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Neutropenic Enterocolitis: The Silent but Serious Threat in Leukemia Care

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Abstract **Case Report**

Neutropenic enterocolitis (NEC) is a severe inflammatory disease of the bowel that occurs in conjunction with neutropenia and poses a significant risk in morbidity and mortality for patients who are immunocompromised, especially those with malignancies undergoing chemotherapy due to blood cancer. The critical clinical features to note are a fever, abdominal pain, diarrhea, and lab results demonstrating profound neutropenia along with increased CRP levels. Thinning and increasing inflammation of the colon wall as well as other characteristic radiologic signs noticeable on CT imaging, are also important indicators. Diagnosis should be made at as early as possible using any of the previously mentioned signs. First, management primarily involves a conservative approach. In-hospital care of NEC includes bowel rest, fluid replacement therapy, wide-coverage antibiotics, and G-CSF to help speed up neutrophil emission. In contrast to these methods, surgery should only be done if the patient is more complex and has additional problems like leaks or worsened blood loss. This article discusses the case of a 27-year-old female with relapsing acute myeloid leukemia who developed NEC during chemotherapy and ultimately acheived favorable outcomes with conservative treatment. The collaborative approach provided prompt solutions that mitigated comprehensive damage by exploring every aspect of care, which this entity improved outcomes for newly diagnosed patients suffering from this condition.

Keywords: Diarrhea, Colitis, Neutropenia, Chemotherapy, immunodepression, antibiotics.

INTRODUCTION

Neutropenic enterocolitis (NEC) is an inflammatory condition of the intestine occurring in the context of neutropenia, often due to chemotherapy-induced myelosuppression or bone marrow disorders. The classical presentation includes fever, abdominal pain, diarrhea, and possibly gastrointestinal bleeding [1]. As a form of gastrointestinal mucositis, NEC poses a significant risk of morbidity and mortality, given its association with severe infections and septic complications. Establishing an early diagnosis is key [1, 2]. The management of NEC remains undefined due to lack of high-quality clinical data. The involvement of a multi-disciplinary team, consisting of the oncologist, infectious diseases specialists and surgeons is highly recommended.

The aim of this article, which reports the case of a 27-year-old patient, is to shed light on this relatively rare entity and to offer a review of the literature in line with the latest recommendations.

CASE REPORT

We present the case of a 27-year-old female with no significant past medical history, currently under follow-up in hematology for relapsing acute myeloid leukemia (AML). She was undergoing chemotherapy with the CLAG-IDA protocol (Cladribine 5 mg/m²/day on days 1–5, Ara-C 2 g/m²/day on days 1–5, Idarubicin 8 mg/m²/day on days 1–3) when she was referred for evaluation of acute watery diarrhea, without discharge or blood, accompanied by atypical diffuse abdominal pain and abdominal distension. These symptoms had been evolving over the past 7 days, with a fever peaking at 40°C and a significantly altered general condition. No other gastrointestinal symptoms, such as vomiting or overt gastrointestinal bleeding, were reported.

On examination, the patient appeared hemodynamically unstable, with hypotension (90/50 mmHg), tachycardia (117 bpm), asthenia, and fever. Abdominal examination revealed moderate ascites, diffuse abdominal tenderness without guarding, hepatomegaly (liver span of 17 cm), and lower limb edema. Laboratory investigations showed pancytopenia

with a white blood cell count of 50,000/µL, platelet count of 4000/µL, and severe anemia (hemoglobin of 5.2 g/L). C-reactive protein (CRP) was elevated at 245 mg/L, and hypoalbuminemia was noted with an albumin level of approximately 20 g/L. Further, the patient exhibited a significant electrolyte disturbance with profound hypokalemia (1.93 mmol/L), although no electrical abnormalities were observed on the ECG.

Stool studies, including copro-parasitology and gastrointestinal PCR, were conducted to rule out infectious etiologies, such as cytomegalovirus (CMV) or Clostridium difficile colitis. Cross-sectional imaging, including CT, revealed regular circumferential wall thickening of the terminal ileum, cecum, and ascending colon, extending to the right colonic angle, with no evidence of stenosis or healthy tissue intervals. Contrast-enhanced imaging demonstrated marked submucosal edema measuring 13.5 mm and diffuse infiltration of mesenteric fat, alongside significant ascites. (Figure 1)

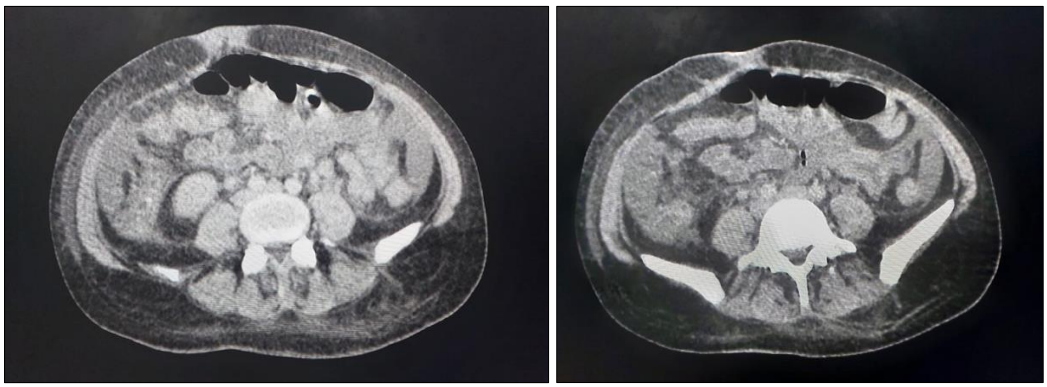

Figure 1: Abdominal CT-Scan images showing bowel wall thickening, submucosal oedema, infiltration of mesenteric fat

The clinical and radiological findings led to the diagnosis of neutropenic enterocolitis, based on major criteria (fever, abdominal pain, thickening of the bowel and colonic wall >4 mm, and neutrophil count of 0) and minor criteria (acute diarrhea and ascites). Given the absence of severe criteria, conservative management was chosen. This approach included bowel rest, intensive fluid resuscitation, correction of hypokalemia, and the administration of broad-spectrum antibiotics (cephalosporin, metronidazole, and amikacin). Additionally, granulocyte colony-stimulating factor (G-CSF) was infused to stimulate hematopoiesis, and albumin was administered to address hypoalbuminemia. The patient also received a transfusion of labile blood products to improve her thrombocytopenia and anemia.

Initially, the patient's clinical course was erratic, but after 10 days of treatment, her condition improved markedly. There was stabilization of her hemodynamic status, resolution of diarrhea, and a significant reduction in abdominal discomfort. Importantly, the patient also recovered from her bone marrow aplasia, with a white blood cell count of 4020/µL and neutrophil count of 1032/µL, indicating restoration of hematopoietic function.

DISCUSSION

Definition and Epidemiology

NEC, also known as typhlitis, from the Greek typhi or “blind” in reference to the blind-ending cecum, which describes neutropenic enterocolitis of the cecum that affects the ileal region as well and can spread to the ascending colon. It is a life-threatening condition with a mortality rate of 30% to 50% [1-5].

NEC primarily affects neutropenic, immunocompromised patients undergoing chemotherapy for hematological diseases such as leukemia, lymphoma, multiple myeloma, aplastic anemia, and myelodysplastic syndromes. However, it has also been observed in patients with immunosuppressive conditions, including AIDS, those receiving solid tumor therapy, and individuals who have undergone organ transplantation. The exact incidence of neutropenic enterocolitis remains unclear [2].

Pathogenesis and Risk Factors

The pathogenesis of Typhlitis is not fully understood and is thought to be multifactorial. Between the diverse components of the disease onset, we find that an intestinal mucosal injury, a neutropenic state, and the immunocompromised status of the patients are the most important elements. The disruption of the intestinal mucosa (intestinal edema, blood vessels dilation, and tearing of the mucosal surface), by cytotoxic chemotherapies, malignant infiltration of the intestinal mucosa, or intramural hemorrhage due to thrombocytopenia enables opportunistic pathogens to invade the gut and bloodstream. Neutropenia further aggravates the risks, causing decreased immunity with failure to control the transmural translocation of pathogens [6].

Some chemotherapy agents can contribute to NE by causing direct damage to the mucosa, impairing intestinal motility and rendering patients more likely to develop intestinal distension and necrosis. Cytotoxic drugs commonly used to treat leukaemic patients, and known to induce mucosal damage and have been associated with the development of NEC, include cytosine arabinoside, vincristine, doxorubicin or idarubicin (like it was the case for our patient here). Other risk factors include prolonged period of neutropenia, previous episodes of NEC and pre-existing bowel abnormalities such as diverticular disease [3].

Furthermore, the use of antibiotics and steroids can alter the enteric bacterial flora, leading to proliferation, exacerbating the inflammatory process in the intestinal wall and resulting in potential complications, such as transmural inflammation, perforation and peritonitis [7].

The microorganisms mostly involved in NEC are polymicrobial and include gram-negative bacilli, gram-positive cocci, anaerobes, and fungi. The organisms most frequently identified include *Pseudomonas aeruginosa, Escherichia coli, Klebsiella spp, viridans group streptococci, enterococci, Bacteroides spp, Clostridium spp, and Candida spp* [8].

Diagnosis

Symptoms usually occur within 30 days of initiation of cytotoxic chemotherapy, often within 2 weeks following completion of therapy and coincide with the neutropenia nadir [3].

Although the classic presentation of NEC includes profound neutropenia, fever > 38.3 °C, right-sided abdominal pain (the location of pain depends on the area of the affected bowel and can at times be diffuse) and diarrhea (bloody or not), patients can present with combinations of symptoms, such as abdominal distension, nausea, vomiting. Abdominal compartment syndrome has been reported in patients with NE presenting with abdominal distension and ascites. Melena or hematochezia are generally less common forms of presentation. Peritoneal signs, shock, abdominal distention, and rapid clinical deterioration can be suggestive of necrosis and a bowel perforation [1].

During the physical examination, tenderness can be found on palpation, and this abdominal pain can be localized in the lower right quadrant or can be more diffuse.

Abdominal imaging could either rely on ultrasounds especially for children or CT- Imaging for adults. Ultrasound patterns of NEC include a doughnut-like hypoechoic, fluid-filled intestinal lumen separated from thickened bowel wall by a thin hyperechoic line of mucosa. While CT findings usually include intestinal wall thickening, mesenteric stranding, intestinal dilatation, and pneumatosis [1-9]. CT is the preferred option as it allows a differential diagnosis from other diseases such as ischemic colitis as well as being specific on the extend of GI involvement and the severity of GI wall inflammation.

Since abdominal symptoms exhibited by patients suffering from NEC are non specific, we should not overlook the wide range of diseases that could also manifest as an acute abdominal pain in neutropenic patients undergoing chemotherapy, including infectious colitis (CMV or Clostridium difficile i.e.), ischemic colitis, Graft-versus-host disease, leukemic infiltrates of the bowel, cholangitis, cholecystitis, acute appendicitis, bowel obstruction, Autoimmune colitis due to check point inhibitors [10].

Histopathological confirmation of the diagnosis or for ruling out infectious or GVHD colitis is challenging, since colonoscopies are contraindicated due to the risk of bowel perforation and the risk of bleeding due to thrombocytopenia is not negligible.

Establishing diagnostic of a NEC is no easy task, as to the lack of standardized diagnostic criteria. Therefore, the diagnosis is based on common clinical, laboratory and radiological findings.

The current major criteria defining NEC are [2-5]:

- Neutropenia < 500 cells/L
- Fever > 38.3 °C
- Abdominal pain
- Abdominal computed tomography (CT) or ultrasound demonstrating > 4 mm bowel wall thickness in a > 3 cm length of bowel.

Some minor criteria that could lead to a diagnosis involve abdominal distension, cramping, diarrhea, and lower gastrointestinal bleeding.

Treatment

Treatment approaches have drifted away from aggressive surgical interventions towards more conservative modalities, and surgical management is certainly not the initial modality of treatment for NEC. In patients without complications, such as bleeding, perforation or peritonitis, non-surgical management, consisting of bowel rest, intravenous fluids, parenteral nutrition, correction of coagulopathy, blood product support and broad-spectrum antibiotic coverage, is a reasonable approach [2-10].

The patient should receive an intravenous broad-spectrum antimicrobial that covers for gram-negative and anaerobic microorganisms as they are the most common organisms causing NEC. Monotherapy with piperacillin-tazobactam, carbapenem, or anti-pseudomonal cephalosporin such as cefepime with

metronidazole can be started empirically. However, if there is a suspicion of mucositis, then concern should be taken for and treatment directed against gram-positive bacteria such as Vancomycin should be used [1-9].

The role of empiric antifungal therapy upfront In NEC is debatable as bacterial causes are the commonest. It should be strongly considered in patients with persistent fever after 4 – 7 days of antibiotic therapy and in those, whose overall duration of neutropenia is expected to last longer than 7 days and should cover Candida spp. And Aspergillus. Recommended options include voriconazole and amphotericin B formulations if mold coverage in addition to Candida is desired or echinocandins for candidemia arising from NEC. Once the patient has been afebrile for at least 2 days and achieved an ANC > 500/cells, intravenous formulations can be deescalated to an appropriate oral regimen. In patients with persisting mucositis, nausea and vomiting, intravenous formulations should be continued till recovery of GI symptoms and ability to tolerate oral intake [3].

The use of granulocyte colony-stimulating factor (G-CSF) may be beneficial in severely ill patients with the intention to accelerate neutrophil recovery, although there are no randomized controlled studies regarding their use [3-9]. Considerations for the use of granulocyte colony-stimulating factor (G-CSF) according to the current American Society of Clinical Oncology guidelines include profound neutropenia (absolute neutrophil <100/mL), uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction, and invasive fungal [1-10].

Surgical management should be avoided in stable pancytopenic patients with NEC because of the increased risk of post-surgical infections, improper wound healing and increased risk of haemorrhage. Surgery is indicated in the case of serious complications such as bowel perforation, persistent gastrointestinal haemorrhage or the development of intra-abdominal complications such as abscesses or necrosis. Primary anastomosis is not recommended, and a two-stage procedure is preferable [3-10].

CONCLUSION

NEC is a rare but serious complication in immunocompromised patients, particularly those undergoing chemotherapy for hematological malignancies. While the pathogenesis remains complex, early recognition and a multi-disciplinary approach are crucial in managing the condition. Although conservative treatment with bowel rest, fluid support, broad-spectrum antibiotics, and granulocyte colony-stimulating factor (G-CSF) remains the mainstay, careful monitoring is essential due to the potential for rapid deterioration. Surgical intervention is reserved for cases with life-threatening complications. Ongoing research is needed to establish standardized diagnostic criteria and optimize treatment protocols, ultimately improving outcomes for affected patients.

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