Successful medical management of neutropenic enterocolitis (typhlitis) in a child with acute lymphoblastic leukemia

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We report a case of acute lymphoblastic leukemia that was complicated by neutropenic enterocolitis (typhlitis) during the initial period of remission-induction chemotherapy. The patient's clinical symptoms resolved after aggressive treatment with intravenous fluids and electrolytes, nasogastric decompression, bowel rest, total parenteral nutrition, broad-spectrum antibiotics, and granulocyte colony-stimulating factor. Netropenic enterocolitis should always be considered in neutropenic leukemic children with the triad of fever, vomiting, and abdominal pain. Gastrointestinal hemorrhage may also accompany the symptoms described above. Plain roentgenogram, ultrasonography and computed tomography of the abdomen are helpful for making the diagnosis of this clinical condition. Early recognition and proper medical management of neutropenic enterocolitis may prevent the need for surgical intervention, and/or be life-saving.

Key words: acute lymphoblastic leukemia, neutropenic enterocolitis, medical management.

Neutropenic enterocolitis (NE), formerly known as typhlitis, is a gastrointestinal condition that occurs in immunodeficient patients who are severely neutropenic and is most often seen in leukemic children during remission-induction chemotherapy[1]. It is rarely encountered as the presenting symptom of acute leukemia[2]. The reported incidence of typhlitis has depended on whether clinical signs or autopsy findings were used as criteria for diagnosis. In a autopsy case review of 170 children who died of acute leukemia, the incidence of NE was found to be 24%[3].

The most frequent symptoms include fever, abdominal pain, diarrhea, and lower gastrointestinal bleeding. Plain roentgenogram, ultrasonography and computed tomography of the abdomen are helpful for making the diagnosis of the disease. Neutropenic enterocolitis is also being reported with increasing frequency in association with other disease states that may produce profound neutropenia, such as lymphoma, aplastic anemia, cyclic neutropenia, and certain solid tumors[4,5]. It is also becoming more common after organ transplantation.

When Wagner et al.[6] first described NE in the 1970s, it was considered a terminal disease. In recent years, the incidence of this condition has been rising due to more aggressive chemotherapy protocols[7]. However, survival rates have also been increasing because of more rapid diagnosis, and prompt medical and surgical therapy[8].

In this report, we describe a 10-year-old girl with acute lymphoblastic leukemia (ALL) who developed typhlitis during remission-induction chemotherapy with daunorubicin and vincristine. Timely diagnosis and a carefully planned treatment strategy prevented risky surgical intervention, and possible death.

Case Report

A 10-year-old girl was admitted to hospital for evaluation of anemia and thrombocytopenia. The child had been healthy until two weeks before admission, when she started to complain of arthralgia. Pallor was the only abnormality on physical examination. Laboratory testing revealed hemoglobin level 7.4 g/dl, white blood cell (WBC) count $4.4x10^9$/L, and platelet count

$36x10^9$/L. Examinations of a peripheral blood smear and a bone marrow aspirate showed 95% blast cells that were characteristic of ALL, with L1-type morphology. All the biochemical test results were within the normal range, except for elevated lactate dhydrogenase (1000 IU/ml).

The patient was diagnosed with ALL, and chemotherapy including prednisolone, L-asparaginase, vincristine, and daunorubicin was started. Three days after she received the second doses of vincristine and daunorubicin, she developed a fever of 38.3°C and began to complain of severe abdominal pain and nausea. Physical examination of the abdomen revealed tenderness and guarding, especially in the right lower quadrant. At this stage, the patient's WBC count was $0.4x10^9$/L and absolute neutrophil count was $02x10^9$/L. Stool testing revealed no Clostridium difficile toxin A, and serology for cytomegalovirus IgM was negative.

The tentative diagnoses of sepsis and NE (typhlitis) were considered. A plain radiograph of the abdomen showed gaseous dilatation of the ascending and transverse colon measuring 6.5 cm in diameter (Fig. 1). Attempts to visualize the area with abdominal ultrasonography failed due to the excessive amount of abdominal gas that was present. Computed abdominal tomography demonstrated dilatation of the cecum and the ascending and transverse colon, as well as air-fluid levels, and thickening of the mucosa in the cecum. The measured wall thickness of the cecum was 8 mm (normal<4 mm) (Fig. 2). The patient was transferred to the intensive care unit. There she was treated with nasogastric decompression, bowel rest, intravenous fluids, and total parenteral nutrition. After specimens for blood, urine, stool, and throat cultures were collected, she was started on ceftazidime, amikacin, metronidazole, and fluconazole. Granulocyte colony-stimulating factor (G-CSF) was added to combat the profound neutropenia. A dopamine infusion (2 μg/kg/min) was started in order to induce splanchnic vasodilatation, and red blood cell and platelet transfusions were administered as needed. The blood culture grew alpha-hemolytic streptococcus that was sensitive to the antibiotics already being given.

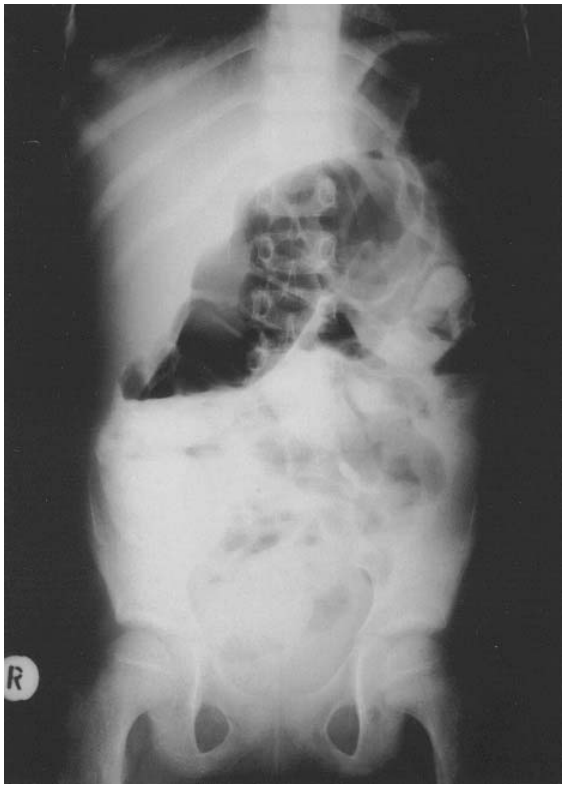

Fig. 1. Abdominal roentgenograph depicting colonic distention of the ascending and transverse colon measuring 6.5 cm in diameter.

After one week of intensive medical treatment, the patient's fever subsided, her abdominal pain disappeared, and her WBC count normalized. At this stage, she could tolerate oral feeding so total parenteral nutrition was gradually discontinued. Dopamine infusion and antibiotic therapy were stopped at the end of first and second weeks, respectively. She restarted remission-induction chemotherapy without further problems three weeks later. Repeated bone marrow aspiration

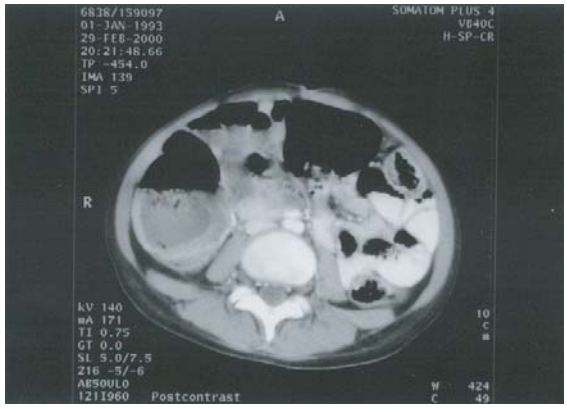

Fig. 2. Computed abdominal tomography demonstrating dilatation of the cecum and the ascending and transverse colon, as well as air-fluid levels, and thickening of the mucosa in the cecum.

revealed complete remission. She has not encountered any recurrent signs or symptoms of NE during 1.5 years on maintenance therapy.

Discussion

Pathologically, NE is characterized by inflammation and edema that may progress to ulceration, necrosis, and perforation of the bowel wall. Inflammatory changes are usually localized to the cecum, but may extend throughout the ascending colon, the appendix, and the terminal ileum. It is not clear why the cecum is the site predominantly affected, but high lymphoid content, decreased vascularity, and high distensibility may predispose this region to injury and infection[3].

The pathophysiology of NE seems to be multifactorial, involving direct toxic effects of chemotherapeutic drugs, decreased host immune defense mechanisms, and leukemic infiltration of the bowel wall[9]. We believe that altered bowel wall integrity secondary to vincristine and daunorubicin, in combination with neutropenia, may have promoted bacterial invasion of the colon in our patient.

The offending organisms in NE are Candida albicans, Pseudomonas aeruginosa, Staphylococcus aureus, and Clostridium spp. Our patient's blood culture grew alpha-hemolytic streptococcus. It was reported that this microorganism was detected in premortem blood cultures from individuals with ALL complicated by NE[3].

The care of patients with this condition must be planned on a case-by-case basis. Due to its multifactorial etiology and the variety of host-defense factors involved, NE presents with a range of mild to severe manifestations. Initially, non-surgical treatment with bowel rest, decompression, nutritional support, blood products, and broad-spectrum antibiotics is recommended. According to Shamberger et al.'s[1] criteria, persistent gastrointestinal bleeding, bowel perforation, and uncontrolled sepsis are indications for surgical intervention.

Our patient had neutropenia and the triad of NE including fever, nausea and abdominal pain. Abdominal tenderness, especially in the right lower quadrant, led to the clinical diagnosis of typhlitis, which was confirmed by abdominal imaging studies. We monitored our patient's clinical status closely by physical examination, biochemical and microbiologic testing, abdominal plain films and ultrasound. She responded well to medical therapy that included drugs for aerobic and anaerobic bacteria, antifungal agents, and supportive treatment with dopamine, blood products, and total parenteral nutrition. There have been no controlled studies regarding G-CSF treatment in patients with NE. It was reported that chemotherapy of breast cancer with epidoxorubicin and docetaxel might cause NE. When these drugs are combined with G-CSF, higher doses could be given to the patients safely[10]. We also used G-CSF for the treatment of neutropenia, which was one of the possible mechanisms underlying NE in our patient. The possible beneficial effect of G-CSF in NE needs to be evaluated.

This report is significant in that it describes a child with ALL and NE who was diagnosed in a timely manner and successfully treated with intense medical therapy. Awareness of the signs and symptoms of NE is key to achieving early and effective intervention in patients with this potentially life-threatening disorder.

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