CASE REPORT

Concomitant typhlitis and *Clostridium difficile* colitis developed after first R-CHOP chemotherapy in a non-Hodgkin lymphoma patient

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SUMMARY

Typhlitis or neutropenic enterocolitis (NEC) is a life-threatening condition that occurs in neutropenic patients. Early recognition is crucial owing to high death rate. We present a case of a 54-year-old man, diagnosed with non-Hodgkin lymphoma who received a first cycle of rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin), oncovin (vincristine), prednisolone (R-CHOP) chemotherapy 10 days prior presenting. He developed fever, mucositis, watery diarrhoea and right lower quadrant pain with rebound tenderness. He also had neutropenia, with an absolute neutrophil count of zero. CT abdomen confirmed the diagnosis of typhlitis, demonstrating characteristic terminal ileum, caecal and right-sided colon involvement. Moreover, stool PCR was also positive for toxigenic *Clostridium difficile*. Therefore, the patient was diagnosed with concomitant typhlitis and *C difficile*-associated diarrhoea (CDAD). He was empirically treated with intravenous cefepime, intravenous metronidazole and oral vancomycin. His symptoms resolved in 10 days. This case illustrated a successful medical treatment of typhlitis in concomitance with CDAD.

BACKGROUND

Typhlitis or neutropenic enterocolitis (NEC) is a rare life-threatening condition in neutropenic patients. Although it is rarely found in adults, this condition should always be one of the differential diagnoses in neutropenic patients with acute right lower quadrant pain. Delay in diagnosis can lead to a fatal prognosis with a death rate of 21–48%. Surgical management should be prompted in complicated cases such as bowel perforation, intractable gastrointestinal bleeding or generalised peritonitis. The superimposed infection by bowel organisms including *Clostridium difficile* is also common. This case also demonstrated concomitant *C difficile* infection. However, current Infectious Diseases Society of America (IDSA) guidelines for *C difficile* infection are not applicable to patients with neutropenia because of depleted white blood cell (WBC) count. This case also emphasises the need for further prospective study to elucidate the management of *C difficile* infection among neutropenic patients.

CASE PRESENTATION

The patient is a 54-year-old man with a recent diagnosis of diffused large B-cell lymphoma and acute kidney injury requiring haemodialysis. He was given

a first cycle of rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin), oncovin (vincristine), prednisolone (R-CHOP) chemotherapy and pegfilgrastim injection 7 days prior to admission. He presented to Einstein Medical Center because of acute onset of fever and oral mucositis for 1 day. Initial physical examination did not reveal a definite source of infection. Complete blood count (CBC) demonstrated low WBC count of $0.2 \times 10^3/\mu\text{l}$ with an absolute neutrophil count (ANC) of zero. The patient was diagnosed with febrile neutropenia and was empirically treated with cefepime as per guideline recommendations. Blood and urine cultures were negative. On day 3 after admission, the patient developed acute right-lower quadrant abdominal pain, watery diarrhoea and vomiting, guarding and rebound tenderness. CT of the abdomen with contrast demonstrated distended terminal ileum, caecum, ascending colon and proximal transverse colon with marked circumferential wall thickening and hyperenhancing mucosa. No intraperitoneal free air was observed (figures 1 and 2). The patient's clinical manifestations and CT findings led to a diagnosis of typhlitis or neutropenic enterocolitis. Stool culture was negative for *Salmonella*, *Shigella* and *Campylobacter* species. However, stool PCR was positive for toxigenic *C difficile* with an absence of the NAP1/027/BI strain. Patient was diagnosed with both neutropenic enterocolitis and *C difficile*-associated diarrhoea (CDAD). Owing to these findings and a complicated course, the patient was continued on cefepime with the addition of intravenous

Figure 1 CT abdomen (cross section) demonstrated distended caecum with circumferential wall thickening and hyperenhancing mucosa.

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Figure 2 CT abdomen of this patient demonstrated distended terminal ileum, caecum, ascending colon and proximal transverse colon with marked circumferential wall thickening and hyperenhancing mucosa. In addition, there was oedema and inflammation with fluid tracking along the right paracolic gutter.

metronidazole and oral vancomycin for treatment of severe CDAD. On day 5 of fever, his ANC was still less than $0.5 \times 10^3/\mu\text{l}$, and micafungin was added for empiric antifungal coverage. He became afebrile and his symptoms resolved in 10 days with conservative treatment. The ANC increased to $1.9 \times 10^3/\mu\text{l}$ prior to discharge.

OUTCOME AND FOLLOW-UP

The patient became afebrile and his symptoms resolved in 10 days with conservative treatment. The ANC increased to $1.9 \times 10^3/\mu\text{l}$ prior to discharge. The patient came to cancer centre for follow-up appointment and was successfully given the second cycle of R-CHOP chemotherapy without complication.

DISCUSSION

Typhlitis or NEC is a rare life-threatening condition that occurs in neutropenic patients owing to compromised integrity of the bowel wall. This condition was initially found in patients with haematological malignancies after receiving induction chemotherapy. Typhlitis has also been reported in patients with solid tumours, including lung, breast, colorectal and ovarian cancers.^{1–5} The risk factors for typhlitis include recent chemotherapy within 2 weeks, the presence of mucositis, stem cell transplantation and prolonged duration of profound neutropenia.^{6–7} The typical clinical manifestations of typhlitis are right lower quadrant abdominal pain, watery or bloody diarrhoea, nausea, vomiting and fever. Symptoms commonly occur 10–14 days after chemotherapy at the nadir of the ANC. The differential diagnosis includes acute appendicitis, CDAD, ischaemic colitis and cytomegalovirus colitis. CT is the diagnostic modality of choice, as it can effectively establish the diagnosis and identify any complications. Barium enema and colonoscopy can be hazardous in this condition since they can precipitate caecal perforation. In typhlitis inflammation typically involves the caecum, terminal ileum and right-sided colon. It predominantly affects the caecum because of stasis of bowel content, high distensibility and limited blood supply.⁸ Common CT findings are colonic wall thickening (100%), mucosal enhancement (28%) and pneumatosis intestinalis (21%).⁹ In CDAD, the CT findings are characterised by a large degree of colonic wall thickening (mean wall thickness of 12 mm), wall nodularity (36%) and a pancolitis picture. Moreover, CDAD findings are almost always limited to the colon, whereas typhlitis can involve any bowel segment.⁹ In

this patient, there was terminal ileum involvement along with the presence of oral mucositis and profound neutropenia, suggesting the diagnosis of typhlitis. However, stool PCR was also positive for *C difficile* which is the confirmatory test for CDAD. Therefore, it was concluded that the patient had these two conditions causing acute abdominal pain and watery diarrhoea, and treatment for both conditions was instituted.

The management of typhlitis should be individualised. In the absence of diffuse peritonitis, bowel perforation or severe gastrointestinal bleeding, medical management with bowel rest, haemodynamic support, correction of cytopenia and broad spectrum antibiotics should be provided. Antibiotics should cover for Gram-positive bacteria, *C difficile* and Gram-negative bacteria including *Pseudomonas*. The recommended monotherapy is piperacillin-tazobactam or carbapenem. Alternatively, combination therapies are cefepime or ceftazidime plus metronidazole.^{7–10} Moreover fungal organisms, such as *Candida* species, can invade the bowel wall and lead to fungaemia. It is recommended that an antifungal agent should be added in neutropenic patients with protracted fever of more than 72 h as this was found to reduce the death rate in typhlitis cases.¹¹ In complicated typhlitis or failure of medical treatment, surgical management should be promptly performed with right hemicolectomy, ileostomy and secondary anastomosis.^{12–13} Early recognition of this disorder in neutropenic patients is very important as mortality rate of this condition can range between 21% and 48%.⁸ Regarding concomitant CDAD, current Infectious Diseases Society of America (IDSA) guidelines for antibiotics are not applicable to neutropenic patients owing to depleted number of WBC.¹⁴ In this case, we classified the patient as severe complicated CDAD by clinical symptoms and decided to give both intravenous metronidazole and oral vancomycin. A previous retrospective study demonstrated 90.9% response rate to oral metronidazole among neutropenic patients with CDAD.¹⁵ However, CDAD among neutropenia has been poorly investigated. Therefore, further large prospective studies are warranted to determine appropriate CDAD treatment in neutropenic patients.

To the best of our knowledge, this is the first case reporting of concomitant typhlitis and *C difficile* colitis in a postchemotherapeutic non-Hodgkin lymphoma patient.

Learning points

- ▶ Typhlitis or neutropenic enterocolitis is a rare life-threatening condition and should always be one of the differential diagnoses in acute right lower quadrant pain in neutropenic patients.
- ▶ CT of the abdomen is the diagnostic modality of choice in this condition, as well as the best test to demonstrate potential complications.
- ▶ Medical treatment with broad spectrum antibiotics, correction of neutropenia, bowel rest and haemodynamic support are the most important steps. If complications develop, surgical treatment should be prompted.

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Competing interests None.

Patient consent Obtained.

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