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Investigation of typhlitis in bone marrow transplant patients in a stem cell transplant unit

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Abstract

Typhlitis is a special type of enterocolitis that specifically develops in immunosuppressive patients with hematological malignancies. Typhlitis is a common consideration after bone marrow transplantation due to high-dose chemotherapy that is used in conditioning regimens those contain high-dose cytotoxic chemotherapeutic agents. Although there are several studies about typhlitis during chemotherapy or in leukemia patients, there is not enough data evaluating its relationship between stem cell transplant in adults. Therefore, the current study aimed to analyze the possible causes that may lead to the development of typhlitis in hematopoietic stem cell recipient patients. This retrospective study included 210 adult patients who underwent bone marrow transplantation between January 2017 and December 2019. Pediatric patients (patients younger than 18 years of age) were excluded. Patients' data were evaluated to determine their effects on typhlitis and the mortality risk of the patients with typhlitis. The analysis of the variables was performed using the IBM SPSS Statistics for Windows version 26 (IBM Corp., Armonk, NY).Variables were analyzed at a 95% confidence level and a *P* value <0.05 was considered significant. Typhlitis developed in 23 (10.9%) transplant patients. Male sex, length of hospital stay, presence of febrile neutropenia, antibiotic and antifungal use, need for switching antibiotics, duration of neutropenia, diarrhea and antibiotic use in days were risk factors for development of typhlitis. It was observed that 100-days mortality was higher in typhlitis group reaching to a statistical significance (*P* < .05). In multiple logistic regression analysis, presence of mucositis and additional source of infection were determined as independent risk factors for the development of typhlitis in bone marrow transplant patients. This study provides valuable information for bone marrow transplant patients through an analysis of risk factors for the development of typhlitis. According to our results, mucositis and additional bacterial infections were found as risk factors for typhlitis therefore it would be beneficial for clinicians to consider these factors in patient follow-up. However, due to the retrospective nature of our study, prospective studies are needed to investigate risk factors and optimum treatment methods for typhlitis.

Abbreviations: BEAM = Carmustine, Etoposide, ARA-C and Melphalan, CI = confidence interval, *E. coli* = *Escherichia coli*, EBMT = European Society for Blood and Marrow Transplantation, ELFA = Enzyme-Linked Fluorescent Assay, ELISA = Enzyme-linked immunosorbent assay, GDH = glutamate dehydrogenase, OS = odds ratio, TPN = total parenteral nutrition.

Keywords: bone marrow transplantation, immunosuppression, risk factors, typhlitis

1. Introduction

Neutropenic enterocolitis (typhlitis) is a special type of enterocolitis that specifically develops in immunosuppressive patients due to high-dose chemotherapy and has unique diagnostic criteria. Some papers define neutropenic enterocolitis as ileocecal syndrome as it is still not a biopsy proven but clinical and imaging based exclusion based entity.[1] Typhlitis is seen in the neutropenic period and significantly affects both success of treatment and survival.[2] Typhlitis is a syndrome associated with a number of clinical scenarios rather than a specific disease.[3] Typhlitis is a predominantly cecum-based disease with high mortality. Clinical presentation is characterized as ileocolonic inflammation and bowel wall thickening. Neutropenia is the major risk factor for its development.[4] Typhlitis should be considered in any severely neutropenic patient who presents with fever and abdominal pain. The location of abdominal pain depends on the location of the neutropenic colitis and is often in the right lower quadrant. Symptoms, including fever, frequently appear during the third week after receiving cytotoxic chemotherapy at a time when neutropenia is most profound.[5] The pathogenesis of typhlitis remains incompletely understood. It probably involves a combination of factors, including mucosal injury by cytotoxic drugs or other means (such as

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immunosuppression due to comorbidities), profound neutropenia and impaired host defense to bacterial translocation.[6] It should always be taken into consideration as the mortality rate is high.[4] Patients may remain febrile until myeloid reconstitution independent of antimicrobial therapy. This, in turn, may lead to increased prescription of antimicrobial medications, increased toxicities, use of resources and selection for resistant microorganisms.[7] A general initial approach to patients with typhlitis without complications includes nonsurgical management with bowel rest, intravenous fluids, nutritional support, blood product support and broad-spectrum antibiotics.[8] Surgical intervention is recommended for individuals with perforation with free air in the peritoneum, persistent gastrointestinal bleeding despite correction of coagulopathy and cytopenias, in the presence of clinical deterioration during close observation and serial examinations or development of another indication for surgery.[9] Surgery is not preferred in these cases because of bleeding, increased risk of infection, and poor healing.[10] Although surgery is avoided by many centers; a metaanalysis showed that surgery did not cause excess risk compared to conservative treatment.[11]

Typhlitis has been observed in adults and children associated with many conditions including solid malignant tumors, the acquired immunodeficiency syndrome and after solid organ and bone marrow transplantation.[12–15] Typhlitis is a common consideration after bone marrow transplantation.[16] Diagnostic criteria for typhlitis were suggested by Gorschlüter et al in a systematic review include fever, abdominal pain, and any bowel wall thickening more than 4 mm seen on imaging in addition to the exclusion of Clostridioides difficile as a cause of the colitis.[17] Evaluating typhlitis in hematopoietic stem cell recipients could provide very valuable data from a medical and scientific point of view. Accordingly, the current study aimed to analyze the frequency of typhlitis and possible factors that may lead to the development of typhlitis in patients who underwent stem cell transplantation.

2. Material and Methods

2.1. Patients

The current study included 210 adult patients who underwent bone marrow transplantation in the stem cell transplantation unit in Medstar Antalya Hospital (EBMT CIC:864) between January 2017 and December 2019. Patients younger than 18 years of age were excluded. Patients' medical records were analyzed retrospectively. Patients' data regarding comorbidities, length of hospital stay, mortality, conditioning regimen, transplant procedure (autologous or allogeneic), infections, isolated microorganisms, duration of antibiotic and antifungal treatments, neutropenia, diarrhea, total parenteral nutrition (TPN) (days), cecum wall thickness, presence of febrile neutropenia and mucositis were evaluated to determine their effects on typhlitis. Mucositis was assessed by using MASCC/ISOO Clinical Practice Guidelines for the Management of Mucositis Secondary to Cancer Therapy.[18] Neutropenic patients who have at least one of those signs or symptoms such as diarrhea, pain or rebound in right lower quadrant, abdominal pain were suspected for typhlitis. Typhlitis was diagnosed with cecum wall thickness > 4 mm by ultrasound.

2.2. Microbiological and radiological procedures

The initial microbiologic workup includes taking blood cultures and stool. Fecal samples were collected from cases in nonsterile, wide-mouth, screw capped containers and immediately transferred to the laboratory, preferably within 2 hours. Specimens were processed for microscopy, culture, and ELISA for C difficile toxin assay and immunochromatographic tests for Entamoeba histoytica antigens.

A direct wet mount for fecal leukocytes and parasites ova, cysts and trophozoites. Stool cultures are done for only to detect Salmonella spp. and Shigella spp.

For toxin assay, C. difficile toxin A + B Stool Antigen ELISA Kit manufactured by bioMeriux vidas, France was used. VIDAS® C. difficile glutamate dehydrogenase (GDH) is a qualitative test that detects the C. difficile antigen, (GDH), in stool specimens to screen patients suspected of having a C. difficile infection. It is used in conjunction with VIDAS® C. difficile Toxin A & B as part of a two-step algorithm. Both tests are based on the ELFA (Enzyme-Linked Fluorescent Assay) technique. The tests were carried out as per manufacturer instructions.

E. histolytica antigen test was supplied by Operon S.A (Zarogosa Spain), and was specifically designed to identify E. histolytica-specific antigen in stool samples by chromatographic immunoassay. The test was carried out as per manufacturer instructions.

Cecum wall thickness was measured by Siemens S200 ultrasound device (Siemens Healthcare GmbH, Erland, Germany).

2.3. Pretransplant procedures

All patients were checked for Hepatitis B, Hepatitis C, Human immunodeficiency virus, Cytomegalovirus, Varicella zoster virus and Epstein barr virus serology. Routine vancomycin resistant enterococcus was not tested to check carrier status before transplant.

As a dietary application; in patients expected to have prolonged neutropenia some diet restrictions were done such as restriction of green leafy vegetables and use of pasteurized dairy product. And there was no difference between autologous or allogeneic transplant procedures. In the neutropenic stage, TPN was started in case of abdominal pain, resistant vomiting or when there was defense and/or rebound in physical examination. TPN initiation was independent from conditioning regimen according to our center experience.

2.4. Transplant procedures and conditioning regimens

According to our center's experience commonly used conditioning regimens for transplant procedures were performed as; for allogeneic transplantation; busulfan and fludarabine were used. Intensity of conditioning regimen is controlled by the modification of busulfan dose, either myeloablative or nonmyeloablative that was defined according to EBMT study by Spyridonidis et al.[19] For autologous transplantation; for myeloma patients high-dose melphalan was used. Commonly used autologous conditioning regimen for lymphoma patients was BEAM (Carmustine, Etoposide, ARA-C and Melphalan).

2.5. postTransplant prophylaxis

Allogeneic stem cell transplantation (including unrelated or haploidentical transplants); as antiviral prophylaxis; valacyclovir 2 × 500 mg until day + 180, for pneumocystis pneumonia prophylaxis, trimethoprim + sulfamethoxazole 160/800 mg/day until day + 180, for antifungal prophylaxis, fluconazole 400 mg/day per oral until day + 90 and for antibacterial prophylaxis, levofloxacin 400 mg/day per oral until neutrophil engraftment.

Autologous stem cell transplantation; as antiviral prophylaxis; valacyclovir 2 × 500 mg, for pneumocystis pneumonia prophylaxis, trimethoprim + sulfamethoxazole 160/800 mg/day, for antifungal prophylaxis, fluconazole 200 mg/day per oral and for antibacterial prophylaxis, levofloxacin 400 mg/day per oral. Discontinuation of prophylaxis in autologous stem cell transplantation patients depended on primary disease or maintenance therapy after transplant.

2.6. Statistical analysis

The analysis of the variables was performed using the IBM SPSS Statistics for Windows Version 26 (IBM Corp., Armonk, NY, USA). The conformity of univariate data to normal distribution was evaluated with the Shapiro–Wilk Francia test. Mann–Whitney U test was used together with Monte Carlo method to compare 2 independent groups with each other according to quantitative data. In the comparison of categorical variables, Pearson Chi-Square, Fisher Exact and Fisher-Freeman-Holton tests were used together with Monte Carlo simulation technique and column ratios were compared with each other and expressed according to Benjamini-Hochberg corrected *P* value results. Odds ratio (OS) with 95% confidence interval (CI) was used to determine how much the patients with a risk factor are at higher risk as compared with those without a risk factor. Machine learning methods were used to predict those with and without typhlitis and to find the variable with the highest significance in this estimation. While applying these models, the training dataset was set to 100% and the test dataset to 0%, as there were 23 patients with typhlitis. Default settings were used in all models. Supervised machine learning methods, namely logistic regression, random forest, K-nearest neighbor algorithm, simple (naive) Bayes classification and neural network (multilayer perceptron and radial basis function) were used to find and predict the variable with the highest significance in the presence of typhlitis. The results of the logistic regression analysis, which is the most successful model among these methods, were reported using the backward stepwise (wald) method. Quantitative variables were expressed as mean (standard deviation) and median (minimum/maximum) and median (25^{th} percentile [q1]/75^{th} percentile [q3]), while categorical variables were expressed as number (percentage, %). Variables were analyzed at a 95% confidence level and a *P* value <0.05 was considered significant.

2.7. Ethics

The study was approved by the Ethics Committee of Memorial Hospitals Group (approval date: 22.04.2021, approval number: 267/2021). Written informed consent was obtained from patients.

3. Results

The study included 210 adult bone marrow transplant patients (118 males, 92 females) with a median age of 50. The mean age of the patients was 47.68 ± 16.82 years. Typhlitis developed in 23 patients (18 males and 5 females).

The patients had different diagnoses including multiple myeloma (33.3%), acute myeloid leukemia (21.4%), nonHodgkin lymphoma (13.8%), acute lymphocytic leukemia (13.3%), Hodgkin lymphoma (11.4%). In 32.4% of the patients, at least one comorbidity such as; hypertension, diabetes mellitus, coronary artery disease, venous thromboembolism, hypothyroidism, chronic renal insufficiency or benign prostatic hyperplasia, was present. Median neutropenia duration was 11 days and the length of stay was 29 days. One hundred and twelve patients (53.3%) had febrile neutropenia and 124 patients (59.0%) had mucositis. Male sex, neutropenia duration, length of hospital stay, presence of febrile neutropenia, and mucositis were risk factors reaching a statistical significance for the development of typhlitis (*P* < .05; Table 1). Hypertension, coronary artery disease, diabetes mellitus were the most frequently observed comorbidities. Lung was one of the most frequent additional infection sources (62.5%) followed by mucositis (oral and gastrointestinal mucosal injury induced by cytotoxic chemotherapy) (14.3%). The most frequent microorganism isolated from the cultures was *Escherichia coli* (48.3 %) followed by *Klebsiella* spp. (17.2%). Piperacillin/tazobactam (45.5%), cefepime + metronidazole (21.4%), piperacillin/tazobactam + teicoplanin (11.6%) were the most frequently used antibiotic regimens in the patients.

The mean neutropenia duration, length of hospital stay and diarrhea duration were 12.02 ± 6.88 days, 30.54 ± 11.03 days and 6.39 ± 3.53 days, respectively. The mean cecum wall thickness was 8.30 ± 2.05 and the mean TPN and antibiotic use time were 14.70 ± 8.69 days and 4.86 ± 3.11 days, respectively (Table 2). The presence of TPN, diarrhea, pathogenic microorganisms in the stool culture and additional infection sources were significantly higher in the typhlitis group (*P* < .05). Antibiotic use, the need for switching antibiotics and antifungal use were higher in the typhlitis group (*P* < .05). Diarrhea duration, TPN time, and antibiotic time (days) were risk factors for the development of typhlitis (*P* < .05). It was observed that 100-days mortality was significantly higher in the typhlitis group (*P* < .05) (Table 3).

In multivariate logistic regression analysis, it was determined that the presence of mucositis (OR, 19.4; 95% CI, 2.61–144.6; *P* = .004) and an additional source of infection (OR, 4.4; 95% CI, 2.12–9.0; *P* < .001) were independent risk factors for the development of typhlitis in bone marrow transplant patients.

4. Discussion

Typhlitis results from a combination of mucosal injury and impaired host defenses to intestinal organisms and therefore, it is expected to develop more frequently in bone marrow transplant patients. In the current study, typhlitis developed in 23 patients (10.9%), which is higher than the literature. In a systematic review including 21 studies by Gorschlüter et al the incidence rate of typhlitis was 5.3% in patients hospitalized for hematological malignancies, high-dose chemotherapy for solid tumors, or aplastic anemia.[17]

Although typhlitis is more commonly observed in children, it has also been described in adults. The median age of the patients with typhlitis in the current study was 54 years and the mean age of the patients had no effect on the development of typhlitis, however, male sex was determined to be a risk factor in the current study. While there was a predominance of cases of acute myeloid leukemia in children with typhlitis in previous studies,[20] the patients in the current study had different diagnoses, which had no effect on the development of typhlitis. So, it is to be expected that the children would have more representation of AML as there would be more such patients in the group. The conditions of the adults in this study are more varied than in children. In addition, the presence of comorbidities was not a risk factor for the development of typhlitis.

In a previous study, there was no significant difference between typhlitis cases and controls with respect to age and comorbidities.[21] Transplant type – either autologous or allogenic and conditioning regimen – had no effect on the development of typhlitis in our study. However, neutropenia duration and presence of febrile neutropenia were significantly higher in the typhlitis.

Typhlitis is a common cause of the life-threatening crisis in immunocompromised and neutropenic patients.[22] As bone marrow transplant patients have many risk factors for immunosuppression and neutropenia, the possibility of the development of typhlitis is quite high. Fever sometimes is not observed in patients with severe neutropenia.[23] This clinical situation should always be kept in mind during the treatment and clinical follow-up period of these patients. Typhlitis should be considered in the differential diagnosis of any severely neutropenic patient. Symptoms frequently appear at a time when neutropenia is most profound and the patient is febrile.[24] In a cohort study, typhlitis was found in 3.5% of 317 severely neutropenic patients.[25] In this respect, the findings of the present study are in line with the literature data.

The presence of mucositis was significantly higher with a statistically significant level in the typhlitis patients in the current study. Cytotoxic therapy-induced intestinal epithelial damage is

Table 1

Clinical features of the patients.

	Total	Patients without typhlitis	Patients with typhlitis	
	n = 210	n = 187	n = 23	*P*
Age, median (q1-q3)	50 (34–62)	50 (34–62)	54 (26–59)	0.890*
Sex, n (%)				0.026†
Male	118 (56.2)	100 (53.5)	18 (78.3)‡	3.1 (1.1/8.8)¶
Female	92 (43.8)	87 (46.5)§	5 (21.7)	
Diagnosis, n (%)				0.067‖
HL	24 (11.4)	22 (11.8)	2 (8.7)	
NHL	29 (13.8)	24 (12.8)	5 (21.7)	
MM	70 (33.3)	66 (35.3)	4 (17.4)	
AML	45 (21.4)	42 (22.5)	3 (13.0)	
ALL	28 (13.3)	22 (11.8)	6 (26.1)	
AA	5 (2.4)	3 (1.6)	2 (8.7)	
ST	4 (1.9)	4 (2.1)	0 (0.0)	
MDS	5 (2.4)	4 (2.1)	1 (4.3)	
Underlying disease, n (%)				0.999†
No	142 (67.6)	126 (67.4)	16 (69.6)	
Yes	68 (32.4)	61 (32.6)	7 (30.4)	
Transplant type, n (%)				0.267†
ALLO	93 (44.3)	80 (42.8)	13 (56.5)	
AUTO	117 (55.7)	107 (57.2)	10 (43.5)	
Conditioning regimen, n (%)				0.431‖
MA Allo	78 (37.1)	68 (36.4)	10 (43.5)	
NMA Allo	16 (7.6)	13 (7.0)	3 (13.0)	
ICE	13 (6.2)	11 (5.9)	2 (8.7)	
HD Melp	68 (32.4)	64 (34.2)	4 (17.4)	
BEAM	34 (16.2)	30 (16.0)	4 (17.4)	
FLU + Cy	1 (0.5)	1 (0.5)	0 (0.0)	
Neutropenia day, median (q1-q3)	4 (2–5)	4 (2–5)	2 (1–4)	**0.032***
Neutropenia time, days median (q1-q3)	11 (8–14)	10 (8–14)	14 (11–21)	**<0.001***
Length of stay, median (q1-q3)	29 (21–36)	29 (21–36)	36 (30–41)	**0.001***
Febrile neutropenia, n (%)				**<0.001†**
No	98 (46.7)	98 (52.4)§	0 (0.0)	24.2 (3.2/183.4)¶
Yes	112 (53.3)	89 (47.6)	23 (100.0)‡	
Mucositis, n (%)				**<0.001†**
No	86 (41.0)	85 (45.5)§	1 (4.3)	18.3 (2.4/138.8)¶
Yes	124 (59.0)	102 (54.5)	22 (95.7)‡	

Statistically significant values are written with bold numbers.

AA = Aplastic anemia, ALL = Acute lymphocytic leukemia, ALLO = Allogeneic transplant, AML = Acute myeloid leukemia, AUTO = Autologous transplant, BEAM = Carmustine, Etoposide, Cytarabine, and Melphalan, FLU + Cy = Fludarabine and cyclophosphamide, HD melp = High-dose melphalan, HL = Hodgkin lymphoma, ICE = Ifosfamide, carboplatin, etoposide, ST = Solid tumor, MA = Myeloablative, MDS = Myelodysplastic syndrome, MM = Multiple myeloma, NHL = nonHodgkin lymphoma, NMA = nonmyeloablative.

*Mann-Whitney U test (Monte Carlo).

†Pearson Chi-Square Test (Monte Carlo).

‡Significant compared with the patients without typhlitis.

§Significant compared with the patients with typhlitis, q1: 25th percentile, q3: 75th percentile.

‖Fisher-Freeman-Halton test (Monte Carlo).

¶Odds Ratio; 95% Confidence interval.

associated with typhlitis due to the translocation of endogenous microorganisms colonizing gastrointestinal surfaces.[7] In a study, mucositis, hematopoietic cell transplantation and receiving chemotherapy in the last 2 weeks were significantly associated with the occurrence of neutropenic enterocolitis in pediatric patients with cancer.[26]

Length of hospital stay was a risk factor for the development of typhlitis in our study indicating an increase in the possible development of additional sources of infections in the hospital. As the length of stay increases, the possible development of infections increases leading to the use of broader spectrum antibiotics called vicious circle in the literature.[27] In our study, it was also observed that the presence of additional infection sources, isolated microorganism antibiotic use and antibiotic time significantly increased the risk of development of typhlitis. In a previous study, broad-spectrum antibiotics were thought to contribute to the process. Additionally, there was a predominance of cases of acute myeloid leukemia.[14] In a study by Nesher et al,[5] it was reported that most of the patients with typhlitis received at least one broad-spectrum antibiotics, emergence of resistant bacteria is due to antibiotic policy in centers increasing the risk of multiresistant bacterial infection. Although any significant association between combination antibiotic therapy and mortality could not be demonstrated due to the risk of bacterial resistance inherent to the population with preexisting antibiotic exposure, almost all patients in their cohort were treated with a combination therapy, as recommended by other authors.[5] In line with those literature data, our clinical approach to febrile neutropenia is empirically beginning with antipseudomonal beta lactam antibiotic and beta lactamase inhibitor (piperacillin + tazobactam). If typhlitis is suspected in the patient, in this case metronidazole is added to piperacillin + tazobactam or cefepime. For patients who have already febrile neutropenia, if typhlitis is suspected we generally switch antipseudomonal beta lactam to carbapenems. In most patients with typhlitis, at least 1 blood culture is positive, usually for a gram-negative organism. Commonly isolated pathogens are *Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Enterobacter taylorae, Morganella morganii and Streptococcus viridans*. *Clostridioides difficile* toxin has also been demonstrated in the

Table 2

Comorbidities, additional infection sources, antibiotics used, and other clinical features of the patients.

Characteristics	N	n (%)
Comorbidities, n (%)	68	
HT		26 (38.2)
Coronary artery disease		15 (22.1)
HT + DM		13 (19.1)
DM		6 (8.8)
BPH		4 (5.9)
Chronic renal insufficiency		2 (2.9)
Venous thromboembolism		1 (1.5)
Hypothyroidism		1 (1.5)
Additional infection source	57	
Lung		35 (62.5)
Mucositis		8 (14.3)
Catheter		7 (12.5)
Cholecystitis		4 (7.1)
Scrotum		1 (1.8)
Bowel		1 (1.8)
Isolated microorganisms	29	
Escherichia coli		14 (48.3)
Klebsiella spp.		5 (17.2)
Clostridioides difficile		3 (10.3)
Streptococcus spp.		1 (3.5)
Coagulase negative staphylococcus		3 (10.3)
Fungus		3 (10.3)
Antibiotics	112	
Piperacillin/Tazobactam		51 (45.5)
Cefepime + Metronidazole		24 (21.4)
Piperacillin/Tazobactam + Teicoplanin		13 (11.6)
Meropenem		8 (7.1)
Meropenem + Teicoplanin		4 (3.6)
Piperacillin/Tazobactam + Metronidazole		3 (2.7)
Imipenem + Metronidazole + Teicoplanin		3 (2.7)
Piperacillin/Tazobactam + Clarithromycin		1 (0.9)
Cefepime		1 (0.9)
Levofloxacin + Teicoplanin		1 (0.9)
Cefepime + Teicoplanin		1 (0.9)
Teicoplanin		1 (0.9)
Imipenem		1 (0.9)

		Mean ± SD	Median (min–max)
Age, years	210	47.68 ± 16.82	50 (18–78)
Neutropenia appearance day, d	208	3.37 ± 3.02	4 (–7–13)
Neutropenia duration, d	208	12.02 ± 6.88	11 (3–56)
Length of hospital stay, d	210	30.54 ± 11.03	29 (15–96)
Diarrhea duration, d	89	6.39 ± 3.5	5 (1–21)
Cecum wall thickness	23	8.30 ± 2.05	8 (6–12)
TPN duration, d	158	14.70 ± 8.69	12 (1–56)
TPN start day, d	158	2.60 ± 4.27	2 (-7–30)
Antibiotic start day, d	112	4.86 ± 3.11	5 (-5–14)
Antibiotic duration, d	112	11.53 ± 7.28	10 (1–50)

BPH = Benign prostatic hyperplasia, DM = Diabetes mellitus, HT = Hypertension, SD = Standard deviation, TPN = Total parenteral nutrition.

stool of some patients.[28] Different types of antibiotic combination regimens were also used in our study for the treatment and microorganisms were isolated from the cultures of the patients, most frequently being *E. coli* (48.3%) followed by *Klebsiella spp* (17.2%). The need for switching antibiotics and antifungal treatment were also significantly higher in typhlitis patients. The rate of invasive fungal disease reaches 20% in patients with typhlitis when enteritis is considered. To avoid treatment delay, antifungal therapy might be systematically discussed in intensive care unit patients admitted for typhlitis with radiologically assessed enteritis.[29]

Presence of diarrhea and diarrhea duration in days were also statistically higher in the typhlitis group in our study. As it is known, diarrhea is a common complication in neutropenic patients and it is a frequent complication of cytotoxic chemotherapy. Typhlitis is a specific disease entity, usually manifesting itself with diarrhea and is thought to be associated with chemotherapy-induced mucosal injury followed by a superinfection usually by Gram-negative antibiotic and may lead to bacteremia.[25] Diarrhea induced by cytotoxic compounds is most likely due to mucositis but may also be due to the alteration of the bacterial flora of the gut.[30] *C. difficile* enterocolitis is one of the most frequent nosocomial etiology of diarrhea in neutropenic patients that can also be treated with fecal microbiota transplantation.[31,32] 100-days mortality were significantly higher in the patients with typhlitis (21.7%) compared to the patients without typhlitis (0.04 %). In our study, typhlitis was found to be associated with high mortality rates as reported in the literature.[10] In the literature, mortality rates of typhlitis can be up to 63% in adults[33] and up to 71% in children.[14] Our study also showed that the development of typhlitis in bone marrow transplant patients

Table 3

Comparison of patients with and without typhlitis regarding factors affecting typhlitis.

	Total	Patients without typhlitis	Patients with typhlitis	
	n = 210	n = 187	n = 23	*P*
Diarrhea, n (%)				**<0.001***
No	122 (58.1)	122 (65.2)†	0 (0.0)	41.3 (5.4/313.3)ǁ
Yes	88 (41.9)	65 (34.8)	23 (100.0)‡	
Diarrhea duration days median (q1-q3)	5 (4–8)	5 (4–7)	8 (6–10)	**<0.001**§
TPN time, days median (q1-q3)	12 (10–18)	12 (9–16)	18 (12–25)	**0.004**§
TPN start day, median (q1-q3)	2 (0–4)	2 (0–4)	2 (0–5)	0.991§
TPN, n (%)				**0.004***
No	53 (25.2)	53 (28.3)†	0 (0.0)	8.7 (1.1/66.2)ǁ
Yes	157 (74.8)	134 (71.7)	23 (100.0)‡	
Stool microorganisms, n (%)f				0.999f
No	203 (96.7)	180 (96.3)	23 (100.0)	
Yes	7 (3.3)	7 (3.7)	0 (0.0)	
Additional infection sources, n (%)				**0.001***
No	151 (71.9)	142 (75.9)†	9 (39.1)	4.9 (2/12.1)ǁ
Yes	59 (28.1)	45 (24.1)	14 (60.9)‡	
Isolated microorganisms, n (%)				**<0.001***
No	168 (85.3)	161 (91.5)†	7 (33.3)	21.5 (7.5/61.4)ǁ
Yes	29 (14.7)	15 (8.5)	14 (66.7)‡	
Need for antifungal, n (%)				**<0.001***
No	169 (80.5)	161 (86.1)†	8 (34.8)	11.6 (4.5/30.1)ǁ
Yes	41 (19.5)	26 (13.9)	15 (65.2)‡	
100-days mortality, n (%)				**0.010**f
No	196 (93.3)	178 (95.2)†	18 (78.3)	5.5 (1.7/18.2)ǁ
Yes	14 (6.7)	9 (4.8)	5 (21.7)‡	
Antibiotic use, n (%)				**<0.001***
No	98 (46.7)	98 (52.4)†	0 (0.0)	24.2 (3.2/183.4)ǁ
Yes	112 (53.3)	89 (47.6)	23 (100.0)‡	
Need for switching antibiotics, n (%)				**<0.001***
No	162 (77.1)	155 (82.9)†	7 (30.4)	11.1 (4.2/29.1)ǁ
Yes	48 (22.9)	32 (17.1)	16 (69.6)‡	
Antibiotic start day, median (q1-q3)	5 (3–6.5)	5 (4–7)	3 (1–5)	**0.001**§
Antibiotic time, days median (q1-q3)	10 (7–14)	9 (7–14)	14 (7–21)	**0.021**§

Statistically significant values are written with bold numbers.

*Pearson Chi-Square Test (Monte Carlo).

†Significant compared with the patients with typhlitis.

‡Significant compared with the patients without typhlitis. q1: 25th percentile, q3: 75th percentile.

§Mann-Whitney U test (Monte Carlo).

fFisher Exact Test (Monte Carlo).

ǁOdds Ratio, 95% Confidence interval.

led to a high mortality. Presence of TPN and TPN time in days were also significantly higher in typhlitis patients. TPN is also a risk factor as an additional infection source, the presence of which can lead to bacteremia that is important in pathogenesis of typhlitis. The guidance for antimicrobial therapy should be according to the patient bacteremia and local resistance pattern. The patient should receive a broad-spectrum antimicrobial that covers for gram-negative and anaerobic microorganisms. Monotherapy with piperacillin-tazobactam, carbapenem, or antipseudomonal cephalosporin such as cefepime with metronidazole can be initiated start empirically.[34] If there is a suspicion of mucositis, treatment for gram-positive bacteria should be taken into consideration.[35] The presence of mucositis and prolonged duration of profound neutropenia are risk factors for typhlitis.[17] According to multiple logistic regression analysis performed in our study, presence of mucositis and additional infection sources were determined as independent risk factors for the development of typhlitis in bone marrow transplant patients.

As far as we know, the first study in autologous stem cell transplant patients was published in 2012 by Gil et al[36] In this study allogeneic stem cell transplant patients were not included and typhlitis ratio was 12% among autologous stem cell transplant patients and this data is similar with our current study. However, only initial diagnosis of lymphoma had only prognostic value. Interestingly, author mentioned the benefit of using abdominal ultrasound that allows early diagnosis and treatment, effective in most patients without surgery which was one of the diagnostic tools in our study. We preferred ultrasound instead of abdominal computerized tomography because patients were neutropenic and ultrasound is portable so we did not have to take the patient out of sterile room in neutropenic period.

Our study has some limitations. One is the retrospective nature of this study. A prospective study with more numbers of patients may provide more data about risk factors and clinical outcomes in hematopoietic stem cell recipients with typhlitis. Another limitation is the patient heterogeneity and surgical interventions. Many centers avoid surgery because of increased risks of bleeding or infection. On the other hand, none of our patients were eligible for surgery. A study with only autologous or allogeneic transplant patients may have different results.

Although there are some limitations, this study shows the importance of typhlitis in stem cell transplant patients which can be seen in an important ratio and effects the survival of transplant.

5. Conclusions

In conclusion, the current study provides valuable information for bone marrow transplant patients, providing an analysis of risk factors for the development of typhlitis. It would be beneficial for clinicians to consider these factors in patient follow-up.

However, due to the retrospective nature of our study, prospective studies are needed to investigate risk factors and optimum treatment methods for typhlitis.

Author contributions

All authors participated in the management of the patient described in this case report. BD collected all the references and was a major contributor in the writing of the article. All authors have read and approved the article.
Conceptualization: BD, RS, LD
Data curation: TT, BD, RS, SY, GK
Formal analysis: BÖ, GK
Investigation: GK, BD, HFK, OG
Methodology: BD, RS
Resources: BD, RS, LD, SY, TT
Supervision: RS
Validation: BD
Writing—original draft: BD
Writing—review and editing: BD

References

[1] Bertozzi G, Maiese A, Passaro G, et al. Neutropenic enterocolitis and sepsis: towards the definition of a pathologic profile. Medicina (Kaunas, Lithuania). 2021;57:638.
[2] Xia R, Zhang X. Neutropenic enterocolitis: a clinico-pathological review. World J Gastrointest Pathophysiol. 2019;10:36–41.
[3] Ettinghausen SE. Collagenous colitis, eosinophilic colitis, and neutropenic colitis. Surg Clin North Am. 1993;73:993–1016.
[4] Portugal R, Nucci M. Typhlitis (neutropenic enterocolitis) in patients with acute leukemia: a review. Expert Rev Hematol. 2017;10:169–74.
[5] Nesher L, Rolston KV. Neutropenic enterocolitis, a growing concern in the era of widespread use of aggressive chemotherapy. Clin Infect Dis. 2013;56:711–7.
[6] Urbach DR, Rotstein OD. Typhlitis. Can J Surg. 1999;42:415.
[7] Bow E, Meddings J. Intestinal mucosal dysfunction and infection during remission-induction therapy for acute myeloid leukaemia. Leukemia. 2006;20:2087–92.
[8] Kirkpatrick ID, Greenberg HM. Gastrointestinal complications in the neutropenic patient: characterization and differentiation with abdominal CT. Radiology. 2003;226:668–74.
[9] Shamberger RC, Weinstein HJ, Delorey MJ, et al. The medical and surgical management of typhlitis in children with acute nonlymphocytic (myelogenous) leukemia. Cancer. 1986;57:603–9.
[10] Cross SJ, Patel JR, Wolf J. Diagnosis and management of typhlitis and neutropenic enterocolitis in children with cancer. Pediatr Infect Dis J. 2022;41:e326–8.
[11] Saillard C, Zafrani L, Darmon M, et al. The prognostic impact of abdominal surgery in cancer patients with neutropenic enterocolitis: a systematic review and meta-analysis, on behalf the Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie (GRRR-OH). Ann Intensive Care. 2018;8:47.
[12] Nagler A, Pavel L, Naparstek E, et al. Typhlitis occurring in autologous bone marrow transplantation. Bone Marrow Transplant. 1992;9:63–4.
[13] Snydman DR, Nesher L, Rolston KVI. Neutropenic enterocolitis, a growing concern in the era of widespread use of aggressive chemotherapy. Clin Infect Dis. 2013;56:711–7.
[14] Sloas MM, Flynn PM, Kaste SC, et al. Typhlitis in children with cancer: a 30-year experience. Clin Infect Dis. 1993;17:484–90.
[15] Till M, Lee N, Soper WD, Murphy RL. Typhlitis in patients with HIV-1 infection. Ann Intern Med. 1992;116(12_Part_1):998–1000.
[16] Al Otaibi A, Barker C, Anderson R, et al. Neutropenic enterocolitis (typhlitis) after pediatric bone marrow transplant. J Pediatr Surg. 2002;37:770–2.
[17] Gorschlüter M, Mey U, Strehl J, et al. Neutropenic enterocolitis in adults: systematic analysis of evidence quality. Eur J Haematol. 2005;75:1–13.
[18] Elad S, Cheng KKF, Lalla RV, Yarom N, Hong C, Logan RM, et al., Mucositis guidelines leadership group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2020;126:4423–4431.
[19] Spyridonidis A, Labopin M, Savani BN, et al. Redefining and measuring transplant conditioning intensity in current era: a study in acute myeloid leukemia patients. Bone Marrow Transplant. 2020;55:1114–1125.
[20] Abramson S, Berdon W, Baker D. Childhood typhlitis: its increasing association with acute myelogenous leukemia. Report of five cases. Radiology. 1983;146:61–4.
[21] Biasoli I, Nucci M, Spector N, et al. Risk factors for typhlitis. Oncol Rep. 1997;4:1029–31.
[22] Katz JA, Mahoney DH Jr, Fernbach DJ, et al. Typhlitis. An 18-year experience and postmortem review. Cancer. 1990;65:1041–7.
[23] Qasim A, Nahas J. Neutropenic Enterocolitis (Typhlitis) [Updated 2021 Aug 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2021.
[24] Song L, Marcon NE. Neutropenic enterocolitis (typhlitis). Waltham, MA: UpToDate. 2017.
[25] Aksoy D, Tanriover M, Uzun O, et al. Diarrhea in neutropenic patients: a prospective cohort study with emphasis on neutropenic enterocolitis. Ann Oncol. 2007;18:183–9.
[26] Moran H, Yaniv I, Ashkenazi S, et al. Risk factors for typhlitis in pediatric patients with cancer. J Pediatr Hematol Oncol. 2009;31:630–4.
[27] Dagli O, Tasdemir E, Ulutasdemir N. Palliative care infections and antibiotic cost: a vicious circle. Aging Male. 2020;23:98–105.
[28] Boggio L, Pooley R, Roth S, et al. Typhlitis complicating autologous blood stem cell transplantation for breast cancer. Bone Marrow Transplant. 2000;25:321–6.
[29] Duceau B, Picard M, Pirracchio R, et al. Neutropenic enterocolitis in critically ill patients: spectrum of the disease and risk of invasive fungal disease. Crit Care Med. 2019;47:668–76.
[30] Jarvis B, Shevchuk YM. Recurrent clostridium difficile diarrhea associated with mitoxantrone and etoposide: a case report and review. Pharmacotherapy. 1997;17:606–11.
[31] Gorschlüter M, Glasmacher A, Hahn C, et al. Clostridium difficile infection in patients with neutropenia. Clin Infect Dis. 2001;33:786–91.
[32] Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of clostridium difficile infection: a systematic review. J Clin Gastroenterol. 2014;48:693–702.
[33] Wade DS, Nava HR, Douglass HO Jr. Neutropenic enterocolitis. Clinical diagnosis and treatment. Cancer. 1992;69:17–23.
[34] Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. Clin Infect Dis. 2011;52:e56–93.
[35] Salazar R, Sola C, Maroto P, et al. Infectious complications in 126 patients treated with high-dose chemotherapy and autologous peripheral blood stem cell transplantation. Bone Marrow Transplant. 1999;23:27–33.
[36] Gil L, Poplawski D, Mol A, Nowicki A, Schneider A, Komarnicki M. Neutropenic enterocolitis after high-dose chemotherapy and autologous stem cell transplantation: incidence, risk factors, and outcome. Transpl Infect Dis. 2013;15:1–7.