IMAGING AND CLINICAL FEATURES OF TYPHLITIS IN PEDIATRIC CANCER PATIENTS ON CHEMOTHEAPHY AT TIKUR ANBESSA SPECIALIZED HOSPITAL

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ABSTRACT

Background: Typhlitis also known as neutropenic enterocolitis is a necrotizing enteropathy of the right colon. It is characterized by the clinical triad of fever, abdominal pain, neutropenia and imaging findings of right-side colonic inflammation. It is most often seen in the setting of severe neutropenia in immunesuppressed patients who are undergoing treatment for malignancies, in those who have undergone organ transplant(s) or have congenital or acquired causes of immunesuppresion. We report the clinical and imaging findings of typhlitis in pediatric cancer patients who have taken chemotherapy in the largest tertiary center in Addis Ababa, Ethiopia over a period of 20 months.

Methods: Medical records of hospitalized patients were screened for plain radiograph, ultrasound and computerized tomographic scan requests for suspected typhlitis in those on inpatient cancer treatment (November 2018- July 2020 G.C). Retrospective case note analysis was done to collect the clinical data of those with typhlitis.

Result: Typhlitis was identified in 4.2% (12/286) of the patients on chemotherapy. Eleven patients (91.7%) had hematologic malignancies (leukemia, lymphoma), 1 patient had a solid tumor (Head and neck embryonal RMS). Most (83.3%) had abdominal pain, diarrhea and neutropenia. Fever was identified in 67.7% of patients. All had ultrasound evidence supportive of typhlitis. All were treated with IV antibiotics. There were no complications requiring surgical intervention. No child died during an episode of typhlitis.

Conclusion: The magnitude of typhlitis was found to be comparable to what is reported in other studies. The clinical findings of abdominal pain, diarrhea, fever in a neutropenic patient who has signs of colonic inflammation should prompt for the diagnosis of this case.

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List of Abbreviations and Acronyms

AAU – Addis Ababa University

ALCL- Anaplastic Large Cell Lymphoma

ALL - Acute lymphoblastic leukemia

AML- Acute myeloid leukemia

ANC - Absolute neutrophil count

APML- Acute promyelocytic leukemia

ATRA- All-trans retinoic acid

BL- Burkitt's Lymphoma

BMT- Bone marrow Transplant

C-Arabinoside- Cytosine Arabinoside

CBC- Complete blood count

CHS - College of health sciences

CI- Confidence interval

CT - Computed tomography

GI- Gastrointestinal

HIDAC- High dose arabinoside C

HIE- Hypoxic ischemic encephalopathy

HL- Hodgkin's Lymphoma

HR- High risk

H&N- Head and neck

LMIC- Low to middle income countries

MRN- Medical record number

NHL- Non- Hodgkin’s Lymphoma

NE - Necrotizing enteropathy

PR - Plain radiography

RMS- Rhabdomyosarcoma

SR- Standard risk

TASH - Tikur Anbessa Specialized Hospital

US – Ultrasound

VCD- Vincristine, cyclophosphamide, doxorubicin

WBC - White blood cells

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1. INTRODUCTION

1.1 BACKGROUND

Typhlitis also known as neutropenic enterocolitis is a necrotizing enteropathy of the right colon (1). It is characterized by fever and abdominal pain in a neutropenic patient (2). It is most often seen in the setting of severe neutropenia in immunesuppressed patients who are undergoing treatment for malignancies. It is also seen in patients who have undergone organ transplants or have congenital or acquired causes of immunesuppresion (1). On imaging, it is characterized by bowel wall thickening, pericolonic fluid and inflammation of the pericolonic fat usually isolated to the cecum, adjacent terminal ileum and ascending colon with left colonic involvement being uncommon (3). A bowel wall thickness cut off value of 0.3 cm or greater is associated with greater sensitivity and accuracy (1,2,4). The definitive diagnosis of typhlitis is based on histologic examination (2).

Currently, the number of immunocompromised pediatric patients is increasing. Children can become immunocompromised due to congenital or acquired causes of immunosuppression such as treatment for malignancy and bone marrow transplantation. These patients are prone to develop different primary disease and treatment related complications. The gastrointestinal system is commonly involved in such processes (3). Typhlitis (enterocolitis) is one of the commonest gastrointestinal complication along with enteritis and colitis which represent isolated inflammatory conditions of the small and large bowel respectively (5). The pathophysiology of typhlitis remains largely unknown but is believed to be multifactorial. It appears to involve a sequence of events in which the integrity of the colonic mucosa is disturbed by either chemotherapy or leukemic infiltration. These changes lead to invasion of the bowel wall by bacteria and occasionally fungi (6). Gram negative rods, gram-positive cocci, enterococci, fungi, and virus have been implicated as causes (7). Some of the pathogens that have been identified from blood cultures are Escherichia coli, Klebsiella pneumonia, pseudomonas aeruginosa, Enterobacter and Morganella species along with fungi like aspergillus and candida albicans (3,5,6). Common complications are sepsis, obstruction and abscess formation (5). There is no optimal agreed upon management for patients with typhlitis but most receive conservative medical management consisting of a combination of bowel rest, total parenteral nutrition and use of broad-spectrum antibiotics. The use of granulocyte colony stimulating factor is also

mentioned. Surgery is reserved for those who have evidence of bowel perforation or abscess formation (2,4,5,6).

1.2 STATEMENT OF THE PROBLEM

The true incidence typhlitis remains largely unknown as postmortem series are rarely done on children. Early postmortem reports from the 1950's to 70's put its incidence at between 10-24% in those with acute leukemia (8,9). More studies done in the 70's and 80's show incidences in those with acute leukemia to be as low as 0.3% in patients with ALL and 2.1% in those with AML (6). Recent studies show overall incidences of lower than 10% in patients on chemotherapy (2,4,10). These wide range of incidences could be attributed to variations in study designs, length of study or imaging modalities used for diagnosis. Most studies tend to agree there is an increased incidence of typhlitis in association with hematologic malignancies (especially leukemias) as compared to solid organ malignancies (5,6,8).

The incidence of typhlitis is only expected to rise with the introduction of more intensive chemotherapy regimens, increase in the number of children on myelosuppressive treatments and with the advent of better-quality imaging modalities (2).

Patients usually present with nonspecific GI complaints like nausea, vomiting and diarrhea prompting the need for a high index of clinical suspicion to aid in early detection of cases. Imaging of the abdomen also plays a crucial role in confirming diagnosis, identifying complications and also ruling out other causes of the patient's symptoms. Thus, typhlitis which was previously considered a terminal disease with reported mortality rates ranging from 50% to 100% (6,7) is no longer a death sentence.

1.3 SIGNIFICANCE OF THE PROBLEM

TASH, located in Addis Ababa, is the only state-owned hospital in Ethiopia providing chemotherapy for the treatment of both adult and pediatric cancer patients. In spite of this, there have been no studies conducted so far with respect to typhlitis in this hospital. This research aims to correlate demographic, clinical and laboratory data with radiologic findings of right colonic wall changes to determine the overall clinical and imaging pattern of the disease in pediatric cancer patients who have undergone chemotherapy. In doing so, this research hopes to contribute to the making of prompt and proper diagnosis so as to reduce patient morbidity and mortality.

2. LITERATURE REVIEW

Typhlitis is a condition clinically defined by the triad of neutropenia, abdominal pain, and fever. Radiologic evidence of colonic inflammation supports the diagnosis while histologic examination confirms it. Some of the radiologic evidences are the presence of bowel wall thickening, a dilated cecum or other colonic segment, an inflammatory mass, pericolonic inflammation, and pneumatosis intestinalis. The definitive diagnosis of typhlitis is based on histologic examination with typical findings being bowel wall edema with mucosal ulceration, necrosis and absent or almost absent acute inflammatory infiltrates (2).

The cecum is always found to be affected by typhlitis very often with extension to the ileum. The ascending and transverse colon may also be involved. Predilection of the cecum may be explained by its distensibility and limited blood supply (7).

Children with cancer are at increased risk of gastrointestinal (GI) complications and in particular, enteritis, typhlitis, and colitis have been increasingly recognized over the last few decades. These diagnoses represent inflammatory conditions of the small bowel, cecum, and large bowel, respectively, and about 5% to 10% of children with cancer will experience these complications during therapy (5).

There have been several long-term studies conducted concerning the risk factors, incidence and imaging appearances of typhlitis. The term typhlitis was first described by Wagner et al. in 1970 as a necrotizing colitis, frequently localized to the cecum and found primarily in leukemic children with terminal disease. Wagner and co-workers had reviewed 191 leukemic children who underwent autopsy between 1958 and 1970 at the Texas Children's Hospital, Baylor College of Medicine, Houston. During this period 296 children diagnosed with acute leukemia died at this hospital. The autopsy rate was 65% and postmortem incidence of typhlitis was 10% (9). In a separate subsequent research done in the same hospital by Katz et al. from 1970- 1987, 353 children with acute leukemia had died, the majority from acute lymphocytic leukemia (ALL). Autopsies were performed on 39% of these patients with the incidence of typhlitis being 24% (33 patients) (8). The postmortem incidence of typhlitis in both studies was greater for those with ALL than for patients with AML.

A retrospective study done in 3171 pediatric patients at St. Jude Children's Research Hospital, Memphis, Tennessee from January 1990- 2001 assessed the incidence of typhlitis based on the clinical triad of typhlitis (neutropenia, abdominal pain, fever) and colonic wall thickening of >0.3cm. The overall incidence was found to be 2.6%. Incidence here was also found to be higher among patients with leukemia/lymphoma (3.3%) as compared to other malignancies (2.4% among patients with solid tumors and 0.6% among patients with brain tumor) (4).

Another retrospective study done at the Schneider Children's Medical Center of Israel from 1995-2005 studied 843 patients with cancer who received chemotherapy. Patients in this study were those who had presented with fever, abdominal complaints and radiologic evidence of large bowel pathology. Forty-two (5%) of the 843 were found to have typhlitis based off these criteria. Seventy six percent had hematologic malignancies while the rest has solid tumors (Ewing sarcoma, Wilms tumor, primitive neuroectodermal tumor, neuroblastoma, rhabdomyosarcoma, and astrocytoma, medulloblastoma, glioma) (10).

At the Royal Liverpool Children's Hospital (Liverpool, United Kingdom) between January 2001 and December 2005, of 345 patients who were on chemotherapy 40(11.6%) were diagnosed with typhlitis. Thirty-three (82.5%) had hematologic malignancies, the rest solid tumors (2).

Attempts were also made in these studies to identity the clinical symptoms and demographic factors related to typhlitis.

In the Texas Children's Hospital study from 1970-1987, of the 33 patients found to have typhlitis, 57% were male and 43% were female. Common symptoms included abdominal pain and distention in 78% of patients and acute lower gastrointestinal bleeding in 35%. All patients were febrile (> 38.5C) (8).

In the study done at St. Jude Children's Research Hospital, 45% of the patients diagnosed with typhlitis were female and 55% were male. The median age at diagnosis was 10 years. Frequent symptoms were abdominal pain (91%), fever (84%), abdominal tenderness (82%), and diarrhea (72%) (4).

At the Schneider Children's Medical Center of Israel, average age at diagnosis was also 10 years. The most common signs and symptoms associated with episodes of typhlitis were abdominal

pain in 89%, abdominal tenderness in 83%, fever in 75% and diarrhea in 64%. GI symptoms like emesis, bloating and nausea were also observed albeit less frequently (10).

At Royal Liverpool's Children's Hospital, of the 40 children diagnosed with typhlitis 57% were boys and 43% were girls. The median age of the patient's at diagnosis was 8.5 years (2).

Most of these studies show that boys have a slightly higher incidence of typhlitis as compared to girls. None have forwarded any theories as to why.

Imaging modalities used in the diagnosis of typhlitis in the afore mentioned studies include plain radiography (PR), ultrasound (US), computed tomography (CT). Barium studies were occasionally used on a study conducted by Sloas et al.

Sloas et al did a retrospective study of 6911 pediatric cancer patients in the 30-year period from 1962-1992 at St. Jude Children's research hospital. They found 20 patients diagnosed with typhlitis. CT and US were found to be more sensitive than radiography or barium studies in demonstrating thickening of the bowel wall, with positive findings in 17 of 20 patients by CT scan and in 13 of 17 patients by US. The false negative rates of CT, US and PR were found to be 15%, 23%, and 48%, respectively. Abnormal findings on CT imaging and ultrasonography included a right-lower-quadrant inflammatory mass and pericecal fluid or inflammatory changes in the pericecal soft tissues. A right-lower-quadrant soft tissue density or mass was the most useful finding on plain radiographs. Although barium enemas usually are avoided in pancytopenic patients because of the risk of bowel perforation and/or infection, two patients underwent barium studies without complications (6).

At the study done in from 1995-2005 at Schneider Children's Medical Center of Israel, X-ray was done in 100% of patients, US in 23%, and CT in 11%. They found no cases in which US or CT findings were positive and x-ray findings were negative. Therefore, on this study the assumption was made that the combination of clinical signs and abdominal x-ray findings were sensitive enough for the diagnosis of typhlitis. The cost-effectiveness, and usefulness of adding another imaging modality was questioned. However, in cases of progressive disease, or when an intra-abdominal complication such as bowel perforation, abscess formation or obstruction was suspected, the recommendation was made that additional imaging modality (CT or US) should be used accordingly (10).

Studies from the time of Sloas et al have shown a progressive increase in the incidence of typhlitis in pediatric patients treated for cancers. Severe immunocompromise resulting from more intensive chemotherapy regimens and bone marrow transplantation have been suggested as contributory factors. Large scale studies concerning the effects of new forms of chemotherapy drugs and regimens are lacking. Several chemotherapeutic agents have been implicated in the pathogenesis of typhlitis. These include anthracyclines and cytosine arabinoside that induce mucosal alterations 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. (2,6,10)

Laboratory finding of severe neutropenia was found to significantly influence severity and duration of illness. Additional findings of thrombocytopenia, electrolyte abnormalities and hyperbilirubinemia found in most patients with typhlitis did not appear to have an effect on disease severity or outcome. (2,5)

There is a paucity of data on the incidence and risk factor for typhlitis in the setting of low to middle income countries (LMIC). Those that have been available are done in reference to patients with acute leukemia. In a study done in the National cancer institute, Cairo between 2012-2016 the incidence of typhlitis was found to be 24% (49/203) with all patients requiring ICU admissions resulting in a high 30-day mortality rate of 44.8% (11). A separate retrospective evaluation of 75 pediatric patients with acute leukemia in Dr. Sami Ulus Children's Hospital, Ankara, Turkey between 2006 and 2009 showed the incidence of typhlitis to be 4.5% with a high mortality rate of 20% (12). Mean age at diagnosis was 7.5 years. Commonly identified symptoms were abdominal pain and tenderness in 100%, fever and nausea in 90% followed by vomiting in 80% and diarrhea in half of the patients. Although the recorded incidences in these two studies appear to be in the range of incidences in high income counties, the mortality rates are markedly higher. These could be attributed to poverty-related factors such as low parental literacy, suboptimal living conditions, distance from healthcare facilities hampering the care and prevention of infections in children with malignancies in LMIC (13).

3. OBJECTIVE

3.1 GENERAL OBJECTIVE:

To describe the imaging and clinical features of typhlitis in pediatric cancer patients undergoing chemotherapy in Tikur Anbessa specialized hospital, Addis Ababa, Ethiopia

3.2 SPECIFIC OBJECTIVES:

To describe the major signs, symptoms and clinical findings (laboratory, chemotherapy regimens and drugs) in patients with typhlitis

To describe the major imaging features consistent with typhlitis on plain radiograph, ultrasound and computed tomography studies

To describe the major forms of cancers commonly found in patients with typhlitis

4. MATERIAL AND METHODS

A retrospective screening of written records of all patients admitted under pediatric hemato-oncology at TASH during a 20-month period between November 2018 and July 2020 G.C was done. Children in whom a clinical diagnosis of typhlitis and a plain radiograph, an abdominal ultrasound or computed tomographic scan had been requested for investigation of abdominal pain were identified. All patients who had a specific diagnosis other than typhlitis on imaging were excluded. For the purpose of this study typhlitis was defined as the presence of the clinical triad (abdominal pain, fever, and neutropenia) and imaging signs (thickened bowel wall>0.3cm) or imaging signs in addition to 2 of the clinical features. Records of patients were also screened for any surgical notes associated with typhlitis. Case notes were analyzed for the details described in the specific objectives of the study.

4.1 STUDY SETTING

The study was set at Tikur Anbessa Specialized Hospital, Addis Ababa University, College of Health sciences, which is located in Addis Ababa, Ethiopia. TASH, located in the nation's capital, is the largest referral as well as teaching hospital in the country. The hospital provides tertiary level referral treatment with over 900 beds and is open 24hrs for emergency services. It

is also the largest state-run hospital providing chemo and radiotherapy services for both pediatric and adult cancer patients.

This study was conducted among pediatric cancer patients who have taken chemotherapy at the specialized pediatric hematology/oncology unit. The unit as a separate entity started operating in April 2013 G.C. It is located on 7th floor of the hospital housing 26 beds. This provides services for 24hours, 7 days a week. There is also a separate out-of-hospital oncology center nearby that has 16 beds for solid tumor patients on its the 2nd floor and an outpatient follow up clinic on the ground that functions 5days a week.

4.2 STUDY POPULATION

The study population consisted of all pediatric cancer patients who were admitted and had received chemotherapy in TASH, Addis Ababa, Ethiopia between November 2018 and July 2020G.C.

4.3 STUDY DESIGN AND PERIOD

The study design was in the form of a facility based retrospective cross-sectional study. The research period was set from November 2018 to July 2020 G.C.

4.4 SAMPLING METHOD

The sampling method used was non-probability convenience sampling method.

4.5 INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA

All admitted patients aged ≤ 15 years with radiologically or histologically confirmed malignancies.

Patients with the clinical triad of abdominal pain, fever and neutropenia with imaging for these complaints and subsequent diagnosis of typhlitis.

EXCLUSION CRITERIA

All admitted patients aged > 15yr.

Patients not started on chemotherapy.

Patients with unconfirmed malignancies.

All patients who have otherwise confirmed causes for symptoms consistent with typhlitis

Those that do not meet the operational definition of typhlitis

4.6 DATA COLLECTION, ANALYSIS AND INTERPRETATION

Data collection was conducted by the primary investigator. The MRN of pediatric cancer patients were collected from the admissions log book at the specialized hemato-oncology ward in TASH. Charts were subsequently reviewed for clinical and imaging findings of typhlitis. Data was then collected using a structured questionnaire. To be included, patients had to be at or below the age of 15 years and have histologic or radiologic confirmation of cancer. PR, US and CT reports were reviewed and findings recorded in the questionnaires. Data was checked for clarity and completeness. Data was entered by primary investigator and analyzed using nonparametric statistical methods with the help of SPSS v22 software package.

OPERATIONAL DEFINITIONS

Typhlitis is clinically defined by the triad of severe neutropenia, abdominal pain, and fever along with radiologic evidence of colonic inflammation (2).

*****Severe neutropenia- is defined as an ANC of <500 cells/mm^3 or an ANC that is expected to decrease to <500 cells/mm^3 during the next 48 h. (14)

*Fever-. A single oral temperature ≥ 38.3°C or oral temperature of ≥38°C for 1 hour or more (oral temperatures are more reliable and thus preferred) or a single axillary temperature of ≥ 37.8°C or axillary temperature ≥ 37.5°C for 1 hour or more. (14)

*Febrile Neutropenia- is axillary temperature ≥ 38.3°C occurring once or ≥ 38°C occurring twice in a 24-hour period (14)

5. ETHICAL CONSIDERATION

Before data collection, written ethical clearance was obtained from the Research and Ethics Committees of the Department of Radiology and Department of Pediatrics and Child Health, Addis Ababa University. Patients' names and MRN numbers were not used. A coding system was adopted instead.

6. PLAN OF DISSEMINATING STUDY

After the formal preparation of the final manuscript, it will be forwarded for peer review and publication. The published manuscript will be forwarded to respective concerned departments.

7. RESULT

7.1 Patient characteristics

A retrospective analysis was done of the medical records of 286 pediatric cancer patients admitted to the oncology ward for chemotherapy between November 2018-July 2020 G.C. Of these 174(60.8%) were male and 112 (39.2%) were female. The mean age at presentation was 6 years (range 3months-13 years). The most commonly diagnosed malignancies were hematologic malignancies (leukemias and lymphomas) constituting about 70.3% of cases.

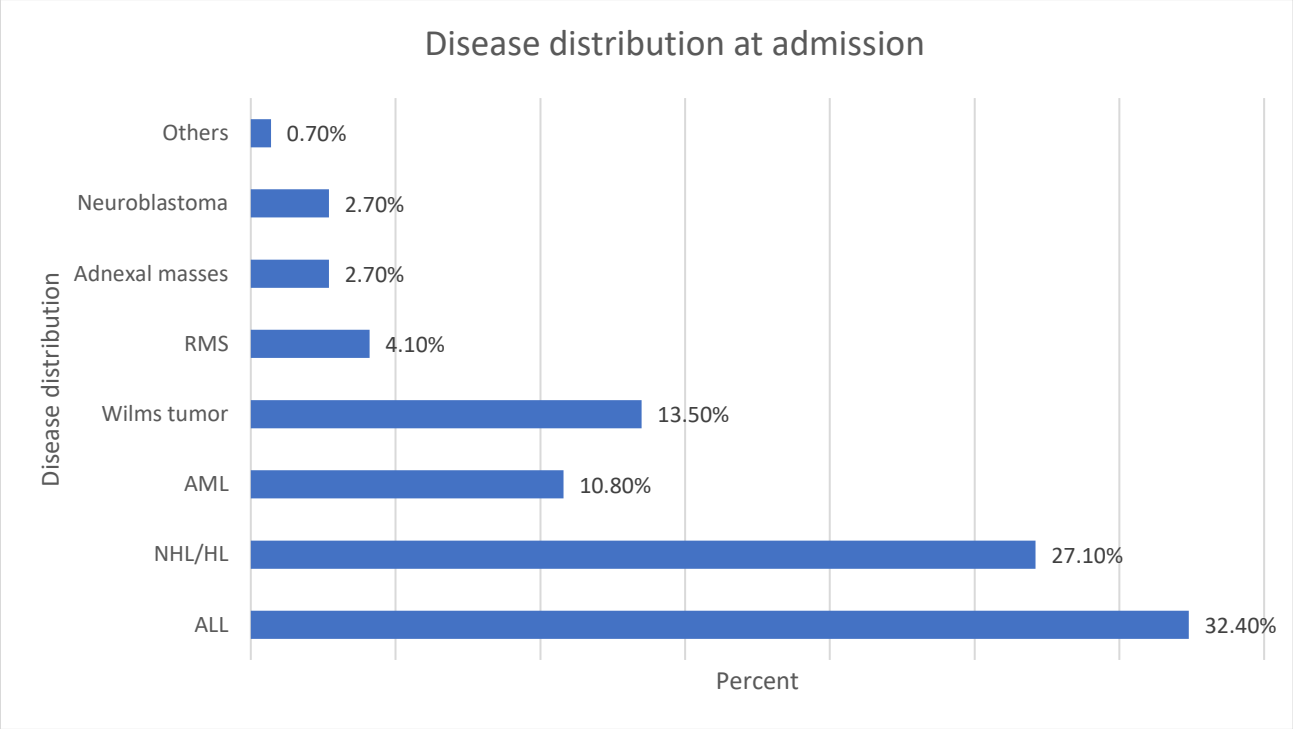

Figure 1 Disease distribution at admission

Twelve patients out of these 286 were identified as having typhlitis; 10 (83.3%) were male and 2 (16.7%) were female. The mean age at diagnosis was 7.7 years (Range 3-12 years). Five patients had been diagnosed with NHL, 4 patients had ALL, 2 patients had AML and 1 patient had a diagnosis of head and neck embryonal RMS. Eleven of the patients (91.7%) had their diagnosis confirmed histologically. One patient with mediastinal NHL had no tissue diagnosis and was diagnosed on imaging alone (via contrast enhanced chest CT).

Table 1 Disease distribution of patients with typhlitis

	Frequency	Percent	Valid Percent	Cumulative Percent
NHL- intrabdominal	4	33.3	33.3	33.3
HR-ALL	3	25.0	25.0	58.3
AML M2	1	8.3	8.3	66.7
AML M3	1	8.3	8.3	75.0
SR-ALL	1	8.3	8.3	83.3
NHL- Mediastinal	1	8.3	8.3	91.7
RMS	1	8.3	8.3	100.0
Total	12	100.0	100.0	

7.2 Patient signs and symptoms

The commonest signs and symptoms associated with typhlitis were abdominal pain and diarrhea seen in 83.3 % of patients followed by fever, vomiting and abdominal tenderness.

Table 2 Signs and symptoms of patients with typhlitis

	Percentage (%)
Abdominal pain	83.3
Diarrhea	83.3
Fever	66.7
Vomiting	50.0
Abdominal tenderness	41.7
Neutropenia	**83.3**

7.3 Laboratory results

Neutropenia was recorded in 10 (83.3 %) patients. Two patients (16.7 %) had typhlitis in the absence of neutropenia. The overall mean ANC was 288.3 cells/mm3 with maximum of 1900 and minimum of 0 cells/mm3 respectively.

Table 3 Absolute neutrophil count of patients

	n (%)
Neutropenia (ANC <500 cells/mm3)	10 (83.3)
Profound neutropenia (ANC <100cells/mm3)	8 (80)
No neutropenia	2 (16.7)
Total	12 (100)

The table below summarizes some of the other important laboratory investigations done for these patients. Renal function tests and liver enzymes were normal in all of the patients who had these investigations. Serum electrolyte levels were determined for 5 (41.7%) of the 12 patients. Isolated hypokalemia and multiple electrolyte imbalances were detected in equal percentages (16.7%)

Table 4 Serum laboratory investigations

Renal function test	**n (%)**
Normal	9(75)
Deranged	0
Liver enzymes	
Normal	5(41.7)
Deranged	0
Electrolyte	
Normal	1(8.3)
Deranged	4(33.3)
Blood/urine/stool culture	0

7.4 Treatment history

7.4.1 Chemotherapy regimen

Twenty five percent of the patients were on HR-ALL 4-drug induction protocol, 25% on NHL ALCL A2 phase and the rest comprising of 8.3 % each were on various treatment regimens according to their primary diagnosis.

Table 5 Primary diagnosis, phase of chemotherapy and days from last chemotherapy

Patient ID	**Primary diagnosis**	**Phase of chemotherapy**	**Number of days from last phase of Chemotherapy**
1	SR-ALL(L2)	3-drug Induction phase	0*
2	Intrabdominal HG-NHL	NHL ALCL A2	4
3	Intrabdominal HG-NHL	NHL ALCL A2	10
4	Intrabdominal HG-NHL	NHL ALCL A2	5
5	AML(M3)	APML	0*
6	HR-ALL	4-drug Induction phase	0*
7	HR-ALL	4-drug Induction phase	0*
8	Intrabdominal HG-NHL	NHL ALCL A1	5
9	HR-ALL	4-drug Induction Phase	0*
10	Mediastinal HG-NHL	NHL ALCL B2	0*
11	Head and neck embryonal RMS	VCD	0*
12	AML(M2)	HIDAC	16

Note: 0* refers to patients who were on chemotherapy when symptoms developed

Of the patients who developed typhiltits, 7 (58.3 %) were on chemotherapy when they developed symptoms. These were all of the 4 patients with ALL on induction phase, 1 patient each with AML (M3), mediastinal NHL and embryonal RMS.

Table 6 Time to developing typhlitis from last phase of chemotherapy

	Frequency	Percent	Valid Percent	Cumulative Percent
On chemo	7	58.3	58.3	58.3
5 days post chemo	2	16.7	16.7	75.0
4 days post chemo	1	8.3	8.3	83.3
10 days post chemo	1	8.3	8.3	91.7
16 days post chemo	1	8.3	8.3	100.0
Total	12	100.0	100.0	

Vincristine (Intravenous) and intrathecal methotrexate were part of chemotherapy in 83.3% of patients. Cyclophosphamide and cytosine arabinoside were used in 50%.

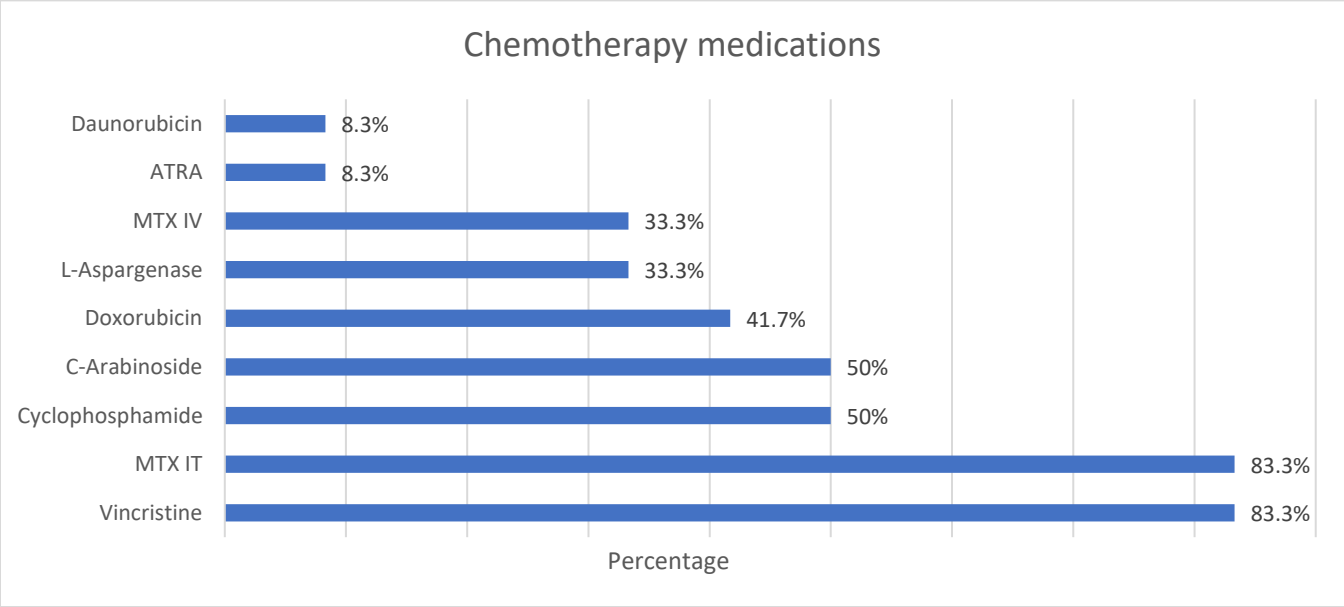

Figure 2 Bar chart of types of chemotherapy drugs taken in percent

Ten patients (83.3%) had received steroid as part of their chemotherapy regimen either in the form of dexamethasone or prednisolone. One of the two patients who have not received steroid as part of chemotherapy (patient with AML) was treated with IV dexamethasone for management of elevated intracranial pressure.

7.4.2 Additional medical management

All of the patients were on IV antibiotics. The most commonly used being IV metronidazole used in 58.3% followed by ceftriaxone and vancomycin being used in 50% of patients each. The least used medications were ciprofloxacin and cloxacillin (8.3% or 1 patient each). The antifungal fluconazole and antiviral acyclovir were used in 25% of patients. Amphotericin B was given to only one patient (8.3%).

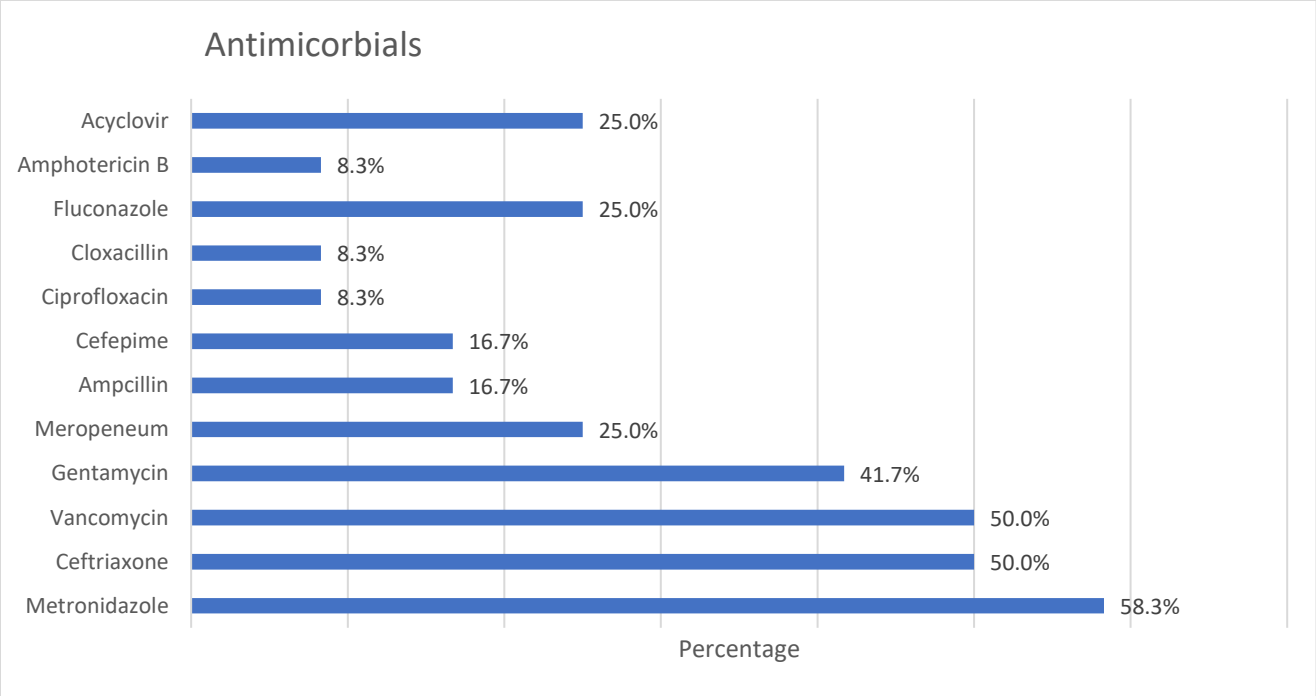

Figure 3 Bar chart of type of antimicrobials taken in percent

History of narcotic use in the 2 weeks prior to developing typhlitis was noted in 25% of cases.

7.4.3 Surgical management

None of the patients underwent surgical interventions.

7.5 Radiologic findings

All patients were evaluated with ultrasound. None of the patients had CT scan or plain radiography done as part of evaluation for typhlitis. The commonest involved site was identified as the combination of cecum and ascending colon in 4 patients (33.3%) followed by involvement of the terminal ileum only in 2 (16.7%).

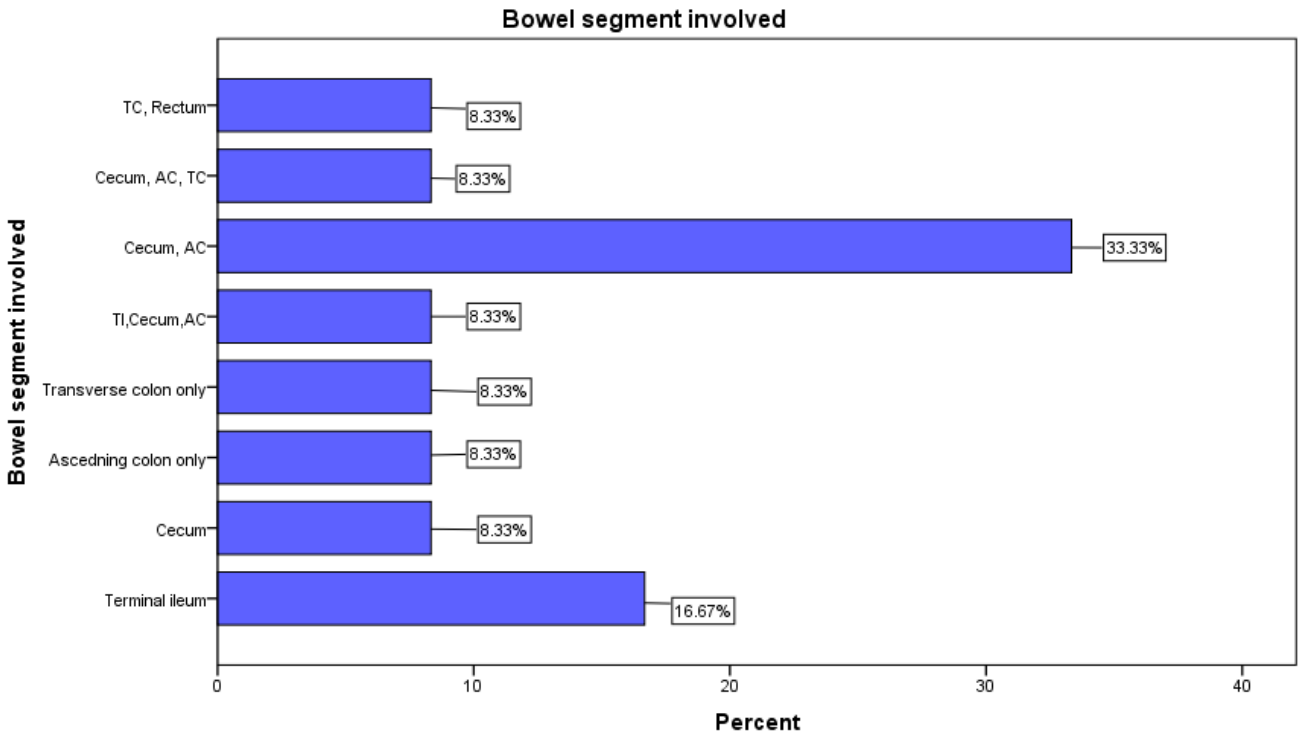

Figure 4 Bar chart of bowel segments involved on ultrasound in percent

Thickness of bowel loops involved is mentioned in 11 out of 12 patients with a mean thickness of 11.1mm (Range 5-40mm).

Terminal ileal distension, presence or absence of inflammatory mass/abscess and free gas was not mentioned in the sonographic reports of any of the patients. Mesenteric fat stranding and history of appendectomy were mentioned in 1 patient each. Peritoneal fluid collection without full descriptive factors (site, size, echogenicity, complexity) was mentioned in one third of cases. The rest of the reports did not comment on the presence or absence of fluid collection.

7.6. Final outcome

Eight of 12 (66.7%) of patients were alive at time of completion of this research. The rest had passed from complications not related to typhlitis.

Table 7 Final outcome of patients with typhlitis

Patient ID	Primary diagnosis	Cause of death
01	SR-ALL	Transfusion related acute lung injury
09	HR-ALL	NA
11	H&N embryonal RMS	Cardiorespiratory arrest 2ry to upper air way obstruction 2ry to mass
12	AML(M2)	Cardiorespiratory arrest 2ry to stage III HIE, Septic shock, AML relapse

8. DISCUSSION

This study describes the clinical and imaging characteristics of patients diagnosed with typhlitis.

Typhlitis is defined by the clinical triad of fever, neutropenia, abdominal pain and radiologic evidence of inflammation of the colonic wall or the presence of 2 of 3 the clinical triads in the presence of radiologic evidence of colonic inflammation.

Our research had found that 4.2% (12/286) of pediatric cancer patients developed typhlitis and this condition was more common in children diagnosed with hematologic malignances (leukemia, lymphoma) which made up 91.7% of the identified patients. Of the hematologic malignancies 75% had NHL and ALL. The mean age at diagnosis was 7.7 years. Males made up 83.3% and females 16.7% of the diagnosed patients. There have been several studies conducted concerning the incidence of typhlitis in pediatric cancer patients, albeit most of them focused on patients with acute leukemias. Incidences ranging from as low as 0.3% (6) to as high as 24% (8,11) have been reported. Most other studies showed incidences in the range of 2-10% (4,9,10,12). These wide range of incidences could be attributed to the different study designs used with higher incidences being reported in those using autopsy as their gold standard (8,9). The mean age at diagnosis of typhlitis in our patients is slightly lower than reported in other studies which report ages of between 8.5-10years (2,4,10). Our study also showed a significantly higher incidence of typhlitis in males whilst previously reviewed literature showed only a slight male predominance (4,8). This could be attributed in part to the overall higher admission rate of males to the ward.

In terms of chemotherapeutic drugs, the multi-drug nature of treatment regimens has made it difficult to definitively establish a causal role for individual drugs although regimens consisting of steroids, vincristine, anthracyclines (doxorubicin, daunorubicin etc.) and cytosine arabinoside have been implicated for their ability to cause bowel hypomotility and mucosal alterations that predispose to the development of typhlitis (1,2,6,10). Our research had found that vincristine was part of the chemotherapy regimen in 83.3% of patients with typhlitis and cytosine arabinoside was used in 50%. Intrathecal methotrexate was part of the treatment regimen in 75% of cases. Vincristine's association with typhlitis in our study could be attributed to the ubiquitous use the drug in the treatment of the majority of hematologic malignancies. Doxorubicin and daunorubicin (anthracycline drugs) were used in less than 50% of the cases. Use of steroid as

part of chemotherapy was recorded in 83.3% of patients. Use of narcotics within 2 weeks of symptoms is thought to be associated with development of typhlitis due to the ability of these drugs to cause bowel hypomotility. In our case, use of narcotics was noted in only 25% of patients.

With respect to clinical signs and symptoms, the most commonly identified were abdominal pain and diarrhea seen in 83.3% of cases followed by fever in 67.7% which is consistent with what is known about the common manifestation of the condition (4,8,10). Degree of neutropenia is known to have strong correlation with duration and severity of illness (2,5). Neutropenia was detected in 83.3% of the patients in our study with 80% of these having profound neutropenia. A correlation of the degree of neutropenia with severity and duration of illness could not be done in our case as the time to resolution of disease could not be clearly ascertained clinically or radiologically.

In our study, typhlitis was diagnosed in all patients by ultrasound (100%). No cases were identified through plain radiography or CT scan. Inflammation of the right-side colon consisting of the cecum and ascending colon was noted in over a third of patients which is consistent with the nature of the disease (2,7).

With respect to complications, none of the patients in our study had died of typhlitis. This is found to be inconsistent with the high mortality rates seen in other low to middle income countries which report mortality rates of around 24 and 45% (11,12)

9. CONCLUSION

Typhlitis is an uncommon complication in children with malignancies. It is more commonly seen in those with hematologic malignancies (acute leukemias, lymphomas). Common symptoms are abdominal pain, diarrhea and fever which in the presence of neutropenia and findings of colonic inflammation should prompt a consideration of this diagnosis.

10. LIMITATIONS AND RECOMMENDATIONS

Due to the retrospective nature of the study, the full data set of patients needed to obtain a complete picture of the disease's status in our hospital could not be achieved. A significant limitation encountered is the missing medical records of more than half of the patients admitted during the study period. This has significantly limited our ability to give a more complete picture of the disease. In addition, incomplete and disorganized documentation of patients' clinical data and inconsistent reporting of imaging findings were encountered. In order to minimize these short comings, we recommend that there needs to be a more organized keeping of patients' medical records and improved recording of patient's clinical and treatment history. We also need to develop the habit of reporting patient's imaging findings in a standardized and more uniform manner. We feel a broader multidepartment prospective study could overcome these limitations and lead to a better understanding of this little studied entity.

11. QUESTIONNAIRE

Topic- Status of Typhlitis in pediatric oncology patients taking Chemotherapy in TASH

Demographic Data-

Patient code_____ Age (Years/Months) _____ Sex M/F

Patient's primary diagnosis_____

Disease confirmed from (mark √ on relevant),

Pathologic specimen- Incisional/Excisional Biopsy_____ FNAC_____

Peripheral Morphology_____ Bone Marrow Biopsy _____ Bone marrow Aspirate____

Imaging- CT _____ MRI_____

Both _____

Clinical Hx		
	Yes (State Duration)	**No**
Current Symptoms		
Abdominal pain (localize if possible)		
Nausea		
Vomiting		
Diarrhea (watery, mucoid, bloody)		
Constipation		
Bleeding per rectum		
Clinical signs		
Fever (Celsius)		
Abdominal tenderness (if localized by physician)		
Laboratory findings	**Normal**	**Deranged**
CBC		WBC count(cell/mm^3) _____

		ANC (cell/mm³) _____ Platelet count (cell/mm³) ____
OFT (if available)		
Electrolytes (if available)		
Blood culture (if available)		
Previous episodes of typhlitis in number		

Treatment History

Chemotherapy	
Regimen	
Dose	
Steroid given as part of chemo	
Phase of treatment	
Time from last chemotherapy (in weeks)	

Additional treatments	**Yes (State medications used)**	**No**
Antibiotic		
Antifungal		
Antivirals		
Narcotics use (within 2 weeks)		
Corrected electrolyte imbalance		
Surgical management		

Imaging findings (Abdominal ultrasound/CT/X-Ray)

Segment(s) of bowel involved _____

Thickness of bowel segment(s) involved (in mm) _____

Proximal ileal distension- Yes ☐ No ☐ Not mentioned ☐

Status of the appendix- Normal ☐ Not identified ☐ Abnormal ☐ Not mentioned ☐

Status of adjacent mesentery- Normal ☐ Edematous ☐ Fat stranding ☐

Not mentioned ☐

Complications identified-

Inflammatory mass or Abscess Yes ☐ No ☐ Not mentioned ☐

Free intraperitoneal gas Yes ☐ No ☐ Not mentioned ☐

Free peritoneal fluid collection Yes ☐ No ☐ Not mentioned ☐

If Yes: Site_____

Volume_____

Simple vs complex_____

Final patient status

Patient outcome Alive ☐ Dead ☐

If dead, state cause of death_____

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