

Abdominal Pain in an Immunocompromised Patient: A Case Report of Typhlitis

Alexander B. Norinsky¹, Majid Kianmajd², Anthony DiPasquale¹, Andrew Caravello¹

¹D.O. Department of Emergency Medicine, Rowan University SOM Kennedy University Hospital, Stratford, NJ, USA.

²D.O. Department of Surgery, Rowan University SOM Kennedy University Hospital, Stratford, NJ, USA.

Corresponding Author: Alexander B. Norinsky, D.O. Department of Emergency Medicine, Rowan University SOM Kennedy University Hospital, Stratford, NJ, USA, **Tel:** 646-241-5695; **Email:** alexnorinsky@gmail.com

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KEYWORDS

Typhlitis; Neutropenic Enterocolitis; Acute Abdomen; Immunocompromised; Chemotherapy.

CASE PRESENTATION

Here we present the case of a 52-year-old female with a known past medical history of non-resectable mixed adenocarcinoma and small-cell lung cancer with metastatic disease to the brain who presented to the emergency department with complaints of sharp, stabbing abdominal pain predominantly in the right lower quadrant and suprapubic region, progressively worsening since earlier that evening. She also experienced several episodes of nonbloody nonbilious vomiting as well as nonbloody nonmelenic mucousy diarrhea. Remaining pertinent medical and surgical histories include seizure disorder, a left-sided thoracotomy with an aborted lung resection, resection of a metastatic lesion in the brain, and placement of a right-sided subclavian port. Of note, she was recently admitted to our hospital for pneumonia and bilateral lower extremity cellulitis. She reported no drug or food allergies, and social history is negative for tobacco, alcohol, or illicit drug abuse (she quit smoking about 2 years ago). She had been on chemotherapy and radiation therapy for the primary lung cancer, however was forced to stop the treatments about 9 months ago secondary to development of pancytopenia and myelodysplastic syndrome.

On physical examination, she was nontoxic but uncomfortable appearing; initial vital signs are as follows: blood pressure 112/52 mmHg, pulse rate 128 beats/minute, breathing 22 respirations/minute, an oral temperature of 98.1 degrees, and saturating 98% on ambient air. She was cachectic (body-

mass index of 20.6), with bitemporal wasting and dry mucous membranes. Cardiopulmonary exam is significant for tachypnea and tachycardia. Her abdomen was soft, nondistended, with severe tenderness to minimal palpation predominantly in the right lower quadrant but without any peritoneal signs, and normal bowel sounds. The rectal examination was deferred by the patient. The remaining physical examination was unremarkable, including resolved lower extremity cellulitis.

Given her significant presentation and past medical history, an extensive work-up was undertaken specifically focused on inflammatory markers, cultures, and imaging of the abdomen. Pertinent findings were as follows: leukopenia (0.5/uL; reference range: 3.7-10.5), neutropenia (22.8%; reference range 37.8-85.8%) with an absolute neutrophil count of 100/uL, absolute lymphocytes count of 100/uL (reference range 800-3,500/uL), and absolute monocyte count of 200/uL (reference range: 300-900/uL), thrombocytopenia (57,000/uL, reference range: 150,000-400,000), a lactic acidosis (2.3mmol/L, reference range: < 2), and c-reactive protein 44.1mg/dL (reference range < 0.5). Her urinalysis, electrolytes, liver function (except for a mild indirect hyperbilirubinemia), coagulation panel, lipase and cardiac biomarkers were within normal limits.

Given the patient's recent hospitalization, course of antibiotics, and presentation with abdominal pain and diarrhea, metronidazole was empirically initiated with a high suspicion for *Clostridium difficile*.

Computed axial tomography of the abdomen and pelvis (unenhanced given her poor baseline creatinine clearance and inability to tolerate oral intake; images 1 and 2) revealed a fairly significant amount of thickening of the terminal ileum, cecum and proximal ascending colon. There was marked surrounding stranding and a mild amount of pelvic free fluid (simple density), tracking presumably from the right lower quadrant. The appendix was normal in appearance, without evidence of pneumatosis or free air.

Cefepime was added, and after consultation with the Infectious Disease service a weight-based dose of vancomycin was started. The patient's hemodynamic parameters remained stable throughout her stay in the emergency department (except for persistent tachycardia; she never became hypotensive or required pressor support). Given her significant presentation, the General Surgery service was consulted emergently as well, and she was placed under the care of the Critical Care service for continued management.

DISCUSSION

Typhlitis, also referred to as neutropenic enterocolitis, is an uncommonly encountered but nonetheless dangerous condition wherein there is significant inflammation of the cecum, ascending colon and ileum. It is encountered most commonly in the immunocompromised population, specifically in those with a depressed myelogenous cell line. Originally described in the pediatric oncologic demographic (specifically blood cancers), typhlitis has been more recently reported in adult cancer patients as well as those with solid malignant tumors and myeloproliferative disease, those having received certain chemotherapeutic agents, and other immunosuppressed states (including AIDS).

The exact incidence and prevalence of typhlitis is unknown as there is as yet no standardized definition, likely due to a limited understanding of the underlying mechanism. Prevailing theories include direct cytotoxic damage of chemotherapy on a particularly sensitive area of the gastrointestinal tract with limited ability for cellular replication (thus, threatening mucosal integrity), localized microbial infection, and/or secondary to the cecum's limited vasculature and compliance making it particularly prone to insult. Furthermore, the recent use of antibiotics may lead to altered native gastrointestinal flora, potentially leading to an overgrowth of undesirable bacteria and fungi, adding to the enhanced inflammatory response. This may have been specifically relevant in our case given her recent admission and course of antibiotics.

The most common chemotherapeutic agents implicated are cytosine arabinoside, etoposide, and daunomycin; although many others, including prednisone, have been associated.

Based on the most recent data, the incidence in the adult population is 5.3% although this is likely an underestimation (ranging from less than 1% to as much as 26%; more data is available of the pediatric population, with numbers quoted as high as one in three-to-four). The bulk of this data is derived from patients actively undergoing intensive chemotherapy, which is different from our case report wherein the last regimen of chemotherapy was undertaken many months prior to this presentation. In addition to a lacking consensus definition, another potential reason for the perceived underestimation is the ever-increasing amount and variety of chemotherapeutic agents currently being utilized, which may lead to more severe episodes of neutropenia.

The most commonly cited diagnostic criteria recommends establishing the presence of fever, abdominal pain, and thickening of the bowel wall beyond 4 mm via CT or ultrasonography [1-3]. Although somewhat nonspecific, when used within the appropriate demographic this can aid the practitioner in quickly risk-stratifying and intervening in this particularly sick population.

Patients usually present with nonspecific complaints and examine nonspecifically: diffuse severe abdominal pain and tenderness which may localize to the right lower quadrant, peritonitis, fevers, vomiting and diarrhea. In the context of these significant but nonspecific history and physical examination features, it is important to consider other more common diagnoses, including appendicitis, intussusception, or obstruction. Nonetheless, in the context of a compromised immune system, neutropenic enterocolitis must remain within the practitioner's purview [4]. Other disease processes to consider in the immunosuppressed include opportunistic infections, pseudomembranous colitis, and mucositis. If undergoing chemotherapy, symptoms usually begin after about 10 to 14 days.

Computed axial tomography (preferably enhanced with oral and intravenous contrast) is the imaging study of choice. Relevant findings include circumferential wall thickening of the cecum as well as the surrounding colon (found in 100% of patients), peri-cecal inflammation and stranding (51%), ascites (43%), bowel dilatation (38%), mucosal enhancement (28%), and pneumatosis intestinalis (21%). CT also helps assess for other potential diagnoses and complications of neutropenic enterocolitis. Abdominal ultrasonography may also be considered, and is an important modality for trending disease and treatment progress. Several studies have found a correlation between the degree of bowel wall thickening and prognosis, as well as estimation of illness duration. Barium enemas is another option, although generally nonspecific with high miss-rates. In general, endoscopy should be avoided due to the risk

of perforation from the inflammatory changes to the already-friable intestine, bleeding from concomitant thrombocytopenia, and prevent colonizing gut organisms in the already-immunocompromised patient. Plain films are of little value and generally nonspecific.

Typhlitis is life-threatening and demands immediate recognition and intervention. Mortality rates are very poor, averaging about 50% (100% if left untreated). Management remains controversial and treatment protocols vary based on each individual case; there is no standardized approach. Conservative medical therapy includes intravenous fluid resuscitation, nil per os with nasogastric tube decompression, broad-spectrum antimicrobial agents (with coverage for gram-negative and anaerobic species). Proposed antibiotic regimens include monotherapy with piperacillin-tazobactam or a carbapenem, or dual therapy with an antipseudomonal beta-lactam plus an aminoglycoside or metronidazole with cefepime or ceftazidime. The practitioner should consider coverage of fungi as well, especially if the patient does not respond to antibiotic therapy. Recombinant granulocyte colony-stimulating factor (G-CSF) may be considered to normalize neutrophil counts (one report found a higher mortality rate when leukocyte counts weren't normalized to above 1000 cells/cu mm). Surgical intervention should be considered in the context of peritonitis, perforation, obstruction, underlying abscess formation or uncontrolled sepsis, persistent gastrointestinal bleeding after resolution of neutropenia and thrombocytopenia, or a worsening state refractory to conservative medical therapy. The procedure of choice is a right hemicolectomy with ileostomy and mucous fistula; alternatives include a cecostomy or total colectomy based on the extent of mucosal necrosis and severity of disease.

There have been no randomized trials to compare medical versus surgical management. One study demonstrated that among 329 cases, 69% were managed conservatively and 31% underwent surgical intervention. There was a mortality rate of 31% in medical group (versus 23% in surgical group). However, the data may represent a more debilitated population in the medical subset too unfit for surgery (thus, by default falling into the medical management category), limiting generalizability [5, 6]. A general algorithm is proposed in Urbach and Rotstein's report, however, again, an individualized approach remains the standard approach.

As mentioned earlier in our case, definitive disposition of these patients should be the closely monitored setting of the intensive care unit, with guidance from multiple disciplines including the surgical, oncology, and infectious disease services.

Our case is interesting in that it represents a fairly standard

presentation of this uncommon life-threatening illness. Although generally described in patient with cancer receiving chemotherapy, this case serves as a good reminder that the disease must be on the list of differential diagnoses in any neutropenic patient with abdominal pain (our patient had her last course of chemotherapy about nine months prior to this presentation). This is also the reason why this manuscript was entitled, nonspecifically, "abdominal pain in an immunocompromised patient," serving as a reminder that it is not limited to those undergoing active chemotherapy.

CONCLUSION

Our patient was discharged on hospital day #10. She developed *Clostridium* bacteremia (specifically, *Clostridium septicum*), for which she was treated with a course of oral vancomycin. (Not explored at length in the body of the manuscript, but it is interesting to note patients with this disease are prone to developing *Clostridium* species infections.) She received multiple units of blood products, and started on metoprolol for new-onset atrial fibrillation. In summary, multiple specialists were closely involved with her care, including the intensivists, cardiology, gastroenterology, infectious disease, and general surgery. Palliative care medicine was consulted, however the patient was very reluctant, stating she wanted to be home with her family and would consider home care with palliative medicine there.

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