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Diagnosis, incidence, and outcomes of suspected typhlitis in oncology patients—experience in a tertiary pediatric surgical center in the United Kingdom

Dhanya Mullassery[a,*], Abdulgader Bader[b], Anna J. Battersby[a], Zeenat Mohammad[a], Emma Louise L. Jones[a], Chetan Parmar[a], Roger Scott[a], Barry L. Pizer[b], Colin T. Baillie[a]

[a]*Department of Pediatric Surgery, The Royal Liverpool Children's Hospital (Alderhey), UK*
[b]*Department of Pediatric Oncology, The Royal Liverpool Children's Hospital (Alderhey), UK*

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Abstract

Background: Typhlitis is clinically defined by the triad of neutropenia, abdominal pain, and fever. Radiologic evidence of colonic inflammation supports the diagnosis. We report a single United Kingdom tertiary center experience with management and outcome of typhlitis for 5 years.

Methods: Hospital computerized records were screened for ultrasound or computerized tomographic scan requests for abdominal pain for all oncology inpatients (2001-2005). Retrospective case note analysis was used to collect clinical data for patients with features of typhlitis.

Results: The incidence of typhlitis among oncology inpatients was 6.7% (40/596) among oncology inpatients and 11.6% (40/345) among those on chemotherapy. Eighteen children had radiologically confirmed typhlitis, and 22 had clinical features alone. Most (93%) patients responded to conservative management. Eighteen children had a variable period of bowel rest, including 12 patients who were supported with total parenteral nutrition. Three patients had laparotomy that revealed extensive colonic bowel necrosis (1), perforated gastric ulcer (1), and a perforated appendix (1). A single child died of fulminant gram-negative sepsis without surgical intervention.

Conclusions: The diagnosis of typhlitis was based on clinical features, supported by radiologic evidence in almost half of the study group. Surgical intervention should be reserved for specific complications or where another surgical pathologic condition cannot reasonably be ruled out.

1. Background

Typhlitis or neutropenic enterocolitis (NE) is a syndrome characterized by fever and abdominal pain in a neutropenic patient [1]. Typhlitis is now well recognized as an important cause of morbidity and mortality in adult and pediatric oncology patients [2-4]. The purpose of our study was to

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* Corresponding author. Research Registrar in Pediatric Surgery Institute of Child Health Royal Liverpool Children's Hospital, L12 2AP Liverpool, UK. Tel.: +44 151 228 4811; fax: +44 151 228 2024.
E-mail address: mdhanya@liverpool.ac.uk (D. Mullassery).

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review our experience with diagnosis, management, and outcomes for patients suspected to have this condition in our pediatric oncology inpatients.

2. Materials and methods

We conducted a retrospective screening of computerized (Meditech, Massachusetts, USA) records of all inpatients admitted under the pediatric oncologists at the Royal Liverpool Children's Hospital (Liverpool, United Kingdom) during the 5-year period between January 2001 and December 2005. Children in whom an abdominal ultrasound (US) or computed tomographic (CT) scan had been requested for investigation of abdominal pain were identified. From this group, after case note review, we excluded all patients who had a specific diagnosis other than typhlitis on imaging or other investigations. For the purposes of this study, we defined *typhlitis* as the presence of the clinical triad (abdominal pain, fever, and neutropenia) or imaging signs (thickened bowel wall) in addition to 2 of the clinical features. Records of patients under oncological care who had a laparotomy during the period were also screened for surgery for suspected typhlitis. Case notes were analyzed for the following details: age at diagnosis, sex, primary oncological diagnosis, chemotherapeutic regimen, clinical findings, imaging results, presence of neutropenia, duration, and management of typhlitis. *Neutropenia* was defined as a neutrophil count of less than $1.65 \times 10^3/mm^3$. Information concerning follow-up and outcome were acquired from the inpatient notes and outpatient letters. Data were recorded on a Microsoft Excel (v2007) database.

3. Results

Five hundred ninety-six patients were admitted (for a minimum of 24 hours) under the oncologists at the Royal Liverpool Children's Hospital during the study period, and there were 345 patients on chemotherapy during this period. There were 40 children with a diagnosis of typhlitis. Twenty-three were boys and 17 were girls. The median age of the patient group was 8.5 years (range, 3 months to 18 years). Twenty children (50%) were referred to a pediatric surgeon with a median duration of symptoms at referral of 2 days (range, 4 hours to 10 days). All children had received chemotherapy within 2 months of the diagnosis of typhlitis (median interval, 10 days; range, 2-60 days). Three patients (2.88%) developed typhlitis after a bone marrow transplant —2 with acute lymphatic leukemia and 1 with medulloblastoma. The incidence of NE was 6.1% for all oncology inpatients and 11.6% for those on chemotherapy. Thirty-three children had hematologic malignancies, and 7 patients had solid tumors. There was no significant difference in incidence between individual diagnostic groups ($P > .05$, extended χ^2, contingency table) or in children undergoing bone marrow transplant (2.88% vs 6.69%; $P > .05$, χ^2); however, the difference in incidence between hematologic malignancies and solid tumors was statistically significant (8.82% vs 3.13%; $P < .001$, χ^2). Table 1 shows the oncological diagnoses of all patients with typhlitis.

Table 1 Oncology diagnoses for patients diagnosed with typhlitis

Oncology diagnosis (total no. of patients)	Patients with typhlitis (%)
Leukemia (283)	27 (9.8%)
Lymphoma (91)	6 (6.6%)
Brain tumor (72)	2 (2.8%)
Other solid tumors (150)	5 (3.3%)

All 40 children had abdominal pain, but localization to the right iliac fossa was seen in only 10 (25%). Thirty-one (78%) children presented with the typical triad of fever, abdominal pain, and neutropenia. The remaining 9 (22%) had imaging features of typhlitis with 2 additional clinical features of the condition. Other clinical features included fever (35), neutropenia (35), diarrhea (20), and per rectal (PR) bleeding (2).

All 40 had an US scan, and 8 children also had a CT scan. Diagnostic features of typhlitis were identified in 15 (37.5%) patients on the abdominal US and 3 (7.5%) on CT scan. Of the positive reports, only 7 specified the location and magnitude of bowel wall inflammation, with the others being reported as "consistent with typhlitis."

Thirty-seven children (92.5%) were treated conservatively. The treatment in this group included antibiotics (40), granulocyte colony-stimulating factor (16), bowel rest (18), and total parenteral nutrition (12). Thirty-three children had an antibiotic regimen for neutropenia, using amikacin and ceftazidime, supplemented in 23 patients with metronidazole to provide anaerobic cover. Of these conservatively treated patients, one child died within 24 hours of diagnosis of typhlitis. The patient had extensive bowel inflammation on CT and US scans, without any evidence of perforation and was never a surgical candidate. After collapse, the child died despite prompt ventilatory and inotropic support. The cause of death was cardiovascular collapse because of fulminating gram-negative septicemia by *Pseudomonas aeruginosa*.

Three children came to surgery. All had US scans showing free fluid in the peritoneal cavity along with thickened bowel wall in the region of ascending colon. The indication for surgery was clinical deterioration despite conservative management, with clinical features suggesting peritonitis. The first child had extensive necrosis of colonic wall from the cecum to the rectosigmoid; subtotal colectomy was performed with a defunctioning ileostomy. The second had a perforated appendix with an associated fecolith and inflammation of the ascending colon. The third child had a perforated gastric ulcer. All three survived. Review of histologic examination of the surgically resected specimens confirmed extensive typhlitis in the first, perforated

appendicitis with a fecolith and a neutrophil infiltrate of the appendix in the second, and perforated gastric ulcer with T lymphocyte infiltration in the third patient.

There were 9 other deaths in the group, where the cause of death was not related to typhlitis.

4. Discussion

Neutropenic enterocolitis, initially described in patients with leukemia [5,6], is an important gastrointestinal complication seen in oncology patients. Early reports of the incidence of typhlitis from autopsies of children with leukemia were between 24% and 38% [4,6]. More recent literature suggests an incidence of between 0.4% and 6% in pediatric oncology patients [3,7,8]. Our data suggest an incidence of 6.7% in all pediatric oncology patients and 11.5% in those who in addition received chemotherapy. The increased incidence of NE in our hematologic malignancies compared with solid tumors is consistent with the current literature.

The diagnosis of typhlitis can often be difficult [9]. In adults, a systematic review of NE demonstrated a marked heterogeneity in clinical practice and the criteria used for the diagnosis of the condition [10]. In our study, all children had abdominal pain as the main presenting symptom, but this was nonspecific in most patients. Not all of our cases had all of the clinical features of NE. Only 31 (78%) had the typical clinical triad of NE. In 9 (22%) of 40, the diagnosis was confirmed using imaging when only 2 or more clinical features were present. This is consistent with the reported 15% of patients with suspected typhlitis on imaging (bowel wall thickness $\geq$ 0.30 on US) who did not have one of more of the typical clinical features (abdominal pain, fever, and neutropenia) [8]. In all suspected cases of NE where imaging was undertaken, only 45% (18/40) had US or CT features supporting the diagnosis. Of these, US was adequate in our experience to confirm the features in most. McCarville et al [8,11,12] recently suggested using a cutoff value of 0.30 cm or more on US to increase both the sensitivity and the accuracy of diagnosis. Other authors have measured the thickness of the bowel wall on US scan and CT and related the measurement to the severity and duration of typhlitis [13]. However, there are no prospective studies to definitively validate this practice. Previous reports have noted increased bowel wall thickness on CT in neutropenic patients with *Clostridium difficile* colitis, cytomegalovirus colitis, and graft-vs-host disease [14] or even appendicitis [15]. The CT scanning has been suggested to be more sensitive in detecting early changes in the bowel wall and complications including perforation, bowel necrosis, and abscesses [16,17]. This imaging technique, however, has the disadvantages of exposure to ionizing radiation, and the procedure may in addition be less well tolerated by sick children [8,11]. Our data would suggest that CT imaging will be necessary in less than 10% of suspected cases.

Of interest in our study were the 2 patients who proved to have a false-positive diagnosis for the condition. These belonged to the group with only 2 of the clinical features of NE, who had imaging and represents 5% of the total thought to have typhlitis. It is uncertain that the outcomes in these cases were in any way influenced by the presence of the malignancy and its treatment. Our data therefore confirm, firstly, that not all cases of NE have the typical clinical or imaging features of the condition and, secondly, that even with typical features of NE, a small proportion will have some other pathologic condition to account for the problem. This questions the specificity of US and highlights the danger of using an imaging diagnosis alone to support a policy of conservative management of typhlitis.

Although typhlitis typically affects the cecum and the ascending colon, it has been reported in the transverse colon, descending colon, and even the rectum [4]. Our experience reflects this with one patient having pancolonic involvement.

The main differential diagnosis of NE is appendicitis, particularly with right-sided clinical features, but abdominal pain in neutropenic patients may also be caused by veno-occlusive disease, graft-vs-host disease, pseudomembranous colitis, and infectious colitis.

The definitive diagnosis of typhlitis is based on histologic examination; bowel wall edema with mucosal ulceration and necrosis with almost absent or absent acute inflammatory infiltrates have been described as typical [18]. This differentiates it from appendicitis where there is significant neurophilic infiltration of the bowel wall. As histologic confirmation is only possible for postoperative patients or at postmortem, this does not assist in the initial management decisions. In our experience, although appendicitis in this group of oncology patients is unlikely based on probability alone, extreme vigilance is required as typical clinical features may be masked or modified by the underlying malignancy or its treatment, as was the case in our patient. Fortunately, this child came to surgery, when the diagnosis was made and the appropriate surgical procedure undertaken.

Although most children in our study were successfully managed conservatively, those children who underwent surgery had clinical features suggestive of bowel perforation and peritonitis. Inability to rule out bowel perforation, other surgical pathologic condition such as appendicitis, and life-threatening hemorrhage are the main indications for operation [19-21]. Where necrosis of the colon has occurred, most authors suggest a right hemicolectomy with a defunctioning ileostomy [7,22,23] because it is judged that primary anastomosis has an unacceptably high incidence of complications in a neutropenic patient. A defunctioning ileostomy alone has been suggested for pancolonic disease but carries the risk of continued postoperative sepsis until the neutrophil count recovers [7]. In line with these recommendations, we performed a subtotal colectomy with a defunctioning ileostomy in the one child with the pancolonic disease.

Certain types of malignancies have previously been reported to predispose to the development of typhlitis [7].

Acute myeloid leukemia has been implicated as having the highest risk [2]. Children treated for Burkitt's lymphoma have been suggested to be at risk for recurrent NE [23]. In our study, we found that there was a higher incidence of typhlitis in hematologic malignancies compared to the solid tumors, but the difference between individual diagnostic groups did not reach statistical significance.

Recent literature suggests an increase in the incidence of typhlitis [8,24,25]. Although severe immunocompromise resulting from intensive chemotherapy and bone marrow transplantation have been suggested as contributory factors, children receiving bone marrow transplant are reported to have a relatively low incidence [26] of typhlitis (2.8% in our study). However, the numbers were too small to judge whether this was significant.

Several chemotherapeutic agents have been implicated in the pathogenesis of typhlitis. These include anthracyclines and cytosine arabinoside that induce mucosal alterations [27] and vincristine that causes bowel hypomotility. It has been proposed that combinations of these treatments may create conditions favorable for bacterial overgrowth and translocation, which predispose to the development of typhlitis. In addition, interactions between chemotherapy agents and other drugs may also contribute to the bowel injury. The multidrug regimens followed for most pediatric malignancies make it difficult to definitively establish a causal role of any agent in the process. Therapeutic measures including selective decontamination and enteral cytoprotective agents including glutamine have been previously suggested in neutropenic patients [28,29] to minimize the potential side effects of chemotherapy agents on the gastrointestinal tract. However, further studies are needed to provide evidence for their clinical use in typhlitis.

Recent reports of outcomes suggest an improvement in the last decade with medical management alone. Reported mortality rates for typhlitis have reduced from 8.2% in the previous decades [3] to 2.5% to 5% in the last decade [8,23]. Our findings support an individualized approach to each patient. A high index of suspicion, early appropriate medical management with antibiotics, and granulocyte colony-stimulating factor supported by total parenteral nutrition in selected cases can achieve a successful outcome in most children. It may be argued that our practice of initiating treatment when there is a clinical suspicion of the condition rather than relying on imaging has resulted in overdiagnosis of typhlitis. Inclusion of children with clinical diagnosis without supportive imaging evidence inevitably skews results with lower rates of morbidity and mortality. However, the false-positive diagnoses of typhlitis provided by imaging in our group demonstrate the importance of clinical expertise.

In our experience, with increasing awareness of the potential complications of typhlitis, more patients are being referred early to pediatric surgeons. It is to be hoped that this will result in improved diagnosis and early intervention with better outcomes.

5. Conclusions

The diagnosis of typhlitis is essentially clinical and may be supported by evidence provided by imaging. Medical treatment is usually successful, and therefore, surgical intervention should be reserved for clear evidence of peritonitis or to rule out other surgical pathologic condition.

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