ISSN 2150-5330 (online)

World Journal of *Gastrointestinal Pathophysiology*

World J Gastrointest Pathophysiol 2019 October 15; 10(3): 36-41



Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Pathophysiology

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Irregular Volume 10 Number 3 October 15, 2019

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World Journal of Gastrointestinal Pathophysiology

Volume 10 Number 3 October 15, 2019

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The *WJGP* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Mei-Yi Liu*

Proofing Production Department Director: *Yun-Xiaojian Wu*

NAME OF JOURNAL
World Journal of Gastrointestinal Pathophysiology

ISSN
ISSN 2150-5330 (online)

LAUNCH DATE
April 15, 2010

FREQUENCY
Irregular

EDITORS-IN-CHIEF
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https://www.wjgnet.com/2150-5330/editorialboard.htm

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PUBLICATION DATE
October 15, 2019

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World Journal of Gastrointestinal Pathophysiology

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World J Gastrointest Pathophysiol 2019 October 15; 10(3): 36-41

DOI: 10.4291/wjgp.v10.i3.36

ISSN 2150-5330 (online)

EDITORIAL

Neutropenic enterocolitis: A clinico-pathological review

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Author contributions: Xia R reviewed the literature and drafted the manuscript; Zhang X provided overall intellectual input, reviewed the literature, acquired the histological images, and edited the final version of the manuscript; all authors approved the final version to be published.

Conflict-of-interest statement: The authors have no conflicts of interest to disclose.

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Manuscript source: Unsolicited manuscript

Received: June 6, 2019
Peer-review started: July 12, 2019
First decision: August 30, 2019
Revised: September 6, 2019
Accepted: September 22, 2019
Article in press: September 22, 2019
Published online: October 15, 2019

P-Reviewer: Cheng DY, Yuksel I
S-Editor: Ma RY

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Abstract

Neutropenic enterocolitis (NE) is a predominantly cecum-based disease with high mortality seen in patients post chemotherapy. The pathogenesis of NE is poorly understood and probably multifactorial involving mucosal injury, neutropenia, and impaired host defense to intestinal organisms. The clinical presentation is characterized as ileocolonic inflammation and bowel wall thickening in patients with neutropenia, fever, and abdominal pain. The pathological features of NE include patchy necrosis, hemorrhage, ulcer, edema, perforation, infiltrating organisms, and characteristically, depletion of inflammatory cells (neutrophils). NE should always be considered as a possible diagnosis in immunosuppressed patients, especially those receiving chemotherapy. High clinical and histological diagnostic discordance rate exists. High index of clinical suspicion and prompt appropriate personalized management are essential to achieve a lower mortality rate.

Key words: Neutropenic enterocolitis; Typhlitis; Chemotherapy; Neutropenia

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Core tip: Neutropenic enterocolitis (NE) is a predominantly cecum-based disease with high mortality seen in patients post chemotherapy. The pathogenesis of NE is still poorly understood. The clinical presentation is characterized as ileocolonic inflammation and bowel wall thickening in patients with neutropenia, fever, and abdominal pain. The pathological features of NE include patchy necrosis, hemorrhage, ulcer, edema, perforation, infiltrating organisms, and characteristically, depletion of inflammatory cells (neutrophils). High clinical and histological diagnostic discordance rate exists. High index of clinical suspicion and timely diagnosis are critical for patient appropriate treatment and improvement of survival.

L-Editor: A
E-Editor: Liu MY

Citation: Xia R, Zhang X. Neutropenic enterocolitis: A clinico-pathological review. *World J Gastrointest Pathophysiol* 2019; 10(3): 36-41
URL: https://www.wjgnet.com/2150-5330/full/v10/i3/36.htm
DOI: https://dx.doi.org/10.4291/wjgp.v10.i3.36

INTRODUCTION

Neutropenic enterocolitis (NE) was also named as typhlitis, typhlenteritis, ileocecal syndrome, or cecitis. NE is a clinical entity described mostly in patients with hematologic malignancies, as well as other immunosuppressive causes such as acquired immune deficiency syndrome (AIDS), therapy for solid tumors, and organ transplant[1-6]. The clinical presentation is characterized as ileocolonic inflammation in patients with neutropenia, fever, and abdominal pain[5,6]. The cecum is the most commonly reported site to be involved[6,7]. The mortality of NE can reach up to 100% due to complications of malignancy, sepsis, or bowel necrosis and perforation[6,8]. In recently years, early recognition and progress in management have reduced mortality substantially[9,10]. A recent study showed a mortality rate of 32.1% in the intensive care units and a hospital mortality rate of 38.8%[11]. The clinical diagnosis of NE relies on major criteria and minor criteria. The major criteria include neutropenia, fever, and bowel wall thickening on computed tomography (CT) or ultrasound imaging. The minor criteria consist of nonspecific symptoms including abdominal pain, distension cramping, diarrhea, or lower gastrointestinal bleeding[11]. The NE patients are often in critical condition which may not permit endoscopic examination or surgical resection. Therefore, the pathologic features of NE have not been well recognized, and a high clinical and histological diagnostic discordance rate has been reported in NE cases[5].

CLINICAL CHARACTERISTICS AND IMAGING

The true occurrence rate of NE is unknown, which has been estimated at about 5% of patients hospitalized for leukemia/lymphoma, aplastic anemia or solid tumors treated with chemotherapy[12]. Neutropenia is the major risk factor for the development of NE. NE can develop in leukemia patients or patients in neutropenic condition receiving high dose chemotherapy to treat malignancies. Other conditions related to neutropenia include multiple myeloma, lymphoma, aplastic anemia, myelodysplastic syndromes, drug-induced neutropenia, cyclical neutropenia, agranulocytosis, and other immunosuppressive conditions such as AIDS and post-transplant patients[6,9]. NE patients usually present with nonspecific abdominal pain, diarrhea, nausea, vomiting, and abdominal distension[6,13]. Symptoms usually present 10-14 d post starting chemotherapy.

The initial diagnosis of NE is usually established by detection of the characteristic CT findings in neutropenic patients presenting with fever, abdominal pain and tenderness. The most common CT findings in NE is bowel wall thickening. Other CT findings include stranding mesentery, dilated bowel, enhancement of mucosa, and intestinal pneumatosis[6]. The abnormal findings mostly involve the ascending colon and cecum[14]. Plain films of the abdomen are nonspecific, but, are useful for detecting free air[6]. Occasionally, abdominal X-ray may show diffusely distended cecum and adjacent dilated small intestine, signs of thumbprinting, or localized pneumatosis intestinalis, suggestive of NE if clinical background fits[15]. Barium enema is contradicted in potential NE patients, due to its risk to cause bowel perforation[16,17]. In addition to CT scanning, detection of micro- organisms in blood and stool cultures and Clostridioides difficile toxin assays can help identify the superposed infection and decide the management of the patients[18].

PATHOLOGY FINDINGS

Histologic examination is the gold standard for the diagnosis of NE[19]. However, colonoscopy is relatively contraindicated in NE patients, as air insufflation may result in bowel perforation[5,20]. In patients who underwent colonoscopy examination or surgical resection of bowel segment, the gross findings in colonoscopy or surgical resection specimen include: Presence of patchy irregularity and nodularity, friable mucosa, and mass-like lesion that mimics malignancy[5,21]. Occasionally, NE causes

perforation of the bowel, a leading cause of death in NE[22]. The cecum and right colon are involved in nearly all the cases (Figure 1). Other bowel segments such as terminal ileum, transverse colon and left colon can also be variably involved. However, NE lesions are not reported in the appendix or rectum so far[5].

The key histopathologic features of NE are marked hemorrhagic necrosis, mucosal ulceration, extensive edema in the submucosa and laminal propria, marked congestion and even deep mural and transmural necrosis (Figure 2A-D)[5]. Most importantly, significant infiltrative inflammation should be absent in NE due to the profound neutropenia. Many cases are accompanied by infiltrating organisms like bacteria or fungus hyphae. However, inflammatory cell infiltration is still depleted despite in background of organism overgrowth[14]. Apoptotic bodies are not prominent in NE cases, distinguishing NE from the graft-versus-host disease, mycophenolate mofetil-induced injury and immune checkpoint inhibitor induced colitis[22].

PATHOGENESIS AND PATHOPHYSIOLOGY

The pathogenesis of NE is poorly understood and probably multifactorial involving mucosal injury, neutropenia, and impaired host defense to intestinal organisms. The initial morbidities of the patients lead to intestinal edema, engorged vessels, and mucosal surface disruption, especially of the ileocolonic segments. Chemotherapeutic agents like cytarabine can directly cause mucositis or predispose to intestinal distension and necrosis, and consequently impair the intestinal motility. The initial intestinal mucosal injury in the background of immunocompromised state of the afflicted patients leads to intestinal edema, vascular dilation, mucosal disruption, and bacterial intramural invasion[5-7]. Moreover, intestinal leukemic infiltration may be a superposed factor in the pathogenesis of NE[23]. Neutropenia and the use of steroids complicate the situation by reducing host defenses against infection. Microbes including variety of bacteria, fungi and cytomegalovirus have been implicated as causes[24-26].

DIFFERENTIAL DIAGNOSIS

Clinically and radiologically, many conditions can overlap with NE and its mimics including acute appendicitis, appendiceal abscess, ischemic enteritis, *Clostridium difficile* colitis, graft-versus-host disease, mycophenolate mofetil-induced injury, and enteric involvement by lymphoma/leukemia[5,6]. Recent high-dose chemotherapy along with the symptoms of fever and abdominal pain, lab finding of neutropenia, and imaging finding of bowel wall thickening will aid the diagnosis of NE. A timely diagnosis and proper management will significantly improve the prognosis[11]. Histopathological findings are the gold standard to distinguish NE from its mimics, if diagnostic tissue especially resection specimen is available for pathology examination. In a multi-institutional histological study of NE lesions, high discordance rate (35%) between clinical and pathologic diagnoses has been reported. Fifteen percent of patients with histologically confirmed NE were not clinically suspected for NE, whereas, twenty six percent of patients with clinically suspected NE were histologically evaluated as non-NE[5].

TREATMENT CONSIDERATIONS

So far, there is no high-quality prospective or retrospective studies on the treatment of NE, and therefore, no recommended uniform management strategy or guidelines for NE yet. A general approach to patients with NE should be individualized depending on the complications and pre-morbidities of the patients. Treatment of NE patients without significant complications such as peritonitis, perforation, or bleeding is mainly supportive including bowel rest and intravenous fluids supplement, and use of antibiotics[11]. Neutropenia is the major risk factor for the pathogenesis of NE. Cytopenia, coagulopathy, and mucosal hemorrhage can cause coagulopathy. Therefore, coagulation should be monitored in patients with NE and be corrected promptly[7,11]. The use of granulocyte colony stimulating factor can hasten neutrophil recovery and may be beneficial in some patients[7,11]. Surgical intervention has been recommended for patients with evidence of bowel perforation, persistent bleeding even after correction of cytopenia and coagulopathy abnormalities, clinical deterioration in spite of the intensive medical intervention, and the presence of other



Figure 1 Gross findings of neutropenic enterocolitis. Cecal mucosa with patchy hemorrhage, necrosis and ulceration.

surgical conditions, *e.g.*, abscess and acute appendicitis[25,27]. Interestingly, patients who recovered from NE are at risk from developing NE again during subsequent chemotherapy. Patients should be fully recovered from NE before a new chemotherapy starts[25].

CONCLUSION

Neutropenic enterocolitis is a predominantly cecum-based disease with high mortality seen in patients post chemotherapy. The diagnosis of NE should always be considered in immunosuppressed patients, particularly those treated with chemotherapy when they present with appropriate symptoms. The pathogenesis of NE is still unclear and probably multifactorial involving mucosal injury, neutropenia, and impaired host defense to intestinal organisms. The clinical presentation is characterized as colonic inflammation and bowel wall thickening in patients with neutropenia, fever, and abdominal pain. The pathological features of NE include patchy necrosis, hemorrhage, ulcer, edema, perforation, infiltrating organisms, and characteristically, depletion of neutrophil infiltration. High clinical and histological diagnostic discordance rate exists. The differential diagnoses of NE include non-specific chronic and acute colitis, graft-versus-host disease associated colitis, malignancy relapse, drug-induced colitis, acute appendicitis, and bowel ischemia. Conservative treatment or surgical intervention should be tailored to the individual patient. High index of clinical suspicion and prompt appropriate treatment is essential to achieve a lower mortality rate.

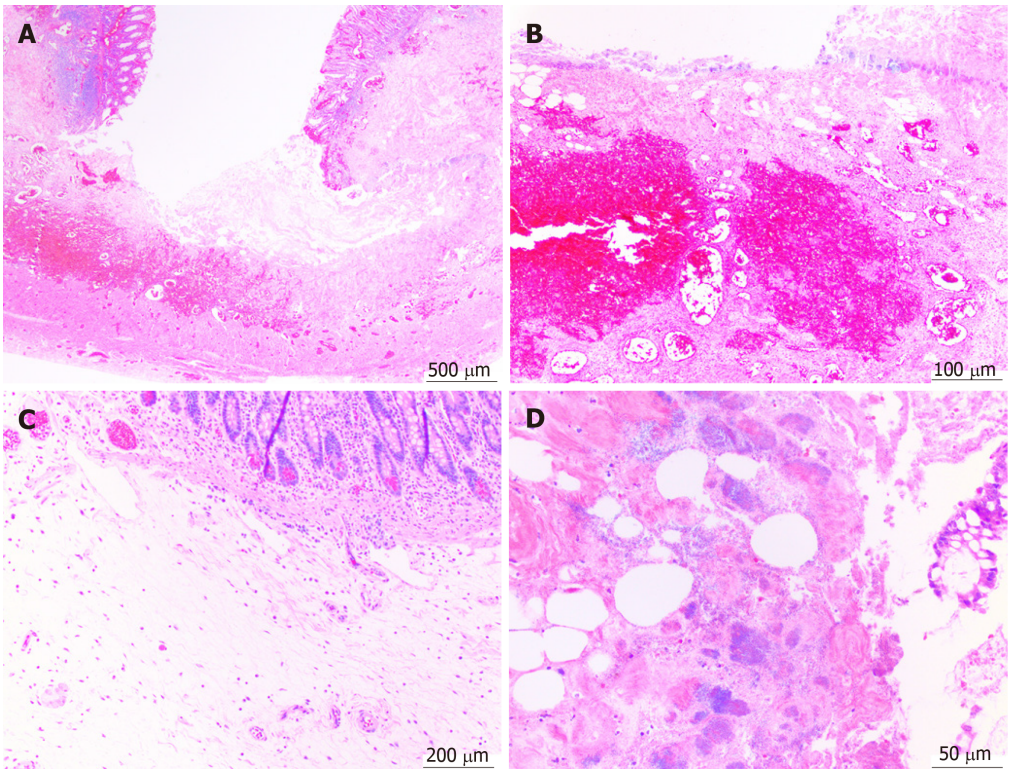


Figure 2 Histologic features of neutropenic enterocolitis. A: Ulceration; B: Hemorrhage and congestion; C: Prominent submucosal edema with paucity of infiltrative inflammatory cells; D: Infiltrative bacteria. Hematoxylin-eosin stain.

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