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Case Report

Neutropenic enterocolitis in a non-immunocompromised patient presenting with lower respiratory tract infection: a case report

Somesh Saha[1], Aakash Guha Roy[2], Shramana Sarkar[2], Shramana Deb[3], Ritwick Mondal[4]*

[1]Department of Critical Care Medicine, Bellevue Clinic, Kolkata, West Bengal, India
[2]Department of Internal Medicine, [4]Department of Rheumatology and Clinical Immunology, IPGMER and SSKM Hospital, Kolkata, West Bengal, India
[3]Department of Neuroscience, University of Calcutta, Kolkata, West Bengal, India

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***Correspondence:**
Dr. Ritwick Mondal,
E-mail: ritwickraw@gmail.com

ABSTRACT

Neutropenic enterocolitis (NEC) has been widely reported in adults with myelofibrotic disorders, solid malignant tumors, bone marrow transplantation as well as in myelotoxic chemotherapy. Here we reported a case of a 66-year-old non-diabetic, hypertensive female without any prior history of immunosuppression or any underlying malignancy or related chemotherapy; who presented with severe dyspnoea, low grade fever and cough. Followed by a course of effective conservative management and initial stabilization, on investigation her TLC was found to be abnormally low with severe neutropenia and a hyperinflammatory response induced myelosuppression with LRTI was suspected. Subsequently, subcutaneous G-CSF, broad spectrum antibiotics were initiated along with supportive management. She developed abdominal distension, diffused pain and tenderness with hypoactive bowel on the following day. After 3 days of G-CSF trial, neutrophil count started to increase along with her overall improvement. CECT was performed with positive findings of multiple colonic short segment involvement without any stricture, pericolic fat stranding and perforation; reflecting towards a resolving neutropenic enteropathy.

Keywords: Neutropenia, Enteropathy, G-CSF, Myelosuppression

INTRODUCTION

NEC pathogenesis is poorly understood and is definitely multifactorial.[1] Neutropenia is prominently a major contributing factor as it decelerates the immune response against colonic mucosal invasion by intestinal microbes. The interaction of pro-inflammatory mediators in the intestinal lumen with innate immunity in the submucosal tissues plays a crucial role in the genesis of the clinical syndrome, including sequence of activation of nuclear factor-kB (NF-kB), upregulation of pro-inflammatory cytokines, enhanced epithelial apoptosis, and mucosal permeability.[2] Some literatures have suggested the predictive role of markers such as C-reactive protein and interleukin-8 in this disease pathogenesis.[3] Initially NEC was amongst the most common finding in patients with underlying hematologic malignancies with ongoing anti-cancerous drugs, which produced high grade intestinal mucosal inflammation.[4] With the enhanced usage of aggressive chemotherapy for a variety of solid tumors, NEC is being reported with higher frequency in this subset of cancer patients.[5,6] Its association is also significant in patients with previous or ongoing immunosuppressive therapy in rheumatological disorders or in post-transplantation scenarios.[7,8] Bone marrow related disorders including myelofibrosis, myelodysplasia, aplastic crisis and long-standing marrow depression have also been found to be other contributing factors.[6,9-11]

CASE REPORT

A 66 years old female, who was a known hypertensive, presented with chief complaints of shortness of breath, low grade fever and dry cough for last 4 days with associated chest pain, palpitation and syncope but no bipedal edema. She was a previously diagnosed case of osteoarthritis and has a surgical history of subtotal thyroidectomy for Hashimoto's thyroiditis. Patient had no history of chemotherapy or intake of any immunosuppressive drugs. On examination, bilateral crept and wheeze were heard, BP was 100/60 mm Hg, pulse rate was 106 /min. An arterial blood gas analysis showed pH-7.427, pO_2-57.7 mmol/l, pCO_2-28.9 mmol/l, HCO3-20.8 mmol/l, base excess of-4.9 mmol/l. Chest X-ray showed multiple air space opacities in middle and lower lobes bilaterally, suggesting LRTI with bronchopneumonia. CRP levels were raised (27.33 mg/dl). Albumin level was found to be low (2.93 g/dl). Type 1 respiratory failure was diagnosed. The TLC was abnormally low (1900 cells/cu.mm) with neutrophils-20%, lymphocytes-68%. LFT, ECG and 2D-echo within normal limit. TROP-I and NT-pro-BNP were raised. Patient was non-reactive for anti-HIV 1 and 2, HBsAg and anti-HCV. Conservative management with BiPAP, nebulization with budesonide was initiated. Injection hydrocortisone was administered. Broad spectrum antibiotics piperacillin/tazobactam was started.

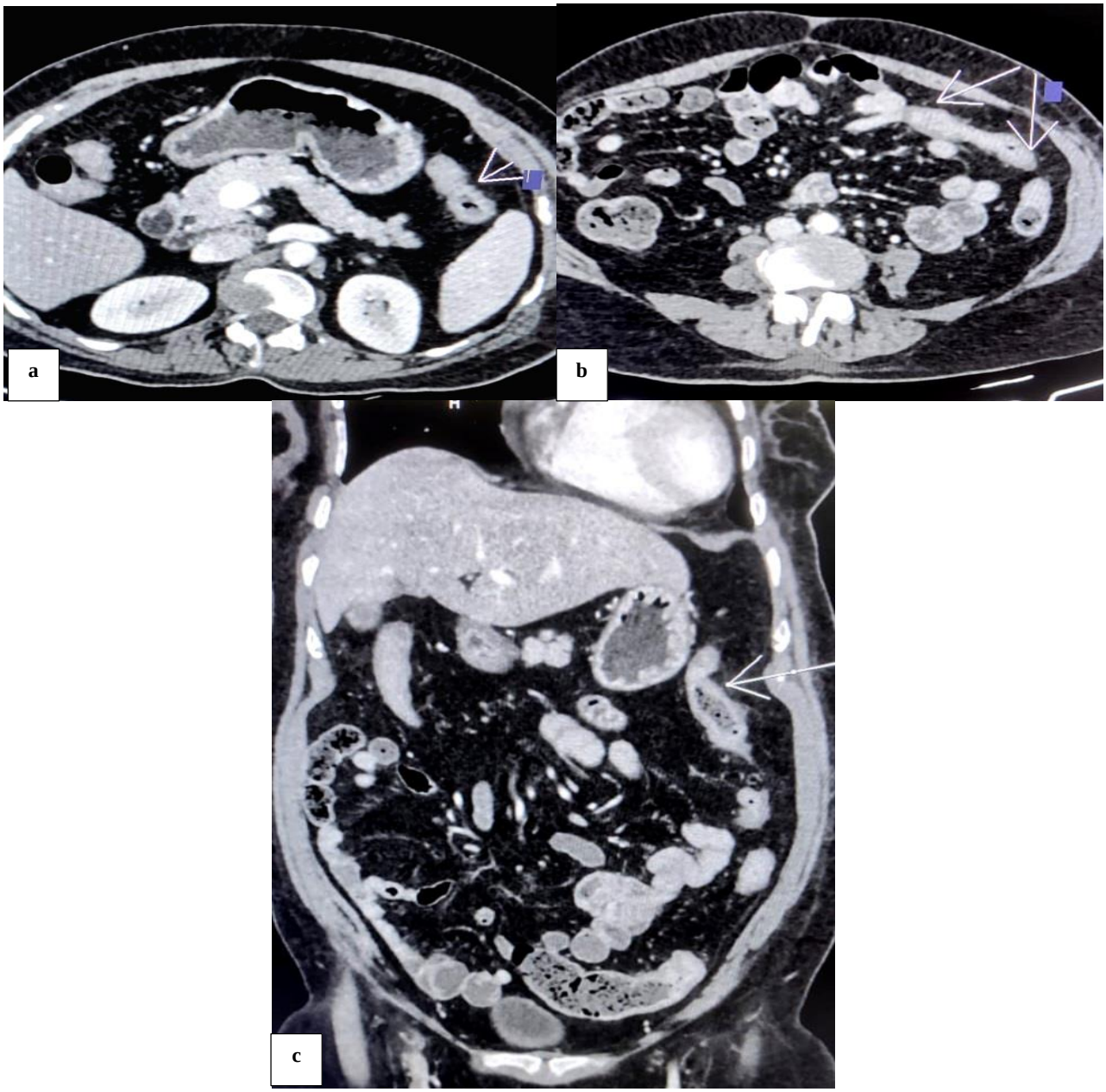

Figure 1: (a-c) 3-4 short segment area of colonic mucosal & wall thickening with mild hyperenhancement without any stricture formation, pericolic fat stranding or perforation (area of involvement has pointed in arrows).

On day 2, CBC report showed TLC-2400 cells/cu.mm with neutrophils-36%, lymhocytes-53%. PBS showed leucopenia and atypical lymphocytes. CRP was 17.68 mg/dl. The cause of neutropenia was probably a hyper-inflammatory response induced myelosuppression. Moreover the sample sent for *C. difficle* toxin assay and PCR came back negative. G-CSF injection was advised to be administered subcutaneously once daily for 3 days. Folate and methylcobalamine was added. Blood sent in BACTEC bottle for culture/sensitivity came out negative after 5 days of automated aerobic incubation.

On day 3, patient complained of nausea, abdominal discomfort and pain. O/E the abdomen was distended, there was diffuse tenderness with hypoactive bowel sounds. The patient was kept NPO. Mebeverine was given. CRP was raised (18.3 md/dl). USG (W/A) showed bowel wall thickening in distal transverse colon and recto-sigmoid junction along with splenomegaly. CECT could not be done at that moment due to her gradual declining condition. Injection drotaverine and syrup sucralfate were given. Piperacillin/tazobactam was replaced with meropenem.

A complete hemogram on subsequent investigation showed improvement with TLC-3200 cells/cu.mm; neutrophils-52%, lymphocytes-34%. PBS showed leucopenia along with immature granulocytes and few monocytoid cells. On day 4, pain abdomen was relatively less as reported by the patient and sluggish bowel sounds were heard. Based on the last hemogram values, G-CSF was withheld. Procalcitonin level was high (1.548 ng/ml). Repeat blood culture/sensitivity was sent which again came out as negative. Meropenem was continued. After 3 days of follow-up, she was much better with normal passage of stool and flatus without any evidence of abdominal pain and tenderness. She was afebrile and could tolerate soft diet. CBC was monitored regularly after withdrawing G-CSF which showed improvement in leukocyte count for three consecutive days as follows-TLC:4200⇒5900⇒6000 cells/cu.mm, with neutrophils: 40%⇒48%⇒62%, lymphocytes: 48%⇒43%⇒31%. Prior to discharge, CECT abdomen was done which showed 3-4 different short segment area of colonic mucosal and colonic wall thickening with mild hyper-enhancement in hepatic flexure, distal transverse colon, distal descending colon and recto sigmoid junction. No pericolic fat stranding or any perforation was identified. No stricture formation was noted; all reflecting towards resolving neutropenic enteropathy (Figure 1). She was discharged after 9 days from stopping G-CSF and the final CBC displayed a TLC of 5800 cells/cu.mm with neutrophils-60%, lymphocytes-34%.

Therapeutic intervention

On day 1, BiPAP was started and nebulization with ipratropium bromide, levosalbutamol, budesonide and formeterol was given. Injection hydrocortisone was given. Broad spectrum antibiotics were initiated. On day 2, injection G-CSF subcutaneously once daily for 3 days was started. On day 3, mebeverine was given for abdominal pain. When pain didn't subside injection drotaverine and syrup sucralfate were given. Injection meropenem IV was also added.

DISCUSSION

Association of NEC in a non-immunocompromised, non-malignant, without any history of chemotherapeutics and immunomodulators in a case like ours had not been reported so far. Association of autoimmune neutropenia with viral respiratory infection had been widely reported (mostly in children) due to either bone marrow suppression or to peripheral destruction. The agents commonly implicated include Epstein-Barr virus, cytomegalovirus, hepatitis A and B viruses, parvovirus, influenza-virus species and measles.[12-14] However, it was unusual in fungal infections unless the bone marrow was extensively involved, as occasionally seen in disseminated histoplasmosis.[15] Although none of the above case studies reported any underlying neutropenia related enteropathy; which made our finding even more exploratory.

Moreover *C. difficile* toxin assay and polymerase chain reaction (PCR) testing were also done in our case which came back negative excluding any possible association of *C. difficile* mediated neutropenic enteropathy. On this note, Kirkpatrick et al suggested specific patterns of bowel wall thickening that may be useful in differentiating between various bowel wall pathologies, suggesting that prominent bowel wall thickening of more than 12 mm with wall nodularity was significantly more common in *C. difficile* associated colitis.[16] Minimal wall thickening less than 5 mm with significant mucosal enhancement is more common in GVHD, whereas the thickness of the bowel wall in NEC was usually around 7 mm (4-15 mm). The imaging characteristics had been incorporated into the definition of NEC. Additionally, an important prognostic finding from Kirk et al suggested that bowel wall thickening of more than 10 mm can be associated with relatively severer disease as well as poorer outcomes. Patients with this degree of bowel wall thickening might benefit from early and aggressive therapeutic intervention.[16]

On the other hand, neutropenia may be an associated feature of collagen vascular diseases. About 50% of patients with systemic lupus erythematosus have white blood cell counts of less than 4.5×109 /l (<4,500 /µl), but severe neutropenia is unusual and should prompt a search for other causes.[17] Splenomegaly and neutropenia (Felty's syndrome) may develop in patients with rheumatoid arthritis.[18,19] Keeping these associations in mind a rheumatological screening was done for this patient which came back negative excluding any such correlation.

CONCLUSION

In conclusion we report here an isolated case of LRTI of viral origin which may have caused severe autoimmune neutropenia and subsequent enterocolitis. Lastly keeping in mind, this association and unlikely predisposition as being reflected by the case in absence of any known scenario reported so far, we must be more vigilant and should not exclude the possibility of neutropenic enteropathy in similar case scenarios.

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