Neutropenic enterocolitis complicating acute lymphoblastic leukaemia

S K Misser
MB ChB

P Corr
MB ChB, MD, FFRad (D) SA, FRCR

Department of Radiology
Inkosi Albert Luthuli Central Hospital
Nelson R. Mandela School of Medicine
Durban

V B Jogessar
MB ChB, MRCP (UK), FRCPath(Lond), FCPath(SA)

Department of Haematology
Inkosi Albert Luthuli Central Hospital
Nelson R Mandela School of Medicine
Durban

Abstract

Neutropenic enterocolitis is a lethal, necrotising inflammation of the caecum and contiguous bowel, found in immunocompromised, neutropenic patients. A high index of clinical suspicion coupled with appropriate imaging modalities allows earlier diagnosis and can expedite the management of these severely ill patients. We describe the clinico-radiological features of this condition in the following case report, as well as a brief management approach to this rare, but increasingly recognised condition.

Case report

A 23-year-old female patient was referred from a peripheral hospital with a 1-week history of fever and frank rectal bleeding. On examination, the patient was pyrexial and pale. Numerous petechial haemorrhages were present on both forearms and shoulders. Shotty cervical and axillary lymph nodes, 4 cm hepatomegaly and 2 cm splenomegaly were palpated. The abdomen was mildly tender but there was no peritonism. Fundoscopy revealed bilateral retinal haemorrhages. Her neurological assessment was unremarkable. An initial chest radiograph was normal.

Full blood count, on admission, revealed a haemoglobin level of 3.3 g/dl, a white cell count of 29.3 × 10^9/l with severe neutropenia (1%), predominance of blast cells (94%) and thrombocytopenia with a platelet count of 9 × 10^9/l. Blood cultures, on admission, were negative.

Bone marrow aspirate and trephine biopsy confirmed the diagnosis of acute lymphoblastic leukaemia. On immunophenotyping, the leukaemia cells were CD19+ (68.7%), CD10+ (83.8%) and CD34+ (86.5%) confirming cALLa+ acute lymphoblastic leukaemia. The absolute CD4 count was 93 cells/µl.

The patient was transfused with packed red cells and platelets, and intravenous antibiotics (amikacin and Tazocin) were commenced. The following day combined induction chemotherapy with vincristine, doxorubicin, cyclophosphamide, cytosine-arabinoside and prednisone was instituted. Following chemotherapy, there was persistent, severe pancytopenia.

Two weeks later, despite continuous high-care treatment, the patient's condition deteriorated. She developed acute, severe abdominal tenderness, pyrexia and hypotension, which necessitated immediate transfer to the intensive care unit (ICU).

Abdominal radiograph (Fig. 1) revealed an abnormal bowel gas pattern with marked gastric and small bowel dilatation, and paucity of air in the right iliac fossa (RIF).

Chest radiograph (Fig. 2) demonstrated air-space opacification bilaterally with areas of confluence in the mid to lower zones, especially on the right in keeping with bronchopneumonia.

Blood cultures confirmed septicaemia with a resistant strain of *Escherichia coli*, sensitive to meropenem only. The pancytopenia deteriorated and the patient developed acute renal failure with anuria. Her abdomen was moderately distended with generalised abdominal tenderness and rebound tenderness in the RIF. Bowel sounds were absent.

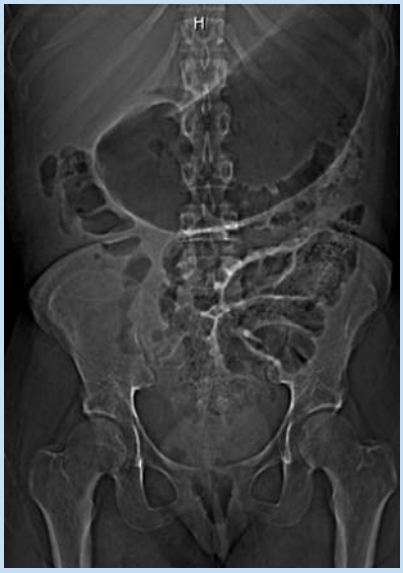

Fig. 1. Supine abdominal radiograph performed while in ICU.

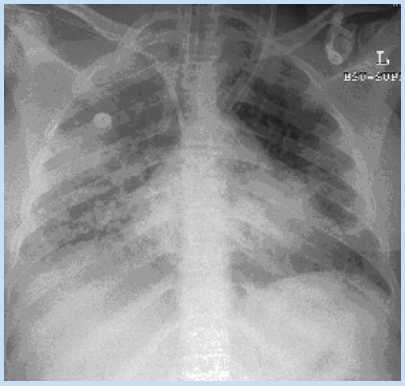

Fig. 2. Bed side unit supine chest radiograph.

Abdominal ultrasound demonstrated free intra-peritoneal fluid, acalculus cholecystitis and bowel wall thickening in the RIF.

Contrast-enhanced computed tomography (CT) scan confirmed presence of ascites and acalculus cholecystitis. There was also marked dilatation of the caecum with extensive bowel wall thickening involving the entire right colon, proximal transverse colon and terminal ileum. Stranding of the surrounding fat was present, indicative of the pericolic inflammatory process. (Figs 3 -7).

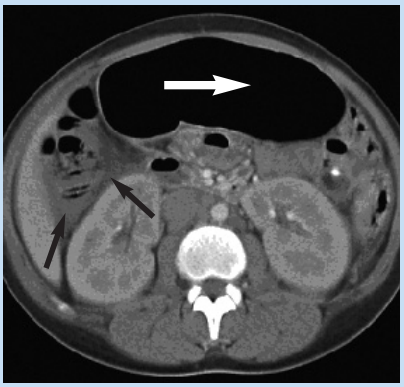

Fig. 3. Contrast-enhanced CT scan at the level of the mid-upper poles of the kidneys demonstrates pericolic inflammatory stranding (black arrows) surrounding the colon, proximal to hepatic flexure, in the anterior pararenal space. Note the distended stomach anteriorly (white arrow).

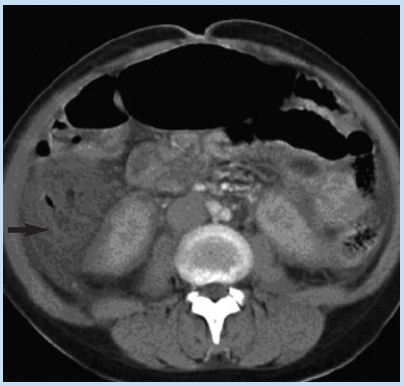

Fig. 4. Contrast-enhanced CT scan at the level of the inferior poles of the kidneys demonstrates marked mural thickening (black arrow) of the ascending colon with pericolic inflammation.

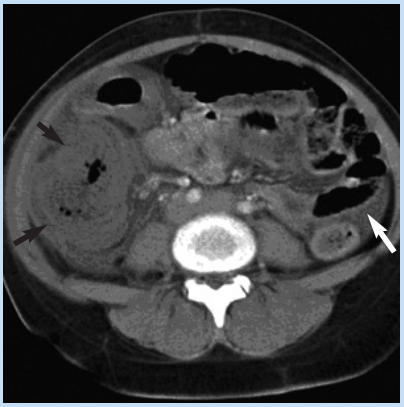

Fig. 5. Contrast-enhanced CT scan demonstrating the thick-walled right colon (black arrows) and mesenteric stranding. Note free fluid in the left paracolic gutter (white arrow).

The radiological features were consistent with a diagnosis of neutropenic enterocolitis (NE). The patient's condition progressively worsened despite supportive therapy, which included inotropic agents, assisted ventilation and broad-spectrum antimicrobials. The patient died in ICU.

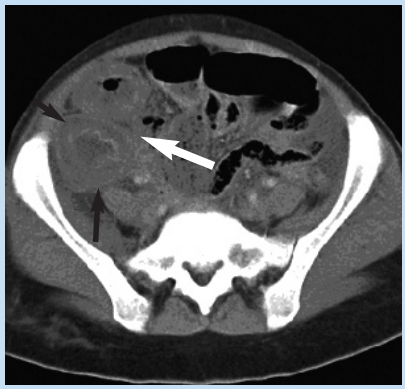

Fig. 6. Contrast enhanced CT scan at the pelvic inlet demonstrating marked caecal wall thickening (black arrows) and inflammatory reaction at the ileocaecal valve (white arrow).

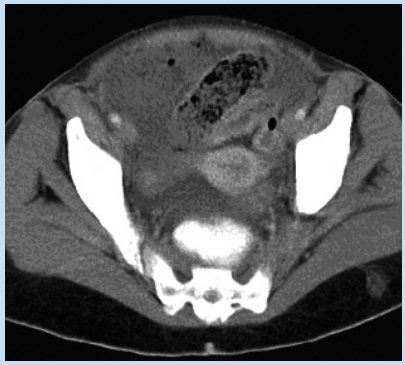

Fig. 7. Contrast-enhanced CT scan at mid to lower pelvis revealed ascites.

Discussion

NE, also referred to as typhlitis, is a life-threatening infectious disease with the epicentre located at the caecum and ascending colon. The term NE partly describes the aetiology and pathology of this condition, which is being reported with increasing frequency. Patients who are profoundly neutropenic due to underlying medical conditions such as leukaemia or AIDS,[1] or who are rendered neutropenic following chemotherapy for an underlying malignancy, are at special risk of developing NE. The chemotherapeutic agents commonly incriminated are Taxol, doxorubicin, cytosine-arabinoside and vinca alkaloids, which are administered in various combinations.

Many mechanisms leading to the development of NE have been proposed. Some authors have provided evidence to suggest that NE is a toxin-mediated disease and prior chemotherapy is unnecessary for its pathogenesis. Others have reported the condition only following combined regimens of chemotherapy. It is postulated that a combination of factors in most patients (as in the patient reported here) precipitates NE.

Autopsy studies identified multiple clostridial species in necrotic bowel wall of patients with NE.[2,3] Clostridia, which are a normal component of the alimentary flora are thought to secrete a necrotising β-toxin. Ordinarily this toxin is inactivated by neutrophil proteases. In severely neutropenic patients, the absence of neutrophil proteases permits clostridial toxin-mediated bowel wall injury.[4] The appendix has the highest carriage rate of clostridia. This is the reason that the inflammatory process and ensuing necrosis are concentrated in the terminal ileum, caecum and right colon.[5]

Following clostridial toxin-mediated mucosal necrosis, secondary bacterial translocation leads to acute septicaemia (Fig. 8). The commonest organisms cultured include *E. coli*, Klebsiella, Pseudomonas, Enterococcus, Candida and Clostridia.[6]

Pathologically, NE is characterised by inflammation and oedema that progresses to ulceration, necrosis and bowel wall perforation.[7]

The differential diagnosis for NE includes acute appendicitis, appendix mass, intussusception, ischaemic colitis or other inflammatory processes, e.g. bacterial gastro-enteritis, viral colitis, inflammatory bowel disease or pseudomembranous colitis.

Blood cultures are an important laboratory investigation that should be performed as early as possible, such that organism isolation and sensitivity can be known early on. This allows rapid, directed antimicrobial therapy.

The findings of plain abdominal radiographs are usually nonspecific and they rarely help in the diagnosis of NE. Occasionally, right colonic and small bowel dilatation, thumb printing, paucity of air in the right colon and soft tissue mass displac-

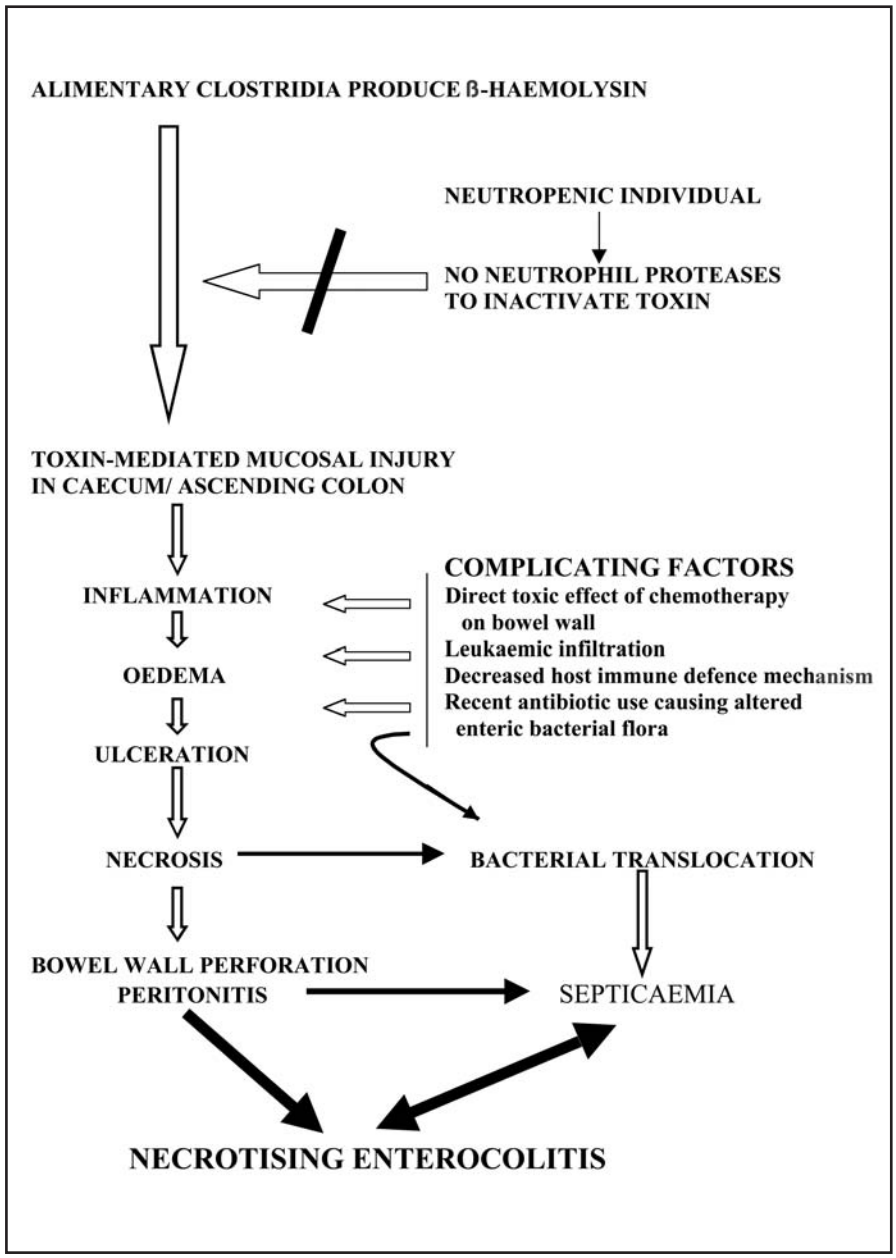

Fig. 8. Algorithm of the pathophysiological processes in NE.

ing small bowel loops may be noted.[8] Free intra-abdominal air is an ominous sign.

Contrast enema, uncommonly performed in NE, may demonstrate rigidity and thickening of the caecum. Barium enema is usually contraindicated as there is a potential risk of perforation.

Ultrasound (US) is a useful additional tool. Bowel wall thickening that produces a target or halo, with echogenic walls is suggestive of colitis, but is nonspecific.[9] It may be used as a follow-up tool to assess gradual decline in bowel wall thickening during treatment.

The diagnostic procedure of choice is contrast-enhanced abdominal CT scan[10] with the lowest false-negative rate of 15%. Severe transmural inflammation, symmetrical circumferential bowel wall thickening of the caecum and pericaecal inflammation can all be accurately depicted.[11,12] High attenuation within the thickened colonic wall may represent haemorrhage. Inflammatory pericolonic stranding of mesenteric fat is common. In addition, CT readily demonstrates complications of NE, viz. pneumatosis coli, pneumoperitoneum, pericolonic collections and abscess formation. These complications may require urgent surgical management.[13]

Endoscopic procedures including colonoscopy and flexible sigmoidoscopy are rarely performed, as they are relatively contraindicated in the setting of neutropenia and thrombocytopenia.

Management is necessarily empiric because there is no diagnostic test that is entirely sensitive and specific for NE. Medical care includes:

- Admission to ICU with close monitoring, especially abdominal US examinations, full blood counts and biochemistry.
- Intravenous fluids, blood and platelet transfusions as required.
- Nil by mouth with nasogastric tube suction.
- Parenteral broad-spectrum antibiotics that cover enteric gram-negative and anaerobic organisms (including Clostridia). Some centres add metronidazole, if pseudomembranous colitis cannot be immediately excluded.[14]
- Postpone all chemotherapy (for leukaemia) until symptoms have completely resolved.[15]
- Discontinuation of medications, which may worsen the condition or confuse the clinical picture, e.g. drugs with anticholinergic side-effects, anti-diarrhoeal agents and narcotics.
- If the patient remains febrile after 72 hours of antibiotic therapy, fungal cultures should be taken and an antifungal agent[16] should be added.
- In addition, viral studies especially for cytomegalovirus (CMV) are advised as CMV colitis may closely mimic NE. Ganciclovir may then be instituted.
- Additional medical support with recombinant Granulocyte Colony Stimulating Factor has been advocated.[17]

Surgical intervention is clearly limited to specific indications, in light of the inherent risks of surgery in the pancytopenic, immunocompromised individual. Shamberger *et al* [13] proposed these indications for surgery:

- Persistent gastro-intestinal bleeding after resolution of neutropenia, thrombocy-

topenia or other clotting abnormality.
- Free intra-abdominal perforation.
- Unrelenting intra-abdominal sepsis ± septicaemia (suggested by clinical deterioration requiring vasopressors or large volumes of fluid).
- Clinical signs or radiological evidence for intra-abdominal abscess.

Surgical procedures performed include:
- Caecostomy and drainage
- Two-stage right hemi-colectomy or total colectomy
- Defunctioning of the colon with a loop ileostomy.

Extensive resection is deemed necessary as necrotic mucosa in the bowel may be concealed by relatively normal appearing serosal surface at operation.

NE carries a poor prognosis with an average mortality rate of 40 - 50%. Earlier detection with better imaging modalities and high index of suspicion has resulted in much lower mortality rates. Joint medical/surgical consultation is vital in the management of the NE patient.

An increase in the neutrophil count is an important indicator of recovery and prognosis.

It is essential that the physician consider the possibility of this potentially fatal condition in any neutropenic patient with the appropriate clinical presentation. Modern imaging modalities have changed NE from being diagnosed as a late-stage disease, best managed with immediate surgery and poor outcome, to a condition recognisable in its early stage and amenable to conservative, active medical management.

References

1. Cutrona AF, Blinkhorn RJ, Crass J, Spagnuolo PJ. Probable neutropenic enterocolitis in patients with AIDS. *Rev Infect Dis* 1991; **13:** 828-831.
2. Moir DH, Bale PM. Necropsy findings in childhood leukaemia, emphasising neutropenic enterocolitis and cerebral calcification. *Pathology* 1976; **8:** 247-258.
3. King A, Rampling A, Wight DG, Warren RE. Neutropenic enterocolitis due to Clostridium septicum infection. *J Clin Pathol* 1984; **37:** 335-343.
4. Newbold KM, Lord MG, Baglin TP. Role of clostridial organisms in neutropenic enterocolitis. *J Clin Pathol* 1987; **40:** 471.
5. Blenkinsopp WK, Dupont PA. Bacteria in necrotising enterocolitis. *Lancet* 1977; **2:** 617.
6. Gomez L, Martino R, Rolston KV. Neutropenic enterocolitis: Spectrum of the disease and comparison of definite and possible cases. *Clin Infect Dis* 1998; **27:** 695-699.
7. Katz JA, Wagner ML, Gresik MV, Mahoney DH, Fernbach DJ. Typhlitis: an 18-year experience and post-mortem review. *Cancer* 1990; **65:** 1041- 1047.
8. Mcnamara MJ, Chalmers AG, Morgan M, Smith SEW. Typhlitis in acute childhood leukaemia: radiological features. *Clin Radiol* 1986; **37:** 83-86.
9. Gootenberg JE, Abbondanzo SL. Rapid diagnosis of neutropenic enterocolitis (typhlitis) by ultrasonography. *American Journal of Paediatric Haematology/Oncology* 1987; **9:** 222.
10. Frick MP, Maile CW, Crass JR. Computed tomography of neutropenic colitis. *Am J Roentgenol* 1984; **143:** 763.
11. Vas WG, Seelig R, Mahanta B. Neutropenic colitis: evaluation with computed tomography. *Journal of Computed Tomography* 1988; **12:** 211-215.
12. Gayer G, Zissin R. Typhlitis: a computed tomography diagnosis. *Israel Medical Association Journal* 2002; **4:** 146-147.
13. Shamberger RC, Weinstein HJ, Delorey MJ, Levey RH. The medical and surgical management of typhlitis in children with acute nonlymphocytic (myelogenous) leukaemia. *Cancer* 1986; **57:** 603.
14. Wade DS, Nava HR, Douglass HO. Neutropenic enterocolitis. Clinical diagnosis and treatment. *Cancer* 1992; **69**(1): 17-23.
15. Keidan RD, Fanning J, Gattenby RA, Weese JL. Recurrent typhlitis: a disease resulting from aggressive chemotherapy. *Dis Colon Rectum* 1989; **32:** 206-209.
16. Marr KA. Empirical antifungal therapy - new options, new tradeoffs. *N Engl J Med* 2002; **346:** 278-280.
17. Hanada T, Ono I, Hirano C. Successful treatment of neutropenic enterocolitis with recombinant granulocyte colony stimulating factor in a child with acute lymphocytic leukaemia. *Eur J Paediatr* 1990; **149:** 811-812.