Successful Surgical Management of Typhlitis in a Patient with Acute Myeloblastic Leukemia

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ABSTRACT

Typhlitis (neutropenic enterocolitis) is a potentially life-threatening complication associated with neutropenia and combination chemotherapy. The incidence of this disease is increasing in both patients with hematologic malignancies and solid tumors with the advent of more aggressive chemotherapy. Here, we describe a patient with acute myeloblastic leukemia in whom typhlitis developed during induction chemotherapy and managed successfully with both medical and surgical intervention during neutropenic period. Our experience reinforces prior reports that intense medical treatment, close observation and emergent surgical intervention has been shown to be life saving.

Key Words: Typhilitis, Neutropenic enterocolitis, AML, Surgical management.

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INTRODUCTION

Typhlitis, from the Greek word "typholon", meaning cecum, was first described by Wagner et al[1]. in 1970 as a necrotizing colitis, frequently localized to cecum, found primarily in leukemic children with terminal disease. The terms "neutropenic enterocolitis", "necrotizing enterocolitis" and "iliocecal syndrome" have been used synonymously by authors. Typhlitis is a potentially life-threatening complication associated with neutropenia and combination chemotherapy. Although it was first reported in patients with leukemia, it may also occur in patients with other advanced malignancies receiving combination chemotherapy for solid tumors[2,3], or bone marrow transplantation[3], and with Castleman's disease[4], aplastic anemia[5], immunosuppression after renal transplantation[6], drug induced-granulocytopenia[7,8], or AIDS[9]. The diagnosis is based on the symptom complex of fever, abdominal pain,

diarrhea, and neutropenia[1,2]. Early diagnosis and prompt initiation of therapy is critical because the disease progress rapidly and advanced stages are nearly always fatal. Optimal management of this condition has been controversial, with some series supporting conservative management whereas others advocate emergent surgical intervention[3].

Here, we describe a patient with acute myeloblastic leukemia (AML) in whom typhlitis developed during induction chemotherapy and was managed successfully with both medical and surgical intervention during neutropenic period.

CASE REPORT

A 22-year-old man was admitted to the hospital because of pancytopenia and diagnosed as AML. A few days before admission he experienced intermittent courses of epistaxis, gingival bleeding and melena.

On admission he had a fever of 39°C, and the pulse rate was 110/min. Physical examination revealed petechia on the extremities and the buccal mucosa, the tonsils were enlarged and erythematous. Submandibulary, supraclavicular and servical lymph nodes, 1 to 2 cm in diameter, were palpated. His liver and spleen were 1 and 3 cm below the costal margins, respectively.

Laboratory tests revealed a hemoglobin level of 7 g/dL, WBC of 230 x 10^9/L, and platelet count of 22 x 10^9/L. ESR was 34 mm/hr. Biochemical tests were within normal ranges except high LDH. Coagulation screening test were slightly prolonged. Examination of peripheral blood smear and bone marrow aspirate showed more than 90% blasts of AML-M4 morphology. Flow cytometric and cytochemical examinations confirmed the diagnosis of AML-M4.

After obtaining blood, urinary and throat cultures, amikacin and piperacillin were started empirically. At the third day of admission the patient was afebrile and he was given three doses of daunorubicin, and cytarabine was administered by continuous infusion for seven days. On the sixth day of chemotherapy, the white cell count declined to 0.5 x 10^9/L and remained below this for the subsequent days. At the 18th day the patient was afebrile and his cultures were negative. The antibiotics were stopped and trimethoprim + sulfamethoxazole was started prophylactically. On day 18, bone marrow aspiration was repeated and found to be hypocelluler without blastic infiltration. On day 21, he developed a fever of 39.5°C with chills and headache. His physical examination was unremarkable except mucositis, and repeated cultures were still negative. Amikacin and piperacilline were restarted. Three days later he was still febrile and vancomycin was added. He had diarrhea on the next day without any abdominal discomfort. No microorganisms were grown on blood and stool cultures. On the following days diarrhea persisted with nausea and vomiting. Amphotericine B was added to therapy empirically. On day 36, he developed abdominal pain with tenderness on deep palpation in both lower quadrants. Radiographs of the chest and abdomen were normal. The patient was still neutropenic (< 0.5 x 10^9/L). The day after he developed tachypnea, tachycardia and his abdominal pain worsened with rebound tenderness. Abdominal ultrasound demonstrated thickening of the bowel loops and minimal intraperitoneal fluid. Since no improvement was noted in the clinical status within the following 24 hours laparotomy was performed. Surgery revealed a perforated cecum and right hemicolectomy and iliotransversostomy were done. Transmural necrosis associated with perforation was histologically evident.

Postoperatively cefoxitin and metronidazole were started. He became afebrile, neutrophil counts returned to normal and repeated bone marrow aspiration revealed complete remission. The patient recovered completely and discharged with his own will two weeks after the operation. He was lost to follow-up.

DISCUSSION

Our patient had typical clinical presentation of typhlitis, which was confirmed by laparoscopic and histopathological findings. He required surgical intervention after the failure of medical management and had favorable outcome despite remaining profoundly neutropenic both in the operative and postoperative periods.

The reported incidence of typhlitis has varied and is dependent on whether clinical signs or pathologic findings at autopsy were used as criteria for diagnosis. In his initial series, Wagner et al.[1] identified the syndrome at autopsy in 10% of 191 patients who died of acute leukemia. Katz et al[10]. reported an incidence of 24% in a postmortem study of 170 patients with acute leukemia. Although the true incidence of typhlitis remains unknown, the incidence of neutropenic enterocolitis is increasing with the advent of more aggressive myelosuppressive chemotherapy.

The cause of this disease is not clear. However, it has been proposed that direct toxic effects of chemotherapy and/or leukemic infiltration of the colon disturb the intact mucosa of the colon. Bacterial invasion of the bowel wall occurs, facilitated by decreased defense due to neutropenia. This is followed by production of bacterial endotoxins with subsequent bacteremia, necrosis, and hemorrhage. Severe complications such as bowel wall penetration, perforation, and peritonitis can result if bone marrow recovery is delayed. If the disease is restricted to the cecum it is called “typhlitis”, however, the terminal ileum, appendix, and ascending colon can be effected[11]. It is unclear why the cecum is always affected in this cycle. The high lymphoid content, decreased vascularity, and increased distensibility of the cecum may predispose this area to injury and infection.

Our patient was given cytosine arabinoside with daunorubicine for induction chemotherapy and had a prolonged course of neutropenic fever despite the administration of broad-spectrum antibiotics. Most of the studies show no differences in chemotherapy between patients who develop intestinal complications and those who do not[10]. Furthermore, the presence of typhlitis in patients with aplastic anemia and in patients with newly diagnosed leukemia supports a multifactorial etiology[5,12]. However, cytosine arabinoside was the most commonly administered chemotherapeutic agent in patients with hematologic malignancies and neutropenic enterocolitis, and it has been shown to induce mucosal alterations in the gastrointestinal tract[13]. Additionally, in a recent report, Ibrahim et al.[14] reported an unexpectedly high incidence of typhlitis in their patients with metastatic breast cancer who were treated with docetaxel-based chemotherapy, which has a known dose-limiting toxic effects such as mucositis and neutropenia.

The management of neutropenic enterocolitis is controversial. Institution of broad-spectrum antibiotics as well as supportive care measures has resulted an increase in survival rates than with medical management alone[2,15]. However, most of the authors suggest that early surgical intervention may be preferable, particularly in patients with rapidly evolving or persistently septic clinical picture, bowel perforation or obstruction, uncontrolled rectal bleeding despite correction of clotting abnormalities[3,5,16].

Initially, mortality rate of this complication approached to 100%, and diagnosed only by autopsy[1,17]. With the advent of supportive care measures, broad-spectrum antibiotics, colony stimulating factors, diagnostic and surgical techniques the mortality rate decreased dramatically, but still as high as 6-55% in recent reports from different centers[2,18].

Since neutropenic enterocolitis may have a wide spectrum of severity, treatment should be individualized. Medical therapy that

includes fluid and electrolyte replacement, initiation of broad-spectrum antibiotics and colony stimulating factors, and correction of coagulation abnormalities should be given, initially. Abdominal ultrasonography and computed tomography can be used both in the diagnosis and follow up of the patient. The clinical status of the patient should be monitored closely and if medical therapy fails, surgical intervention should be operated immediatealy without hesitation of neutropenia and poor risk of the patient.

In this report we presented a case with typhlitis, successfully treated with surgical management. Our experience reinforces prior reports that intense medical treatment, close observation and emergent surgical intervention has been shown to be life saving.

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