roent 180:733–736, 2003