TYPHLITIS - IS IT RARE OR ARE WE JUST MISSING IT?
A REPORT OF TWO CASES IN THE PHILIPPINE GENERAL HOSPITAL

GMM Silla, M.D., MLO Daez, M.D.
UP-Philippine General Hospital

SIGNIFICANCE: Typhlitis or Neutropenic enterocolitis (NE), a well recognized cause of morbidity and mortality in adult and pediatric oncology patients. [1,2,3]. With varying incidences at 0.8 to 26%, no randomized trials or high quality studies addressing aspects of the diagnosis and management. [4] Reporting of severe complications will help in unifying a general approach to this condition.

CLINICAL PRESENTATION: We report two cases of young male patients with hematologic malignancies who underwent induction chemotherapy, and later on presented with fever, abdominal pain and diarrhea. The first eventually had persistent hematochezia and shock while the second had a more prominent right lower quadrant pain mimicking appendicitis but without peritoneal signs.

MANAGEMENT: Computerized tomography both showed edematous bowel walls on the right colon. The first case had the classic ileocecal wall thickening while the second case had a more edematous and reactive appendix but involved the ileocecal area. Septic work-up was both done, with the first case had concomitant Clostridium difficile infection; he had severe gastrointestinal hemorrhage indicating surgical intervention, but patient and family were not amenable. Conservative medical management done but he succumbed to sepsis eventually; the second patient was able to recover without any surgical intervention and was sent home after completing antibiotics.

RECOMMENDATION: The treatment to patients with typhlitis is highly individualized, although a general approach can be suggested. In those presenting with milder cases medical management with bowel rest, nasogastric suction, fluid resuscitation, intravenous antibiotics, nutritional support can be done. Surgical intervention is indicated only in selected situations

KEYWORDS: case report, typhlitis, neutropenic enterocolitis, necrotizing enterocolitis, febrile neutropenia

Background

Typhlitis is a life-threatening, necrotizing enterocolitis occurring primarily in neutropenic [5] post induction chemotherapy patients, with highest risk in Acute Myelogenous Leukemias [1]. This should always be a differential in those with neutropenia and acute right lower quadrant pain, as delay in diagnosis has a mortality rate of 21-48%[6]. The reported incidences of neutropenic enterocolitis in adults in the literature vary considerably from 0.8% to 26%.

In the Philippines, there is no data on the profile and incidences of patients diagnosed with this condition and the clinical nature of its diagnosis pose difficulty to accurately describe the incidences.

Concomitant infections such as Clostridium difficile can add to its complications. The characteristic right lower quadrant pain can also be difficult to differentiate from appendicitis. Differentiation between the two diagnoses in neutropenic patients rely on imaging, as inflammation in appendicitis is limited to the appendix, while typhlitis primarily involves the cecum, ileocecal area, and ascending colon [7].

Because of increasing incidence [8] of this life-threatening disease entity, [9] early diagnosis and an appropriately therapeutic program are the essential factors to improve survival rate.

Case 1

A 35-year old male with Acute Myelogenous Leukemia was referred to the Gastrointestinal service for hematochezia. This was noted 2 weeks after he had induction chemotherapy with 3 + 7 protocol (3 days of Doxorubicin 50mg + 250cc D5W x1h + 7 days of Cytarabine 250mg in 500cc PNSS x20h). He initially presented with minimal hematochezia and vague abdominal pain which later on localized to the right hemiabdomen, persistent fever. Patient had elevated white blood cell counts (WBC), with Absolute Neutrophil count of zero and platelet ranging 6-10x10^9/L. Supportive transfusion of platelet concentrate and Packed RBC was done. The hematochezia was initially attributed to the thrombocytopenia. However, despite the platelet levels going up, the patient still had persistent lower gastrointestinal bleeding. Neutropenic enterocolitis and Clostridium difficile (C. difficile) infection were both considered since he already had prior antibiotic (Piperacillin-Tazobactam) use for a dento-alveolar abscess. An abdominal CT scan (**Figure 1**) done revealed ileocecal wall thickening consistent with Neutropenic enterocolitis. Surgical consult done, however the patient and family did not

accept the risks of OR hence did not consent. Medical management started with parenteral nutrition, NGT decompression, nothing per orem Empiric IV antibiotics (Meropenem and Vancomycin) to cover for enteric pathogens, especially C. difficile were started. Patient however further deteriorated despite adequate antibiotics and supportive transfusions without recovery of his neutrophil counts. Family signed advance directives and eventually the patient succumbed to sepsis.

Case 2

This is a case of a 23-year old, male, diagnosed with B Cell Acute Lymphoblastic Leukemia, refractory to treatment hence had re-induction chemotherapy with augmented Berlin-Frankfurt-Munster protocol then hyper CVAD + Rituximab 6 months prior. He presented with sudden onset fever, diarrhea and abdominal pain. During his present admission, he is on palliative chemotherapy with Prednisone and 6-mercaptopurine. On assessment, there was right lower quadrant abdominal tenderness, abdominal distention but had no peritoneal signs, no Rovsing's or Iliopsoas' sign. His CBC showed elevated white counts (WBC 20.4x10^9/L), with 0.77 blasts, absolute neutrophil count (ANC) of 627/mm^3; thrombocytopenia (Platelet 14x10^9/L) and anemia (Hemoglobin 92 g/L). Abdominal ultrasound showed an inflamed tubular structure 2.7x4cm where a blind ended structure without fluid collection was seen. Surgical consult was sought with consideration of Acute Appendicitis. A CT scan was also done **(Figure 2)** which showed minimally enhancing and edematous bowels in the right lower quadrant representing thickened cecal walls or matted terminal ileum which may be due to leukemic infiltration or an inflammatory process, reactive appendiceal inflammation was also noted. The consideration at this point was typhlitis, and was managed conservatively by placing patient on absolute NPO, NGT decompression and was started on parenteral nutrition. Intravenous antibiotics (Meropenem) was completed for 14 days. Blood cultures done showed no growth of organism. He had concomitant herpes labialis hence was also on Acyclovir for 7 days. Symptom resolution was noted and diet progressed until he was able to tolerate solid food. There was improvement of ANC=1,224/mm^3 and platelets after supportive transfusions and G-CSF injections. On repeat imaging after 1 week of conservative medical management., there was resolution of bowel wall edema and appendix looked normal. Patient was discharged improved and is now back on his palliative chemotherapy regimen.

Discussion

Neutropenic enterocolitis (NE), also known as ileocecal syndrome, cecitis, necrotizing enterocolitis or typhlitis, is an inflammatory process involving segments of terminal ileum, cecum and ascending colon that could progress to ulceration, necrosis and perforation. This syndrome is characterized by fever and abdominal pain in a neutropenic patient. More common in adults with hematologic malignancies such as leukemia, lymphoma, multiple myeloma, aplastic anemia, and myelodysplastic syndromes, as well as other immunosuppressive causes such as AIDS, therapy for solid tumors, and organ transplant [10], and is now well recognized as an important cause of morbidity and mortality in this population. However, despite this condition being relatively frequent, there are no randomized trials or high quality cohort studies addressing the aspects of diagnosis and management [4]. The reported incidences of neutropenic enterocolitis in adults in the literature vary considerably from 0.8% to 26% [11,12]. The incidence per episode of neutropenia was 7.4% in ALL and 28.5% in AML [13}. One systematic review published in 2005 suggested a pooled incidence of 5.6% in hospitalized adults with hematological malignancies, chemotherapy for solid tumors, and aplastic anemia [12]. The reported mortality also varies with rates as high as 50% [13]. Variability of its incidence reflect the diversity in its definitions, diagnosis, such that some studies use – cinical signs only, cinical signs plus radiology, or histopathologic confirmation [11].

Neutropenia is the sine qua non condition for typhlitis and other risk factors are not very clear. In a study among children with hema-oncologic malignancies, variables associated with typhlitis were, age > 16 yrs and some drug combinations that include – idarubicin, cyclophosphamide, methotrexate and carboplatin. [15] In another study, an increased incidence of gastrointestinal complications, including typhlitis, was observed in 35 patients with AML who received a combination of three drugs (idarubicin, etoposide and cytarabine) in the induction regimen [4].

The exact pathogenesis of NE is not completely understood but typically involves intestinal damage, microbial invasion, ulceration and bowel necrosis. Most common site of involvement/s are the terminal ileum and cecum. Infiltration by neoplastic cells may also cause additional risk and result to ulceration and perforation. [14] Chemotherapeutic agents

lead to mucosal injury and predispose to bowel distention and necrosis. Acute myelogenous leukemia presenting as typhlitis even before chemotherapy is said to be partly because of intestinal leukemic infiltrates, which is another pathogenic factor. Its predilection to the cecum may be explained by its distensibility and limited blood supply (Davila) [15]. Microbial invasion also plays an important role in this condition's pathogenesis, commonly Gram negative bacilli, Gram positive cocci, Enterococci, Fungi and Virus. Bacterial translocation and bacteremia is also frequently seen in these patients. [16] One systematic review of published case studies found a significantly lower mortality rate in patients receiving antifungal agents for the treatment of NE. [17]

Patient's with absolute neutrophil counts less than 500u/L are at an increased risk. Symptoms appear within two weeks after completion of chemotherapy and usually during low WBC levels, commonly described are right lower quadrant abdominal pain, fever, diarrhea associated with nausea, vomiting, abdominal distention. Gastrointestinal bleeding is less common but may be severe enough to cause hemodynamic instability; necrosis and perforation may present with peritoneal signs, shock or rapid deterioration. Wade *et al,* reported that the 22 patients in their study had been leukopenic for > 1 wk before the onset of abdominal pain and that all patients had severe neutropenia [18]. Leukocyte count recovery after the onset of NE seems to be associated with survival [19].

Neutropenic enterocolitis is diagnosed by detection of characteristic contrast-enhanced abdominal computed tomography (CT) findings. According to a study by Vogel in 2010, those patients with a longer duration of neutropenia until date of CT scan had more generalized bowel involvement. The other CT findings include, intramural gas (pneumatosis intestinalis), thickened bowel demonstrating three layers that comprise an inner and outer layer of high attenuation (target sign), multiple tubular, tortuous opacities on the mesenteric side of the ileum that are aligned like the teeth of a comb or comb sign. CT scan findings in correlation to patient's clinical features are used as the basis for diagnosis in susceptible patients. Other imaging tests such as abdominal plain films will show distended bowels or free air near the diaphragm supporting a local perforation or pneumoperitoneum. Ultrasound will likely give equivocal results and may show an enlarged cecum with characteristic echogenic thickening of mucosa, with or without fluid collection.

Antimicrobial therapy, targeting local enteric pathogens should be instituted early once this

condition is recognized. No trials have been performed evaluating efficacy of different regimens. Coverage for Pseudomonas aeruginosa, Escherichia coli, other enteric gram-negative bacilli and anaerobes should be kept in mind. Fungal coverage must be started once fever persisted after more than 72hours of broad spectrum antibiotics. Local epidemiology and the hospital's antibiogram and resistance patterns should be considered in choosing a regimen. No studies on duration that is most effective for this condition yet, however, it can be maintained for 14 days following recovery from neutropenia. Supportive therapy including bowel rest, nasogastric suction, IV fluids, nutritional support. Recombinant G-CSF has been used to hasten recovery.

Surgery is reserved for those patients with perforations, severe hemorrhage despite correction of cytopenias, and clinical worsening during intensive monitoring. It is generally avoided due to high risk of infection, poor wound healing and bleeding due to the concomitant primary condition of patients. However, most patients that had surgical indications had better survival than those who were managed medically for fear if surgical complications. A study by Shamberger in 1986 used four criteria for surgical intervention (1) persistent gastrointestinal bleeding after resolution of neutropenia and thrombocytopenia and correction of clotting abnormalities; (2) evidence of free intraperitoneal perforation; (3) clinical deterioration requiring support with vasopressors, or large volumes of fluid, suggesting uncontrolled sepsis; and (4) development of symptoms of an intra-abdominal process, in the absence of neutropenia, which would normally require surgery. Subsequent chemotherapy for these patients would still put them at risk for another episode of typhlitis.

Conclusion

Typhlitis is a life-threatening condition that occurs in neutropenic patients. Given the widespread, aggressive use of systemic chemotherapy, patients are at risk for this potentially lethal complication and that timely diagnosis and recognition of this condition is needed to somehow curtail its high mortality rate.

Reference

1. Urbach DR, Rotstein OD. Typhlitis. Can J Surg 1999;42(6):415-9.

2. Sloas MM, Flynn PM, Kaste SC, et al. Typhlitis in children with cancer: a 30-year experience. Clin Infect Dis 1993;17(3):484-90.

3. Katz JA, Wagner ML, Gresik MV, et al. Typhlitis. An 18-year experience and postmortem review. Cancer 1990;65(4):1041-7

4. Portugal, Marcio Nucci (2017): Typhlitis (neutropenic enterocolitis) in patients with acute leukemia: a review, Expert Review of Hematology, DOI: 10.1080/17474086.2017.1280389

5. Rolston KV, Bodey GP, Safdar A. Polymicrobial infection in patients with cancer: an underappreciated and underreported entity.; Clin Infect Dis. 2007;45(2):228. ; The University of Texas, M.D. Anderson Cancer Center, Houston, TX 77030, USA

6. Junpaparp P, Buppajarntham S, Madueno FV, et al. BMJ Case Rep Published online: doi:10.1136/bcr-2013- 008894

7. McCarville MB, Thompson J, Li C et al (2004) Significance of appendiceal thickening in association with typhlitis in pediatric oncology patients. Pediatr Radiol 34:245–249

8. Sloas MM, Flynn PM, Kaste SC, et al: Typhlitis in children with cancer: a 30-year experience. Clin Infect Dis 1993;17:484-490

9. Wade DS, Nava HR, Douglass Jr HO. Neutropenic enterocolitis. Clinical diagnosis and treatment. *Cancer* 1992; **69**: 17-23 [DOI: 10.1002/1097-0142(19920101)69:1<17::AID-CNCR2820690106>3.0.CO;2-X]

10. Gorschlüter M, Mey U, Strehl J, Ziske C, Schepke M, Schmidt-Wolf IG, Sauerbruch T, Glasmacher A. Neutropenic enterocolitis in adults: systematic analysis of evidence quality. *Eur J Haematol* 2005; **75**: 1-13 [PMID: 15946304 DOI: 10.1111/ j.1600-0609.2005.00442.x]

11. Salazar R, Sola C, Maroto P, et al. Infectious compli- cations in 126 patients treated with high-dose chemo- therapy and autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 1999;23:27–33.

12. Jones GT, Abramson N. Gastrointestinal necrosis in acute leukemia: a complication of induction therapy. Cancer Invest 1983;1:315–320.

13. Altinel E, Yarali N, Isik P, Bay A, Kara A, Tunc B. Typhlitis in acute childhood leukemia. Med Princ Pract 2012;21(1):36-39.

14. El-Matary W, Soleimani M, Spady D, Belletrutti M. Typhlitis in children with malignancy: a single center experience. J Pediatr Hematol Oncol 2011;33(3):e98- 100.

15. El-Matary W, Soleimani M, Spady D, Belletrutti M. Typhlitis in children with malignancy: a single center experience. J Pediatr Hematol Oncol 2011;33(3):e98- 100.

16. **Davila ML**. Neutropenic enterocolitis. *Curr Opin Gastroen- terol* 2006; **22**: 44-47 [PMID: 16319675 DOI: 10.1007/ s11938-006-0043-2]

17. **Ettinghausen SE**. Collagenous colitis, eosinophilic colitis, and neutropenic colitis. *Surg Clin North Am* 1993; **73**: 993-1016 [PMID: 8378836 DOI: 10.1016/S0039-6109(16)46137-2]

18. Vogel, Monika. Department of Diagnostic and Interventional Radiology. Eberhard-Karls-Universitat Hoppe-Seyler-Str. 3 . CT features of Neutropenic Enterocolitis in Adult Patients with Hematologuc Disease undergoing chemotherapy

Appendix

a. CT scan of case 1

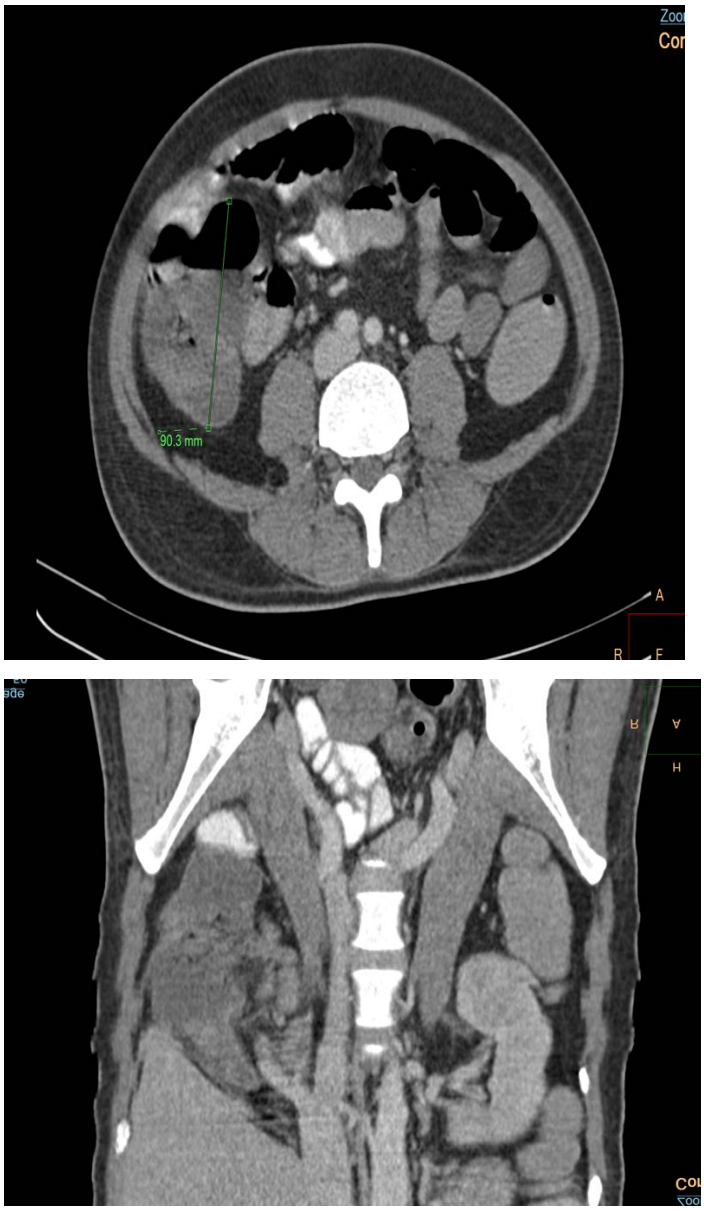

Figure 1. Abdominal CT scan (cross-section and frontal) showing distended cecum and circumferential wall thickening

b. CT scan Case 2 - At the onset of symptoms

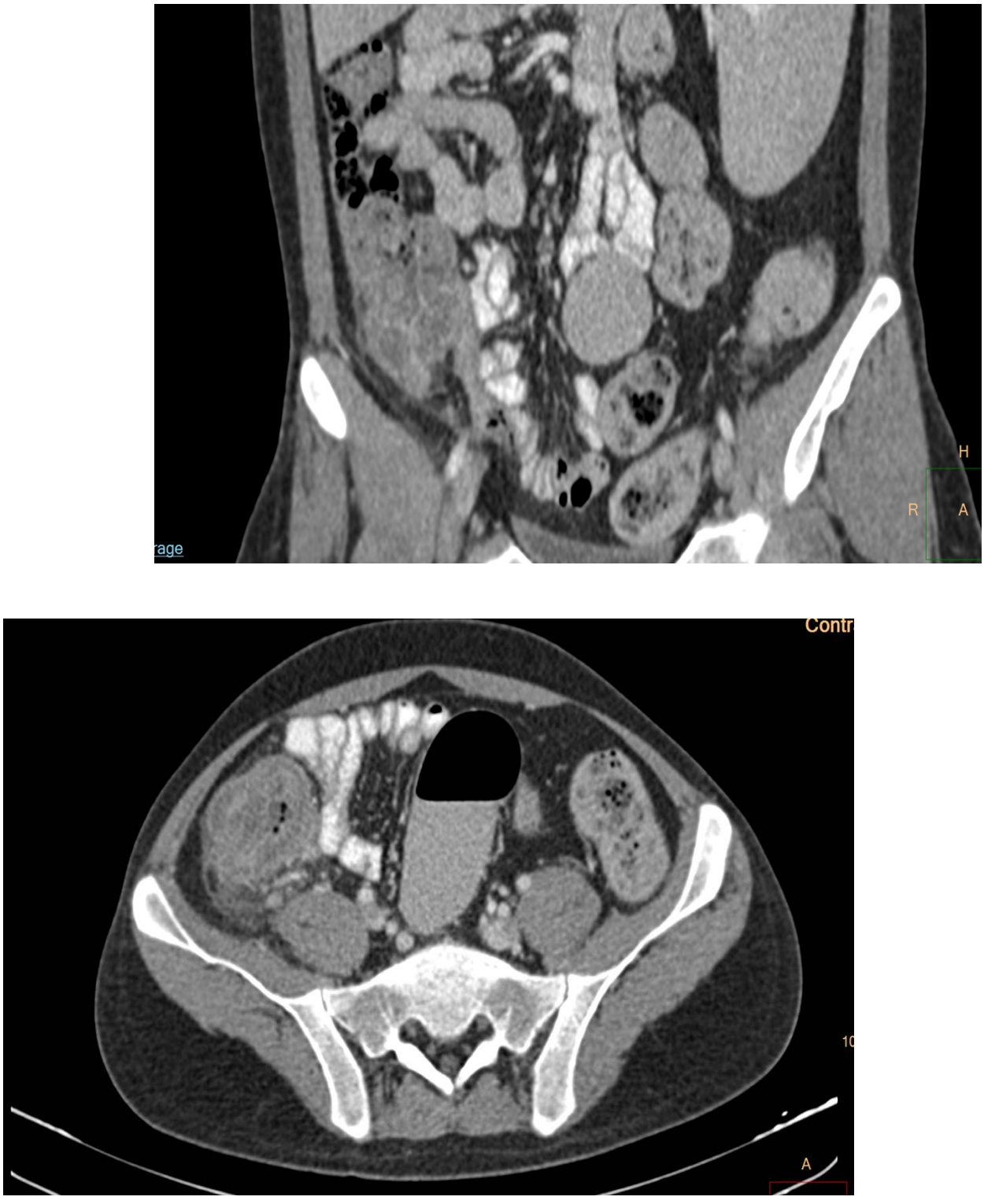

Figure 2. Abdominal CT scan (frontal and cross section) showing the edematous cecum and appendix

c. CT scan post medical management

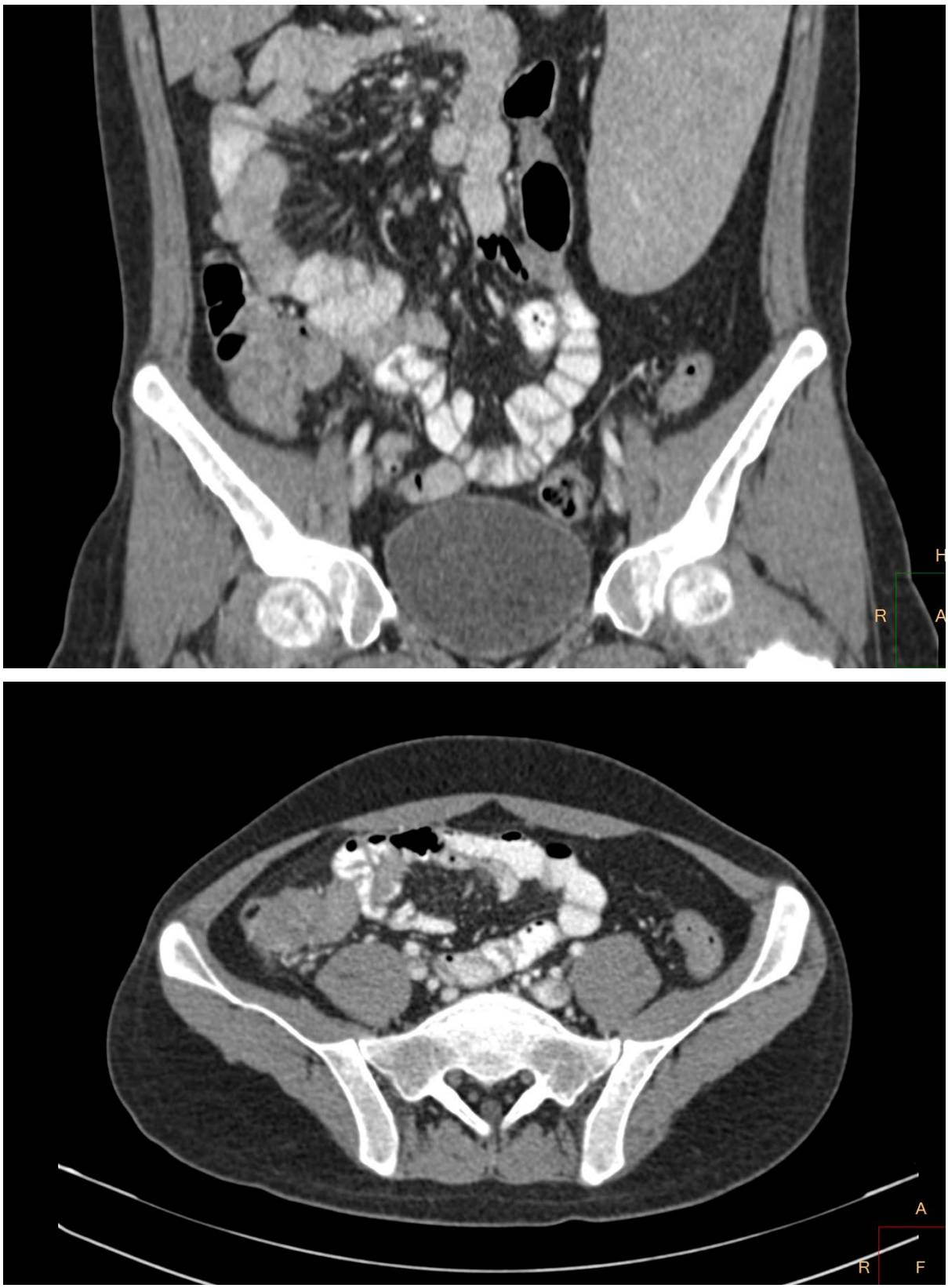

Figure 3. Abd CT scan (Frontal and cross section) taken 1 week after conservative medical management showing resolution of bowel wall edema and distention