Journal of Cancer Research and Practice

journal homepage: www.ejcrp.org

Case Report

Neutropenic Necrotizing Enterocolitis: A Life-threatening Complication after Aggressive Chemotherapy for Leukemia

Chih-Ching Chin[1], Junping Shiau[2,3]*, Chi-Wen Lou[2], Mei-Ren Pan[4], Fang-Ming Chen[2], Ming-Feng Hou[2]

[1]Department of Pathology, E-DA Hospital, Taiwan
[2]Division of Breast Surgery and Oncology, Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung Medical University, Taiwan
[3]Department of Surgery, Kaohsiung Municipal Siaogang Hospital, Taiwan
[4]Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

Abstract

Neutropenic enterocolitis can occur after aggressive chemotherapy with a wide range of severity from mild to life threatening. Neutropenic necrotizing enterocolitis (NNE) is a catastrophic condition that has rarely been discussed in the literature. Here, we present the case of a 27-year-old previously healthy female who was diagnosed with acute myeloid leukemia and underwent a first course of chemotherapy. Severe neutropenia, high fever, and abdominal pain were noted 5 days later. After medical treatment had failed, emergent laparotomy was performed. Several patches of transmural necrosis were seen at the jejunum, and resection with primary anastomosis was done. However, more newly formed necrotic patches were found over the small bowel during second-look surgery 2 days later. This report emphasizes that NNE is an irreversible ongoing process refractory to medical or surgical treatments, and physicians should be cautious of this syndrome when using aggressive chemotherapy.

Keywords: Leukemia, necrotizing enterocolitis, neutropenic enterocolitis

Introduction

Neutropenic enterocolitis (NE) was first described in the 1970s after treatment of childhood leukemia,[1] and it is now recognized to be a severe gastrointestinal complication in patients receiving aggressive chemotherapy. The frequency of NE is 1%–17% in patients with hematologic malignancy, and the mortality rate is about 22.3%–50%.[2,3] NE has several synonyms, including typhlitis, ileocecal syndrome, and neutropenic necrotizing enterocolitis (NNE).[1] It usually occurs in pediatric patients and rarely in adults. The typical manifestation of NE is characterized by a triad of abdominal pain, persistent fever, and diarrhea containing blood.[4] For treatment, many reports have

Submitted: 03-Jun-2021 **Revised:** 22-Jul-2021
Accepted: 23-Jul-2021 **Published:** 07-Mar-2022

Access this article online

Quick Response Code:

Website: www.ejcrp.org

DOI: 10.4103/JCRP.JCRP_19_21

Address for correspondence: Dr. Junping Shiau, Division of Breast Surgery and Oncology, Kaohsiung Medical University Chung-Ho Memorial Hospital, No. 100, Ziyou 1st Road, Sanmin District, Kaohsiung City 807, Taiwan.
E-mail: gp5066@gmail.com

How to cite this article: Chin CC, Shiau J, Lou CW, Pan MR, Chen FM, Hou MF. Neutropenic necrotizing enterocolitis: A life-threatening complication after aggressive chemotherapy for leukemia. J Cancer Res Pract 2022;9:37-40.

suggested conservative medical care including adequate hydration, bowel rest, broad-spectrum antibiotics, and granulocyte-colony-stimulating factor (G-CSF) support, while surgery is rarely needed unless peritonitis or perforation occurs.[5,6] Herein, we report a case of severe NNE with ongoing transmural necrosis of the small bowel. This case serves to remind physicians to be aware of this life-threatening complication after chemotherapy.

Case Report

A previously healthy 27-year-old Taiwanese female without any abdominal surgery history initially presented to our emergency department due to persistent headache, dizziness, tinnitus, and dyspnea for 2 weeks. She denied fever, chills, abdominal pain, or changes in bowel habits. Laboratory data showed white blood cell count = 4080/μL (segment = 8%, lymphocyte = 82%, and monocyte = 30%), hemoglobin = 5.3 g/dL, hematocrit = 15.9%, and platelet count = 59000/μL. Under the suspicious of leukemia, a bone marrow biopsy was arranged after blood transfusion, which confirmed acute myeloid leukemia with monocytic differentiation. Microscopically, there was diffuse infiltration of myeloblasts and promonocytes accounting for about 20%–30% of mononuclear cells, and the CD34-positive and CD68-positive cells were around 15% and 55%, respectively.

She received a first cycle of induction chemotherapy with cytarabine 150 mg/m^2 on day 1–7 and daunorubicin 60 mg/m^2 on day 1–3 in a hematology ward. On day 8 after completing chemotherapy, she complained of persistent abdominal cramping pain and watery diarrhea. Her body temperature was 38.8°C, and laboratory data showed absolute neutrophil count (ANC) =600/μL, platelet count = 40 × 10^3/μL, and hemoglobin = 10.0 g/dL. A contrast small bowel roentgenogram showed distended bowel loops without mechanical obstruction [Figure 1a]. Emergent abdominal computed tomography showed small bowel distension and bowel wall edema but no sign of pneumatosis [Figure 2]. After being refractory to 2 days of conservative treatment, a general surgeon was consulted for emergent laparotomy due to concerns of bowel perforation. During the operation, several transmural ischemic patches were noted in the jejunum, but no macroscopic bowel perforation or dirty ascites were found. Grossly, the colon and the other parts of the small bowel were intact [Figure 3]. Primary resection of the ischemic segment with primary anastomosis was performed smoothly.

After the operation, intravenous broad-spectrum antibiotics and antifungal medication were administered before blood cultures revealed *Klebsiella pneumoniae* infection. Partial parenteral nutrition and crystalloid fluid were also prescribed. However, diffuse abdominal pain persisted, followed by bloody diarrhea, abdominal distension, and high fever. Severe neutropenia persisted despite the continuous use of G-CSF. Second-look laparotomy was performed 3 days later after the presentation of peritoneal signs. More newly formed noncontinuous transmural ischemic patches on the jejunum and proximal ileum were found [Figure 4], necessitating further resection and leaving approximately 130 cm of the small bowel

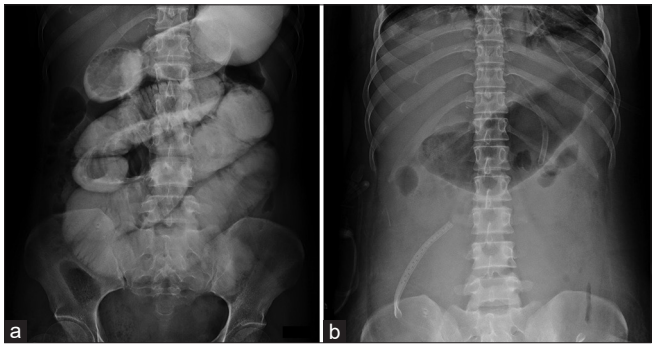

Figure 1: Contrast small bowel series before the first operation showed distended bowel loops (a). After the second operation, a physical examination revealed no bowel movements, and an abdominal roentgenogram showed no bowel gas (b)

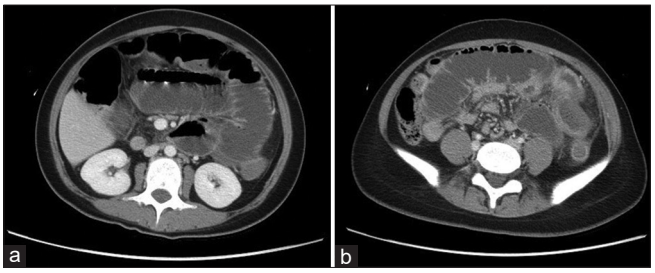

Figure 2: (a and b) Computed tomography of the abdomen showed distended small bowel loops and air-fluid content. The bowel wall showed edematous change but no ischemic signs such as pneumatosis

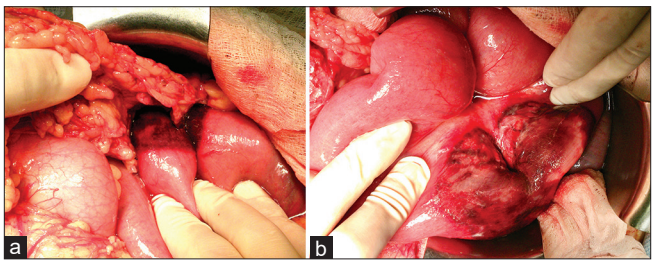

Figure 3: (a and b) In the first surgery, several transmural ischemic patches were noted in the jejunum, and there was no macroscopic bowel perforation or dirty ascites

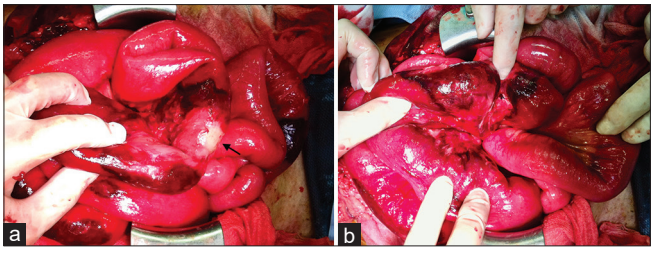

Figure 4: (a and b) In the second surgery, more noncontinuous transmural ischemic patches were found on the jejunum and proximal ileum. Several areas showed ischemic necrosis (arrow)

after primary anastomosis. Despite intensive care, she had neutropenic fever (ANC = 400/ml and temperature = 38.5°C) despite high-dose G-CSF treatment. A physical examination after surgery revealed no bowel sounds, and an abdominal roentgenogram showed a silent bowel without gas [Figure 1b]. Pancytopenia and severe septic shock aggravated with acute respiratory distress syndrome occurred, and she died 5 days after the second surgery.

A pathologic examination of the first surgery showed diffuse hemorrhagic omentum. The affected small intestine had eroded mucosa and transmural hemorrhage with necrosis, and bilateral margins showed regular mucosal folds with mild congestion. A pathologic examination of the second surgery showed that the ischemic intestine involved both the jejunum and proximal ileum, measuring around 100 cm in length. The serosal surface was edematous, and the color was tan brown. A pseudomembrane could be seen in the center of the ischemic segment, characterized by elevated yellow-white nodules or plaques on the serosal surfaces. The ischemic area involved the full thickness of the bowel wall and led to gangrene.

Discussion

NNE has been reported to occur in up to 5.3% of cancer patients with neutropenic episodes, especially 7–10 days after completing chemotherapy,[6] and the incidence is higher with more aggressive chemotherapy. NNE may not only occur when treating hematological neoplasms but also when treating solid tumors with taxane-based therapies.[4] In addition, NE has also been associated with gemcitabine, cytosine arabinoside, vincristine, doxorubicin, cyclophosphamide, 5-fluorouracil, leucovorin, and daunorubicin.[7]

Clinical manifestations of NE vary widely, and the most common sites of NE are the cecum, colon, and terminal ileum.[8] In the early stage, fever, abdominal pain, and impaired bowel function (either constipation or diarrhea) may mimic the common chemotherapy-associated bowel syndrome.[7] In severe cases, nausea, vomiting, abdominal cramping, watery diarrhea, and septicemia may occur, and lower gastrointestinal bleeding can highly suggest the diagnosis of NNE.[9]

The mechanism of NE is not well understood, and many hypotheses have been proposed such as disruption of gastrointestinal mucosa integrity, increased leukemic infiltration in the bowel wall, anemia-induced bowel wall ischemia, hemorrhagic necrosis due to thrombocytopenia, paralytic ileus caused by drugs, and bacterial translocation.[3,5,9]

Ultrasonography and computed tomography are the most commonly used evaluation tools, however, a definite diagnosis is still difficult due to a lack of specific indicators. Images may only disclose a distended ileus, ascites, fluid-filled bowel, or thickened bowel wall. Air bubbles inside the bowel wall (pneumatosis) is the most commonly used specific sign indicating bowel ischemia and necrosis, however, it is rarely seen in NE or NNE.[10] In our case, a severely distended small bowel was the only sign on computed tomography, and this made a definite diagnosis difficult.

Medical supportive care is the cornerstone in treating NE, while surgery is rarely needed and reserved for those developing an acute syndrome of ischemia or perforation. Previous reports have shown that definitive resection of ischemic bowel segments can reduce overall mortality, however, early identification is difficult due to the ongoing process of NNE.[5] In our case with NNE, the transmural necrosis of bowel segments was found to be more extensive in the second operation, which was not apparent in the first operation, and surgical resection was of limited help in this scenario. When using aggressive chemotherapy, carefully monitoring the dose and the early prevention of neutropenia are the most important steps to prevent life-threatening NE or NNE.

Conclusion

NE is not an uncommon complication after aggressive chemotherapy, and patients usually recover after conservative treatment. However, NNE seemed to be an irreversible ongoing process refractory to medical treatment or surgical intervention in our case. Physicians should be aware of this syndrome when using aggressive chemotherapy.

Informed consent

The informed consent process is one of the central components of the ethical conduct of research with human subjects. The patient's family members were informed that some of the medical records and pictures may be used in medical articles for publication. They all agreed to the use of the medical records.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Wagner ML, Rosenberg HS, Fernbach DJ, Singleton EB. Typhlitis: A complication of leukemia in childhood. Am J Roentgenol Radium Ther Nucl Med 1970;109:341-50.
2. Gorschlüter M, Glasmacher A, Hahn C, Leutner C, Marklein G, Remig J, *et al.* Severe abdominal infections in neutropenic patients. Cancer Invest 2001;19:669-77.
3. Gomez L, Martino R, Rolston KV. Neutropenic enterocolitis: Spectrum of the disease and comparison of definite and possible cases. Clin Infect Dis 1998;27:695-9.
4. O'Connor K, Dijkstra B, Kelly L, McDermott EW, Hill AD, O'Higgins N. Successful conservative management of neutropenic enterocolitis: A report of two cases and review of the literature. ANZ J Surg 2003;73:463-5.
5. Wade DS, Nava HR, Douglass HO Jr. Neutropenic enterocolitis. Clinical diagnosis and treatment. Cancer 1992;69:17-23.
6. Gorschlüter M, Mey U, Strehl J, Ziske C, Schepke M, Schmidt-Wolf IG, *et al.* Neutropenic enterocolitis in adults: Systematic analysis of evidence quality. Eur J Haematol 2005;75:1-13.

7. Vehreschild MJ, Meissner AM, Cornely OA, Maschmeyer G, Neumann S, von Lilienfeld-Toal M, *et al.* Clinically defined chemotherapy-associated bowel syndrome predicts severe complications and death in cancer patients. Haematologica 2011;96:1855-60.
8. Wach M, Dmoszynska A, Wasik-Szczepanek E, Pozarowski A, Drop A, Szczepanek D. Neutropenic enterocolitis: A serious complication during the treatment of acute leukemias. Ann Hematol 2004;83:522-6.
9. Ebert EC, Hagspiel KD. Gastrointestinal manifestations of leukemia. J Gastroenterol Hepatol 2012;27:458-63.
10. Cartoni C, Dragoni F, Micozzi A, Pescarmona E, Mecarocci S, Chirletti P, *et al.* Neutropenic enterocolitis in patients with acute leukemia: Prognostic significance of bowel wall thickening detected by ultrasonography. J Clin Oncol 2001;19:756-61.