Neutropaenic enterocolitis: A Medical/Surgical Oncological Dilemma

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Abstract

Neutropaenic enterocolitis (NE) is a life-threatening condition characterised by an inflammation of the colon and/or the small bowel in the background of chemotherapy-induced neutropaenia. A 16-year-old girl with acute myeloblastic leukaemia (AML) developed fever, right-sided abdominal pain and tenderness with severe neutropaenia. Initial ultrasound findings suggested acute appendicitis for which she had surgery. She developed recurrent symptoms 3 weeks later. Abdominal computed tomography (CT) scan showed features of NE, but she succumbed to the illness. Another 17-year-old boy with AML developed fever and severe right-sided lower abdominal pain and tenderness, following completion of induction chemotherapy. He was neutropaenic and abdominal CT was typical of NE. He was managed nonoperatively and symptoms resolved. The diagnosis of NE can be a dilemma. A high index of suspicion is needed to avoid a misdiagnosis of acute appendicitis.

Keywords: Appendicitis, chemotherapy, neutropaenia, neutropaenic enterocolitis, typhlitis

Introduction

Neutropaenic enterocolitis (NE), also called typhlitis, is a life-threatening condition characterised by inflammation of the caecum, colon and or small bowel in the background of neutropaenia. It is a gastrointestinal complication of cancer chemotherapy seen in patients receiving agents with a high potential to cause mucosal damage.[1,2] Unfortunately, NE is commoner in children than in adults.[3,4]

Early recognition is essential not only for prompt treatment but also for the prevention of unnecessary operative intervention which can increase morbidity. We document two identical cases recently seen in our facility, highlighting our experience.

Case Reports

Case 1

She was a 16-year-old who was being managed for acute myeloblastic leukaemia (AML) (t 6,9 positive). She received induction chemotherapy (cyclophosphamide, oncovin, cytosine arabinoside and prednisolone) and developed fever (39°C) and abdominal pain afterwards. She had marked tenderness in the right iliac fossa (RIF). She had anaemia, neutropaenia (total white blood cell ['TWBC'] of 0.9 × 10³/uL with absolute neutrophil count ['ANC'] of 0.7 × 10³/uL) and thrombocytopaenia. Abdominal ultrasound showed sonographic features of appendicitis. She was placed on antibiotics, granulocyte-colony stimulating factors (G-CSFs) and had platelet and red cell transfusions. She, then, had an appendectomy and recovered well.

However, within 3 weeks’ post-surgery, symptoms recurred and repeat abdominal ultrasound done showed a thickened and inflamed caecal wall measuring 4.5–5 mm. The omentum also appeared thickened and echogenic. Abdominal computed tomography (CT) scan showed a thickened wall of the terminal ileum with marked surrounding mesenteric fat stranding. A diagnosis of NE was made. She had prolonged neutropaenia and her TWBC was 0.6 × 10³/uL with ANC of 0.5 × 10³/uL. She was managed conservatively with...
antibiotics, platelets, red cell transfusions and G-CSF but succumbed to the disease.

**Case 2**

The second case was a 17-year-old boy who was diagnosed with AML. He developed fever and severe abdominal pain 2 days following completion of induction chemotherapy (cytarabine/doxorubicin). Pain was localised to the RIF with marked tenderness.

His TWBC was $0.6 \times 10^9/uL$ and ANC was $0.3 \times 10^9/uL$. He also had thrombocytopenia. Abdominal CT scan showed pneumatosis intestinalis involving the caecum as well as widespread bowel wall thickening [Figure 1]. A definitive diagnosis of NE was made. He was managed conservatively with bowel rest, intravenous fluids and broad-spectrum antibiotics. He also had platelet transfusions and G-CSF. Symptoms resolved after 7 days, granulocyte count returned to normal and he was discharged.

**Discussion**

NE is a severe gastrointestinal complication seen in cancer patients. There is a paucity of global data on the incidence of NE, especially in children with malignancies. Some literature suggests an incidence between 0.4% and 6% in paediatric oncology patients. NE is more common in haematological malignancies than in solid malignancies. Similarly, it is more common in patients with AML compared to those with acute lymphoblastic leukaemia. Intensive chemotherapy and induction treatment often precede the onset of symptoms as seen in our patients. Chemotherapeutic agents implicated include those that disrupt mucosal integrity such as cytosine arabinoside (79%), etoposide (62%) and daunomycin (46%). Other implicated agents include doxorubicin, methotrexate, vincristine, irinotecan, taxanes and prednisone. Our patients developed symptoms following treatment with doxorubicin, cytosine arabinoside and prednisolone which are well implicated in the aetiology of NE.

The process appears to begin with mucosal disruption, secondary intramural infection and subsequent oedema, induration and bowel wall thickening. Reduced gut mucosal proliferation induced by chemotherapeutic agents may lead to the insufficient replacement of mucosa lost by natural desquamation and so mucosal integrity may be lost. Chemotherapeutic agents may in themselves alter mucosal integrity causing destruction of the mucosa. The pathologic process appears to have a predisposition for the terminal ileum, appendix and caecum, irrespective of the aetiologic factors. Ulceration and inflammation with necrosis of the affected region may progress to perforation and sepsicaemia. Various bacterial and/or fungal organisms, including Gram-positive cocci, Gram-negative bacilli, anaerobes and *Candida* spp., are often seen infiltrating the bowel wall. Polymicrobial infection is also frequent.

The setting of severe neutropaenia with ANC <500 cells/uL with typical symptoms should prompt consideration of NE. Regarding the frequency of symptoms, abdominal pain/tenderness is almost always present in 100% of cases; other symptoms sometimes seen are fever, vomiting and diarrhoea. These clinical features are not pathognomonic or specific for NE. It, thus, mimics other surgical differentials of an acute abdomen, especially acute appendicitis, making diagnosis difficult and challenging. Our patients both presented with features classical of acute appendicitis.

The characteristic abdominal ultrasound features of NE are echogenic, asymmetric thickening of the mucosal wall with transmural inflammatory reaction and areas of different echogenicity caused by oedema, necrosis and/or haemorrhages. A mural thickness of 5 mm or more is considered characteristic. Both of the patients had thickened walls of the caecum and one had a thickness of 5 mm. The imaging modality of choice, however, is the CT scan. It typically shows pneumatosis intestinalis, fat stranding, bowel wall thickening and ileus. Free intra-peritoneal air will be seen if bowel perforation has occurred. Serial CT scanning is sometimes employed in monitoring the response to treatment.

The definitive diagnosis of NE is histological. Bowel wall oedema, mucosal ulceration and necrosis with near absent or acute inflammatory infiltrates have been described as typical. This differentiates it from appendicitis where there is significant neutrophilic infiltration of the bowel wall. Histologic confirmation is possible for post-operative patients or at post-mortem; thus, this does not assist in the initial management.

Supportive care is the mainstay of management and consists of bowel rest with nasogastric decompression, adequate fluid replacement, G-CSF, platelet, red cell transfusions and broad-spectrum antibiotics. Surgical intervention is often indicated in cases with persistent gastrointestinal bleeding and intestinal perforation. The main prognostic factors are neutrophil recovery and overall time of neutropaenia. Reported mortality rates range from 2.2% to 48% but are
sometimes as high as 50%–60%, especially if not recognised early.[5,7]

**CONCLUSION**

The diagnosis of NE can be a dilemma. A high index of suspicion is needed to identify this condition in high-risk patients so as to reduce the associated morbidity and mortality when erroneously diagnosed and treated as acute appendicitis.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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