



## Unusual Presentation of Acute Typhlitis with Necrotizing Granulomatous Lymphadenitis in a Healthy Teenager

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### Abstract

Typhlitis is a rare necrotizing inflammation of the cecum generally associated with immunosuppression. We report the unusual case of an otherwise healthy teenager diagnosed with acute typhlitis and found to have necrotizing granulomatous lymphadenitis on multidisciplinary workup. A 17-year-old female was admitted for 1 month of worsening lower abdominal pain, nausea, vomiting, diarrhea, and weight loss. She was recently admitted at an outside hospital for acute typhlitis diagnosed on computerized tomography (CT) which improved with empiric antibiotics. Repeat CT on admission demonstrated marked wall inflammation at the ileocecal valve with bilateral renal abnormalities and right lower quadrant (RLQ) adenopathy, raising concern for lymphoma. Pediatric gastroenterology, hematology-oncology, and surgery were consulted. Colonoscopy demonstrated a hard mass arising circumferentially from the appendiceal orifice into the cecum; snare or resection was deferred due to concern for perforation. Non-specific changes were shown on mass surface and surrounding intestinal mucosa biopsies. Laparoscopic surgical biopsy of the peri-appendiceal lymph node demonstrated necrotizing granulomas without signs of an oncologic process. Testing for bacterial and fungal etiologies were sent. After extensive discussion with the family and multidisciplinary team, the decision was made to repeat outpatient imaging after discharge to determine a management plan, including possible surgical resection of the ileocecal valve. Follow-up CT demonstrated an improved inflammatory process consistent with typhlitis and no evidence of mass. No further intervention or follow-up was planned. Multidisciplinary collaboration led to shared decision-making with the family to delay intervention which ultimately led to avoidance of ileocecal valve resection with potentially long-term complications.

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### Introduction

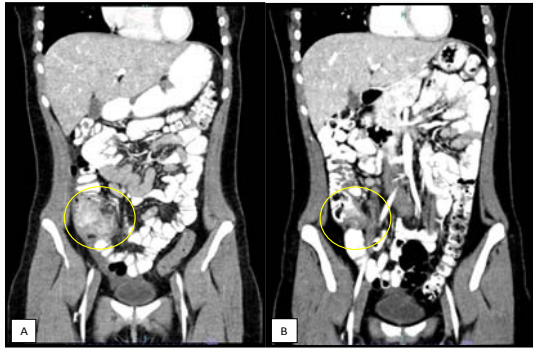
Typhlitis is a rare and life-threatening condition characterized by necrotizing inflammation of the cecum that may extend to the ileum, ascending and transverse colon [1]. The most common symptoms are fever, diarrhea, and abdominal pain; however, presentation is often obscured by non-specific symptoms of nausea, vomiting, and abdominal distension [1-4]. Typhlitis, also called neutropenic enterocolitis, is often associated with malignancy or immunosuppression in the setting of intense chemotherapy, making it uncommon in immunocompetent patients [1].

While pathogenesis is unclear, injury or ulceration to the intestinal surface appears to lead to a cascade of mucosal disruption, wall edema, and vessel engorgement with vulnerability to intramural bacterial infection [1]. Mortality ranges from 2.2% to 48% but can be as high as 60% without early recognition [4-5]. We report a case of typhlitis in an otherwise healthy teenager which warranted collaboration between primary and specialist teams due to its unusual presentation.

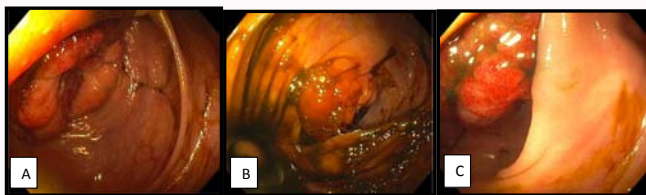
### Case Description

A 17-year-old previously healthy female presented with 1 month of lower abdominal pain with worsening nausea, non-bloody, non-bilious vomiting, and non-bloody diarrhea for 5 days. Abdominal pain was described as stabbing and intermittent. Poor oral intake was secondary to post-prandial nausea and vomiting. Weight loss of 1.8 kg (4lb) was reported over the prior 2 weeks. The patient endorsed intermittent chills, but denied fever, night sweats, fatigue, or upper respiratory infection symptoms. The patient was up-to-date on all vaccinations and attended high school locally. She denied recent travel and lived at home with her family, 1 dog, and 3 cats.

Three days prior to presentation, the patient was admitted for 2 days at an outside hospital



**Figure 1:** (A) Admission CT abdomen pelvis with contrast (B) Repeat imaging after 3 weeks.



**Figure 2:** Multilobular mass found in the cecum arising from the appendix (A-C).

for intractable abdominal pain. Abdominal ultrasound was normal, followed by a CT scan that showed marked wall thickening of the cecum and proximal ascending colon with stranding and fluid; while the appendix was not clearly delineated, there was no visualized appendiceal dilation or abscess. Labs were notable for white blood cells (WBC) of  $15 \times 10^9$  cells/L. Based on imaging findings, she was given a diagnosis of presumed typhlitis. While appendicitis could not be completely ruled out, general surgery was consulted and recommended non-operative management. The patient was initiated on ceftriaxone and metronidazole. Leukocytosis and pain improved with a benign abdominal exam on discharge, and she was prescribed a one-week course of oral ciprofloxacin and metronidazole. Stool studies to evaluate potential causes of typhlitis and a colonoscopy in 6-8 weeks were recommended on an outpatient basis.

Over the course of the next three days, the patient experienced worsening symptoms of nausea and vomiting which limited oral intake despite antibiotics and presented to our hospital. Vitals at admission were as follows: temperature 36.2°C (97.2°F), pulse 64, respiratory rate 16, blood pressure 118/74, oxygen saturation 97% on room air. Physical exam was significant for periumbilical abdominal tenderness to palpation and delayed capillary refill of 2-3 seconds. Labs were notable for elevated creatinine 1.4 mg/dL [0.42-0.90], aspartate aminotransferase (AST) 33 U/L [5-30], uric acid 8.8 mg/dL (repeat the next day 8.3 mg/dL) [3-5.9], erythrocyte sedimentation rate (ESR) 39 mm/Hr [0-20], and C-reactive protein (CRP) 2.8 mg/dL [0-0.9]; fecal calprotectin was sent. Complete blood count (CBC), complete metabolic panel (CMP), magnesium, phosphorus, and lactate dehydrogenase (LDH) were normal. Urinalysis was non-infectious, and urine pregnancy test and gastrointestinal panel (GIP) were negative. Chest radiography was unremarkable.

CT abdomen and pelvis with contrast demonstrated marked focal non-obstructive wall thickening at the ileocecal valve with patchy decreased density within bilateral upper renal poles, left greater than

**Table 1:** Differential Diagnosis.

Acute typhlitis
Pseudomembranous colitis
Mediastinal mass
Inflammatory bowel disease (Chron's disease, ulcerative colitis)
Appendicitis
Abdominal abscess
Ischemic colitis
Infectious colitis (bacterial, viral, fungal, parasitic)
Malignancy (lymphoma, appendiceal neoplasm)
Celiac disease
Intestinal obstruction
Mesenteric adenitis
Pyelonephritis

right as well as the left lower pole, raising concern for pyelonephritis, and RLQ adenopathy raising concern for lymphoma (Figure 1A). Imaging was reviewed by pediatric gastroenterology (GI), pediatric hematology-oncology, and pediatric surgery teams. Given the constellation of persistent symptoms along with concerning CT scan and lab results, the initial diagnosis of typhlitis at the outside hospital was revisited, and the differential diagnosis was broad at this time (Table 1). The patient initially continued her home oral antibiotics but after one dose of each, they were held to allow for further workup. Due to inability to tolerate oral intake, she was started on IV fluids.

On hospital day (HOD) 3, the patient underwent an endoscopy and colonoscopy with pediatric GI, which identified mild gastritis and a hard, malignant-appearing and multilobular mass in the cecum (Figure 2A-C). The mass demonstrated erythema, edema, and friability with associated erythema at the ileocecal valve near the base of the mass; however, no bleeding was identified. The mass was not amenable to direct biopsy because of its location, but cold forceps biopsy was performed for collection of surface tissue. Mucosal biopsy nearby the mass demonstrated acute colitis with crypt microabscess formation and granulomatous inflammation associated with crypt rupture, though without significant crypt architectural disorder. Visualization of the remainder of terminal ileum to distal rectum was normal with unremarkable biopsies. No *Helicobacter* organisms were seen on hematoxylin and eosin (H&E) stained sections.

On HOD5, due to concern for lymphoma, the patient underwent laparoscopic mesenteric lymph node biopsy with pediatric surgery. Removal of omental adhesions to the RLQ exposed a firm round mass coming from the cecum adjacent to the terminal ileum, while the remainder of the bowel appeared normal. Enlargement of mesenteric lymph nodes was observed, and the largest and closest peri-appendiceal lymph node to the cecum was removed for surgical pathology. The specimen demonstrated necrotizing granulomatous lymphadenitis without evidence of malignancy.

On HOD7, the infectious disease team was consulted and suggested additional workup to rule out rare infectious etiologies of her abdominal findings. Given the patient's cat exposure, bovine exposure, and history of travel to Mexico 10 months prior, the patient underwent serum testing for *Mycoplasma* and *Bartonella* and urine antigen testing for *Coccidioides* and *Histoplasma*. Aerobic and anaerobic bacterial, fungal, mycobacterial stains and cultures on

existing tissue were also sent.

Conversations were had between the primary hospital team and the consulting teams on the uncertain diagnosis. After extensive discussion with the patient, family and multidisciplinary team, it was decided that the patient was clinically stable for discharge with a plan to follow up in approximately 2 weeks for repeat CT scan. Further management, including potential surgical resection of the mass, would be decided pending results of those scans. At the time of discharge (HOD8), abdominal pain was well-controlled and the patient had good toleration of oral intake with acetaminophen for pain and ondansetron for nausea as needed.

Two weeks after discharge, the patient endorsed only 1 day of mild abdominal pain since discharge with normal intake and elimination. Repeat CT abdomen pelvis with contrast demonstrated improved inflammatory findings at the cecum consistent with typhlitis. There was no obvious evidence of mass, and terminal ileum and kidneys had a normal appearance (Figure 1B). Based on the improvement seen on her repeat imaging, the GI and general surgery teams recommended not to proceed with further surgical intervention or biopsy.

At 2-month GI follow-up, repeat fecal calprotectin was 31.1 mcg/g (versus initial 84.6 mcg/g). Given the reassuring imaging and lab findings and clinical resolution of symptoms, no further imaging or intervention, including repeat colonoscopy, was recommended.

## Discussion

Typhlitis is a subtle diagnosis, and there is scant research that describes the frequency and pathogenesis of the disease, especially among immunocompetent patients [6]. Typically, immunosuppression confirmed by history or laboratory testing in the appropriate clinical context is generally thought to tip off typhlitis as a potential diagnosis [7]. However, typhlitis screening labs have also been shown to be non-specific [1]. Given the evolving workup, our multidisciplinary team was challenged to discern the etiology of her symptoms.

In our patient, the absence of B symptoms along with normal CBC and LDH were reassuring against bone marrow suppression or rapid cell growth to suggest underlying malignancy, such as non-Hodgkin's lymphoma. Chest radiography was also reassuring against mediastinal mass. While initial hyperuricemia gave pause early in the diagnostic workup, elevated levels could be explained by her mild acute kidney injury demonstrated on her spike in creatinine which was likely secondary to dehydration, which normalized with IV fluids. Nevertheless, initial impressive CT findings that demonstrated bilateral kidney involvement, suggesting possible renal infiltration, and mesenteric lymphadenopathy raised concern for lymphoma. While kidney findings on CT were postulated to stem from a developing pyelonephritis, the patient had a bland urinalysis and lack of flank pain or dysuria.

While CT findings before colonoscopy could be explained by inflammatory bowel disease favoring Crohn's disease given ileocecal valve involvement versus infectious colitis, there was no evidence of these diagnoses given normal mucosal appearance during the procedure and normal subsequent biopsies. It was suspected that colitis-type symptoms and diarrhea were related to inflammation seen on imaging and irritation surrounding the mass seen on colonoscopy. Because typhlitis is conventionally seen in cytopenic patients, colonoscopy is seldom indicated due to risk of bleeding

and perforation [8-9]. Hence, our case may be a rare example of the appearance of typhlitis and extent that bowel wall inflammation on gross examination. At the time, visualization of a malignant-appearing appendiceal mass was worrisome irrespective of the non-specific intestinal biopsies, prompting the decision to proceed with peri-appendiceal lymph node sampling for further pathology delineation.

When surgical lymph node biopsy demonstrated necrotizing granulomas without evidence of lymphoma, it was deemed warranted to expand testing for bacterial and fungal etiologies given the impressive findings on colonoscopy and CT imaging. Vexingly, infectious workup was unremarkable. Generally, the literature attributes typhlitis to various offending organisms, such as anaerobes, *Candida* species, gram-positive cocci, gram-negative bacilli. Moreover, infections are often polymicrobial and can progress to bacteremia if the bowel wall is perforated [5].

Extensive discussion was had among the team and family to determine next steps, given her inconclusive workup. While lymph node biopsy was reassuring against lymphoma, only surface tissue was collected of the observed mass, and there was a strong consideration of surgical resection to clarify definitive pathology. The hospital medicine and GI teams had continued concern for malignancy based on the gross appearance of the mass on colonoscopy, but the oncology team felt the reassuring lab workup made lymphoma less likely. Given its location, the benefits of analyzing direct tissue of the concerning mass were weighed against the risks of surgery, which included the removal of the ileocecal valve and potential long-term adverse effects. Ultimately, shared decision-making led to delaying intervention and planning for serial CT scanning, which is suggested as the main criterion for establishing the diagnosis and monitoring progression of typhlitis [10-13]. Abdominal ultrasound, which in our case was normal, is generally the primary mode of imaging due to its speed and sensitivity for appendicitis, a key differential diagnosis, before proceeding to CT imaging [10]. Conservative treatment, including bowel rest, IV antibiotics, and close monitoring, is the primary recommendation in the treatment of typhlitis; early detection is paramount to avoid surgery which can raise the risk of morbidity [1,14].

There are few examples in the literature of otherwise healthy young patients diagnosed with typhlitis. *Reyes et al.* described the case of a 25-year-old female with no significant past medical history who presented non-specific complaints of recurrent RLQ pain and diarrhea with strikingly similar cecal thickening on CT imaging to our patient; the patient improved with bowel rest, pain control, and IV antibiotics for presumed appendicitis at the time [15]. *Ufuk et al.* shared the case of typhlitis in a 60-year-old female diagnosed with typhlitis demonstrated on CT in the setting of COVID-19 pneumonia; while the patient had no history of immunosuppression, pancytopenia at the time was thought to result from bone marrow suppression from viral infection [16]. Further attention should be brought to the potential for typhlitis to occur in healthy patients and remain a differential diagnosis and possible mimic for more likely diagnoses of appendicitis or infectious colitis.

## Conclusion

This report shares the rare example of typhlitis in a healthy teenager and reveals the discourse between our multidisciplinary team in the face of a challenging diagnosis. Typhlitis should be considered

in the workup of vague abdominal symptoms in all patients despite immune status and serial imaging can be useful in avoiding invasive procedures. More research is required on the origin and development of typhlitis in healthy patients.

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