

Neutropenic Enterocolitis in Breast Cancer Patient after Taxane Containing
Chemotherapy

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ABSTRACT

Neutropenic enterocolitis or typhlitis (from the Greek *typhlon*, meaning caecum) is defined as a necrotizing colitis with inflammation of the cecum and surrounding tissues. Although this condition occurs primarily in severely myelosuppressed and immunosuppressed patients with leukemia, it may also occur in those with other advanced malignancies receiving myelosuppressive chemotherapy. It has been described most recently in patients with solid tumors who receive taxane-based therapy.

A 60-year old woman with medullary breast cancer stage IIIB underwent neoadjuvant chemotherapy with TAC (doxetaxele 100 mg/m² , doxorubicin 50 mg/m² and cyclophosphamide 600 mg/m²) . Sixth days after TAC chemotherapy, she had abdominal pain and vomiting. Abdomen CT scan showed diffuse circumferential thickening of ileum wall typical for ileitis , narrowing of the lumen, disturbance of peristaltic . This abdomen CT scan was thought as abnormalities pictures of neutropenic enterocolitis .

Neutropenic enterocolitis should be considered in patient with abdominal symptoms especially during the granulocyte nadir following chemotherapy. Increased awareness of this rapidly progressive and potentially fatal disease leads to accurate diagnosis and the prompt treatment that can decrease morbidity and mortality.

Keywords : neutropenic enterocolitis, solid tumor, chemotherapy

INTRODUCTION

Netropenic enterocolitis or typhlitis (from the Greek *typhlon*, meaning caecum) is defined as a necrotizing colitis with inflammation of the cecum and surrounding tissues.^{1,2,3} The terms “neutropenic enterocolitis”, “necrotizing enterocolitis” and “ileocecal syndrome” have been used synonymously by authors.³ It is the most common gastrointestinal complication in patients with leukemia. Although this condition occurs primarily in severely myelosuppressed and immunosuppressed patients with leukemia, it may also occur in those with other advanced malignancies receiving myelosuppressive chemotherapy.¹ It has been described most recently in patients with solid tumors who receive taxane-based therapy. Also reported are cases associated with multiple myeloma, medication-induced neutropenia, cyclic neutropenia, agranulocytosis, and HIV disease.²

The reported incidence of netropenic enterocolitis has varied and is dependent on whether clinical signs or pathologic findings at autopsy were used as criteria for diagnosis. Netropenic enterocolitis has been identified at autopsy in 10%-24 % children who died of acute leukemia.^{3,4}

The clinical presentation can be quite dramatic, and the outcome may be devastating. Mortality rates are high, and treatment is controversial, with options varying from conservative medical management to surgical intervention.⁵

Here we report a case of neutropenic enterocolitis during standard dose chemotherapy for breast cancer . This case is being important to be reported due to it being rarely found . Increase awareness and early recognition of the condition is paramount to a potentially good outcome.

CASE ILLUSTRATION

A 61-year-old woman was admitted to Hasan Sadikin hospital because of abdominal pain and vomiting two days prior to admission. These symptoms happened at the sixth day after the third cycle chemotherapy with doxorubicin, cyclophosphamide, and epirubicin (TAC) for breast cancer. She received doxorubicin 50 mg/m² (total 140 mg), cyclophosphamide 600 mg/m² (total 950 mg), and epirubicin 30 mg/m² (total 90 mg). She had left medullary breast cancer stage IIIB since September 2005 and received neoadjuvant chemotherapies. The first 2 cycles of her chemotherapies were epirubicin and cyclophosphamide. Because there was no response with those chemotherapies, on the third cycle we changed with TAC regimen. The histopathology of her breast cancer was medullary carcinoma with lymphatic and perivascular infiltrations, estrogen and progesterone receptor negative and HER2-neu receptor positive 3.

On physical examination, she looked severely ill, fully alert. The blood pressure, pulse, and temperature were within normal limits. There were no abnormalities on heart and lung examination. From the abdomen examination we found moderately distended with tenderness on the whole abdomen and decreased bowel sound. There was no sign of dehydration.

Laboratory findings showed haemoglobin 10 g/dL, haematocrit 30%, white blood count 10,000/mm³, neutrophil 12/mm³, platelet count 142,000/mm³, urea 36 mg/dL, creatinine 0.59 mg/dL, blood glucose 238 mg/dL, ionized calcium 4.3 (4.7-5.2 mEq/L), magnesium 2.41 mg/dL (1.7-2.55 mg/dL), phosphorus 6 mg/dL (2.5-4.8 mg/dL), sodium 126 mEq/L, potassium 3.9 mEq/L. Abdominal radiographs revealed multiple dilated loops of small bowel with air-fluid levels (Figure 1). Contrast-enhanced

abdominal CT scan showed diffuse circumferential thickening of ileum wall typical for ileitis, narrowing of the lumen, disturbance of peristalsis. There was partial obstructive ileus with dilatation of proximal jejunum and duodenum. The colon still contained fluid and air. This abdominal CT scan was thought as abnormalities pictures of neutropenic enterocolitis (Figure 2).

We treated her with bowel rest and decompression using nasogastric and rectal tube, parenteral nutrition, granulocyte colony stimulating factor (filgrastim 300 mg/day subcutaneous), intravenous cefepime 1 gram bid. Five days after growth factor administration, her neutrophil count was increased to 8750 /mm³. We also give her 2 units packed red cells because her hemoglobin level dropped to 8.8 gr/dL. She had no fever during her hospitalisation. At the sixth day of treatment, her general condition improved, no abdominal pain and distention. She got enteral nutrition at the sixth day. The antibiotic was stopped after 7 days administration. At hospital discharge, her hemoglobin level was 11.3 gr%, white blood count 8,300/mL and platelet 127,000/mL.

She underwent modified radical mastectomy on October 2005 and radiotherapy 6000 cGy. After finished radiotherapy she received chemotherapy with 4 cycles of Classical CMF (oral cyclophosphamide 100 mg/m² days 1-14, intravenous methotrexate 40 mg/m² day 1 and 8, intravenous 5-FU 600 mg/m² day 1 and 8). She got complete response.

DISCUSSION

Cooke was the first to describe submucosal hemorrhage and appendiceal perforation in children with leukemia. A disease process, called "typhlitis",

“ neutropenic enterocolitis” or “ileocaecal syndrome” is usually found in the terminal ileum, ascending colon and caecum.⁶

Patients who become neutropenic after getting combined chemotherapy are at special risk of developing neutropenic enterocolitis. It is a potential complication of any hematologic or solid malignancy treated with aggressive chemotherapy.⁷ The key to diagnosis is prompt recognition of the clinical features. Commonly, symptom begin during the granulocyte nadir following chemotherapy. Patients at greater risk are those with fever ($>38.5^{\circ}\text{C}$) and an absolute neutrophil count (ANC) less than 500/dL. Initially, the patient may present with watery diarrhea, nausea, and vomiting, which is followed by fevers, abdominal pain, distention, and polymicrobial sepsis. Abdominal tenderness is usually concentrated in the right lower quadrant, but may be diffuse or absent in patients receiving corticosteroids. The caecum is sometimes palpable as a boggy mass. Acute lower gastrointestinal bleeding may also occur.^{1,2,7} Conditions that may present in a similar fashion include *Clostridium difficile* colitis, intussusception, ischemic colitis, and appendicitis. Other conditions that need to be considered include vincristine-induced ileus, L-asparaginase-induced pancreatitis, drug-induced cholestasis and cholecystitis, fungal infections, and pain associated with mesenteric lymph nodes.²

The pathogenesis of this disorder is unclear. Chemotherapy may damage gastrointestinal tract by destroying the rapidly dividing mucosal cells, which then coupled with neutropenia allows bacterial invasion of the bowel wall.⁶ The preferential targeting of the caecum may be secondary to its unique properties, such as greater distensibility, decreased vascular perfusion, and increased lymphatic drainage.¹ The temporal

association of administration of cytotoxic agents with the subsequent onset of neutropenic enterocolitis suggests that drug-induced mucosal injury plays a significant role in this disease.⁸ Neutropenic enterocolitis is thought to result from a combination of factors, including neutropenia, chemotherapy- or radiotherapy-induced destruction of normal mucosa, intramural hemorrhage caused by severe thrombocytopenia, and change in the normal gastrointestinal flora caused by antibiotics, antifungal agents, and colonization by hospital flora.^{2,4,5} Other precipitating factors contributing to mucosal damage include local bacterial or fungal infection with mucosal injury, necrosis of mural leukemic infiltrates, instrumentation, stasis of bowel contents with epithelial erosion and mucosal ischemia from sepsis-induced hypotension.⁸ Besides the caecum, neutropenic enterocolitis can involve ileum, ascending colon, appendix and small intestine (terminal ileitis).⁷ Certain chemotherapeutic regimens or medical conditions predispose the gastrointestinal tract to bacterial invasion either from the direct toxic effects of the agent (mucositis) or from the agent causing distention and necrosis. Neutropenia or steroids complicate the situation by reducing host defenses against infection. Transmural necrosis and perforation may then develop in the presence of neutropenia. Agents most commonly associated with neutropenic enterocolitis include cytosine-arabioside (79%), etoposide (62%), and daunorubicin (46%). Other implicated agents include doxorubicin, methotrexate, vincristine, taxane-based chemotherapeutic agents, and prednisone.² Takaoka reports the first case of neutropenic enterocolitis during standard-dose combination chemotherapy of nedaplatin and irinotecan in testicular cancer.⁸

Neutropenic enterocolitis must be considered in the differential diagnosis of any profoundly neutropenic patient (absolute neutrophil count < 500/ μ l), who presents with

fever and abdominal pain, usually in the right lower quadrant. Symptoms often appear 10-14 days after cytotoxic chemotherapy, at a time when neutropenia is most profound and the patient is febrile. Additional symptoms may include abdominal distention, nausea, vomiting, and watery or bloody diarrhea. Peritoneal signs and shock suggest the possibility of bowel wall perforation.⁹

Plain films are both nonspecific and insensitive for detection of neutropenic enterocolitis. Findings on plain films may include a right-lower-quadrant soft tissue density or mass, a fluid-filled cecum with dilated small bowel and minimal or no large bowel gas, and an ileus. Pneumatosis intestinalis of the cecum and ascending colon has been described, but its significance remains unclear. CT imaging and ultrasonography are more sensitive and specific than plain radiography or barium enema. Findings on both ultrasonography and CT include a right-lower-quadrant inflammatory mass and pericecal fluid, or inflammatory changes in the pericecal soft tissues. CT may reveal bowel wall thickening, a right-lower-quadrant mass, pericecal fluid, and pericecal soft-tissue inflammatory changes.^{2,10,11} CT is the preferred diagnostic modality since it appears to have lower false-negative rate of diagnosis (15%) than ultrasonography (23%) or plain abdominal films (48%).⁹

Ultrasonography may reveal an enlarged cecum with characteristic echogenic thickening of the mucosa, with or without fluid collection.⁸ Intestinal wall thickness (outer wall to luminal surface) less than 5 mm measured by ultrasonography is considered normal. In 44 (50%) of 88 patients with neutropenic enterocolitis, ultrasonography revealed pathologic wall thickening (mean 10.2 ± 2.9 mm, range 6-18

mm). The mean duration of symptoms was significantly longer in this group (7.9 days) than among patients without mural thickening (3.8 days). Patients with bowel wall thickness of more than 10 mm had a significant higher mortality rate (60%) than did those with bowel wall thickness \leq 10 mm (4.2%).¹²

Although there is some debate regarding medical versus surgical treatment of neutropenic enterocolitis, clearly, aggressive medical management and return of the neutrophil count are essential for survival. Patients treated conservatively have higher mortality rates when leukocyte counts do not return to levels greater than 1000 cells/dL. Recovery of the leucocyte count is fundamentally related with the survival of patients. Prolonged leucopenia may allow continued bacterial invasion of the bowel wall with persistence of the bowel lesion, followed by necrosis and perforation.^{2,6} Younger patients tend to do better than older patients. The general consensus regarding conservative treatment is that broad-spectrum antibiotics, bowel rest, abdominal decompression, and nutritional support are essential.^{2,6}

The following are criteria for surgical intervention: 1) persistent gastrointestinal bleeding after resolution of neutropenia and thrombocytopenia and correction of clotting abnormalities; 2) evidence of free intraperitoneal perforation; 3) suggestion of uncontrolled sepsis based on requirement for large volumes of fluid or vasopressors; and 4) in the absence of neutropenia, development of an intra-abdominal process that requires surgical intervention.^{2,9}

Our patient's symptoms and clinical presentations, along with laboratory and radiographic findings suggested to neutropenic enterocolitis. She responded quickly to

conservative therapy (bowel rest and decompression, intravenous fluid and nutrition, growth factor and antibiotic). In this past 5 years, in Hasan Sadikin Hospital Bandung, there was no report of neutropenic enterocolitis as a complication of patients with either leukemia or other advanced malignancies receiving myelosuppressive chemotherapy. In this case, the typical abdominal symptoms (vomiting, abdominal distention and tenderness) occurred after receiving TAC (doxorubicin, adriamycin, cyclophosphamide) chemotherapy and happened at grade 4 neutropenia (neutrophil $12 /\text{mm}^3$.) When doxorubicin is administered at dose $100 \text{ mg}/\text{m}^2$ every three weeks, 70-90 % patients develop grade 3/4 neutropenia. Neutropenic enterocolitis has also been reported in patients with metastatic breast cancer who receiving doxorubicin $60\text{-}90 \text{ mg}/\text{m}^2$. Stemmler et al reported 2 patients (metastatic breast cancer and non-small-cell lung cancer) , treated on a weekly scheduled with single agent doxorubicin $40 \text{ mg}/\text{m}^2$ who develop severe neutropenic enterocolitis.¹³

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. Initially, mortality rate of this complication approached to 100%, and diagnosed only by autopsy. With the advance 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.³ Most death attributed to transmural bowel necrosis, perforation and sepsis.⁹

CONCLUSION

Neutropenic enterocolitis should be considered in patient with abdominal symptoms especially during the granulocyte nadir following chemotherapy. Prompt recognition of the predicting signs such as massive watery diarrhea , abdominal pain and development of paralytic ileus is a key to appropriate management of this serious syndrome. Although neutropenic enterocolitis mainly happen after high dose chemotherapy, it can happen during standard dose chemotherapy .Careful history taking, physical examination and radiographic studies (plain abdominal x-ray , ultrasonography or abdominal CT) can establish the diagnosis. It is important to consider the possibility of this rapidly progressive and potentially fatal disease in any neutropenic patient, because increased awareness leads to accurate diagnosis and the prompt treatment that can decrease morbidity and mortality.

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