ORIGINAL ARTICLE

WILEY

Neutropenic enterocolitis in pediatric leukemia patients treated with intensive chemotherapy in Upper Egypt

Ereen Refaat Fouad[1] | Ahmed Mohammed Morsy[1] | Hosam Eldein Mostafa Kamel[2] | Amany Mohamed Ali[1]

[1]Department of Pediatric Oncology, South Egypt Cancer Institute, Assiut University, Assiut, Egypt
[2]Department of Radiology, South Egypt Cancer Institute, Assiut University, Assiut, Egypt

Correspondence
Ahmed Mohammed Morsy, Pediatric Oncology Department, South Egypt Cancer Institute, Assiut University, Assiut, 71515, Egypt.
Email: ahmedmohammed7829@yahoo.com

Received: 31 October, 2019
Accepted: 14 January, 2020

ABSTRACT

Importance: In low resource countries, there has been scarcity of research on the risk factors associated with neutropenic enterocolitis, a serious complication that commonly develops during treatment of cancer patients.

Objective: To identify the pattern of intestinal complications in pediatric leukemia patients treated with intensive chemotherapy, including those with neutropenic enterocolitis; to assess the outcome; and to evaluate the risk factors associated with the mortality in these patients.

Methods: During the period from June 2015 to December 2016, a prospective study was carried out on pediatric patients diagnosed with acute leukemia who received induction/or re-induction phases of chemotherapy at South Egypt Cancer Institute. Patients with documented episodes of intestinal complications were included in the study. Recovery or death from an episode of intestinal complication was utilized as the primary outcome measure for the study. Using univariable and multivariable methods, potential risk factors associated with mortality were delineated by logistic regression analysis, both for the entire intestinal complications episodes as a whole and for those episodes of neutropenic enterocolitis only.

Results: Out of 88 documented episodes of intestinal complications from 77 patients; 58 episodes were identified as neutropenic enterocolitis from 47 patients. In those patients who were having episodes of neutropenic enterocolitis, the presence of abdominal tenderness (*OR* 4.529, 95%*CI* 1.062–19.317, $P = 0.041$); a longer duration of neutropenia (*OR* 1.215, 95%*CI* 1.030–1.434, $P = 0.021$); and hemodynamic instability (*OR* 17.023, 95%*CI* 4.095–70.772, $P < 0.001$), were found to be independently associated with worse outcome.

Interpretation: In Upper Egypt, the use of intensive systemic chemotherapy during the induction phase of acute leukemia was found to be associated with potentially lethal intestinal complications. A high index of clinical suspicion is warranted.

KEYWORDS
Neutropenic enterocolitis, Acute leukemia, Induction chemotherapy, Intestinal complication, Pediatric oncology

DOI: 10.1002/ped4.12174

INTRODUCTION

Children diagnosed with acute leukemia, the most common childhood cancer, are at a particular risk for developing intestinal complications which may be related to either recurrent episodes of infection, prolonged periods of neutropenia, corticosteroid exposure, and/or frequent administration of antibiotics.[1] They also receive intensive chemotherapy that adversely affects the developmental integrity of the intestinal mucosa.[2]

Neutropenic enterocolitis (NE) is the most common among all causes of intestinal complications developing during treatment of pediatric cancer patients.[3] NE or what is also a so-called ileocecal syndrome or typhlitis,[4,5] is a life-threatening condition as a result of an inflammatory, hemorrhagic and/or necrotizing involvement of the lower intestinal tract.[6]

As it is difficult to diagnose gastrointestinal complications based on the clinical findings only in many cases;[7] the diagnosis of NE needs to be supported by radiologic imaging as the clinical manifestations are not pathognomonic and are often blunted in patients with severe neutropenia. Bowel wall thickening as demonstrated by ultrasound or multi-slice computed tomography (MSCT) is one of the main criteria to establish the diagnosis.[8]

In the present study, we have investigated the pattern, outcome and risk factors associated with intestinal complications in pediatric leukemia patients during induction/or re-induction chemotherapy phases, according to our experience in South Egypt Cancer Institute, the largest referral cancer center in Upper Egypt.

METHODS

Ethical approval

The study protocol was approved by the Institutional Review Board (IRB) at our institute and the study was conducted in accordance with the guidelines provided by Declaration of Helsinki on Ethical Principles for Medical Research. Written informed consent was obtained from all the patients' parents before their enrollment in this study.

Patients selection

Patients who developed symptoms or signs related to intestinal complications during induction/or re-induction chemotherapy for acute leukemia during the period from June 2015 to December 2016 at the Pediatric Oncology Department in South Egypt Cancer Institute, either was subjectively reported by the patient or detected by the examining physician; were further assessed by close follow up through a thorough clinical history, physical examination and serial abdominal ultrasonography. Patients who had potential episodes of NE, were considered to be eligible for inclusion in the study if they fulfilled all the following criteria; they had a diagnosis with acute leukemia either acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) admitted to receive the induction/or re-induction chemotherapy phases of the treatment or within the recovery phase (nadir) of this chemotherapeutic phase, and had an absolute neutrophil count (ANC) less than or equal to 1.0×10^9/L. Patients whose age were more than 18 years, those who had other diagnoses, or patients with acute leukemia, but were admitted to receive other treatment phases, were excluded from the study.

Study patients

Demographic data of patients; i.e., gender and age; clinical information regarding the disease and the received treatment; and also, data of intestinal symptoms and signs such as abdominal pain, tenderness, distension, constipation, vomiting, and/or diarrhea were noted and analyzed. Other associated clinical and laboratory data such as; the presence of fever, defined as a temperature of $\geq$ 38.0 °C; patient general condition, including hemodynamic stability; presence or absence of neutropenia, whether it was mild with an ANC of $(0.5–1.0) \times 10^9$/L, severe $< 0.5 \times 10^9$/L, or profound $< 0.1 \times 10^9$/L; also, the duration of the neutropenia was documented.

Clinical management and treatment strategies

For the purpose of the study, any patient suggested on a clinical basis to have an episode of NE were considered for further laboratory and radiographic investigations. Any radiologic signs of abnormal findings, such as bowel wall thickening, free intra-peritoneal fluid, bowel loops dilatation, reduced intestinal loops motility and air in the bowel, were subjected to investigate the findings for a potential occurrence of an intestinal complication and to make consensus about confirmation of diagnosis regarding type of an intestinal complication episode, in correlation with patients' clinical presentations, as was summarized by Dietrich et al.[9] Episodes of intestinal complications, including those of NE, were documented by a well-trained resident physician under supervision of specialists and consultants of the pediatric oncology department in collaboration with oncology surgeons and radiologists in our institute.

A consensus was made between different specialties, that whether a certain patient with an eligible episode of intestinal complication to be included in the study, based on the collected clinical, laboratory and radiographic findings. Once an episode was included in the study, the episode was documented and the patient was followed up till recovery or occurrence of death. Also, other episodes repeated in the same patient were included in the study provided that they met the eligibility criteria for inclusion in the study.

Data associated with potential comorbidities such electrolyte disturbances, hypoalbuminemia, impaired renal or hepatic function, any clinical or radiologic data suggestive of sequel of intestinal complication episodes such as intestinal hemorrhage, perforation, obstruction or peritonitis also were noted. MSCT abdomen was performed as per case basis. During the follow up period for any patient with a documented episode of intestinal complication, the management was mainly conservative,[10-12] or surgically[13,14] accordingly as on per case basis.[15]

Statistical analysis

Continuous variables were expressed as mean (± standard deviation) or median (range). Categorical variables were presented as proportions or percentages. The chi-square (χ^2) was used to test differences between groups for categorical variables, or Fisher exact test, when appropriate. Binary logistic regression analysis, "odds ratios" (*ORs*), was used to assess effects of baseline demographic, clinical and radiologic study variables on the patient mortality from episodes of intestinal complication or NE. Variables in the univariable analysis with a *P*-value arbitrarily set to $P = 0.1$ were included in the multivariable analysis. All statistical tests were described with 95% confidence interval (95%*CI*) and an arbitrary *P*-value was set at $P = 0.05$. All *P* values were two-tailed. Statistical analyses were performed using SPSS, version 20.0, for Windows (SPSS Inc., Chicago, IL).

RESULTS

The study included a total of 77 patients with mean age was 8.35 years (standard deviation = 4.78). Of all patients, 42 (54.5%) were males and 35 (45.5%) were females; 49 (63.6%) was diagnosed to have ALL and 28 (36.4%) had AML. Out of 77 patients who had intestinal complications; 67 patients had only one episode of intestinal complications during the study period, 9 patients had 2 episodes and only 1 patient had 3 episodes. Patient characteristics categorized according to type of intestinal complication were shown in Table 1. Death occurred in 22/77 (28.6%) of patients; 18/47 (38.3%) patients died as a consequence of NE episodes, and 4/30 (13.3%) of patients died due to other types of intestinal complications. The main cause of death in our study was irreversible septic shock and multi-organ failure. Management of patients was mainly conservative. Only 3 patients in whom surgical intervention was needed. Out of these 3 patients, only one had NE.

Out of 88 episodes of intestinal complications; 58 (65.9%) were due to NE (typhlitis) episodes, followed by 21 (23.9%) due to acute gastroenteritis episodes, then other conditions that included paralytic ileus 4 (4.6%), intussusception 3 (3.4%), appendicitis 1 (1.1%), and pneumatosis intestinalis 1 (1.1%). In our study, all the episodes that repeated more than once were in patients with NE. Factors predictive of outcome for all intestinal complications as a whole, and for NE episodes in pediatric leukemia patients during the induction phase of chemotherapy were shown in Table 2 and 3, respectively.

TABLE 1 Patient characteristics by the type of intestinal complications (neutropenic enterocolitis vs. other intestinal complications)

Variables	Neutropenic enterocolitis (*n* = 47)	Other intestinal complications (*n* = 30)	*P*
Gender			
Male	26 (55.3)	16 (53.3)	0.864
Female	21 (44.7)	14 (46.7)	
Age (years)	8.51 (4.71)	8.10 (4.94)	0.716†
Diagnosis			
ALL	25 (53.2)	24 (80.0)	0.017‡
AML	22 (46.8)	6 (20.0)	
Outcome (death)			
No	29 (61.7)	26 (86.7)	0.018
Yes	18 (38.3)	4 (13.3)	

Data are presented as *n* (%) or mean (standard deviation). If not otherwise specified, all comparisons were made using the Pearson Chi-square test. †Independent *t*-test was performed. ‡Fisher's exact test was performed. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

Our study revealed that there is no difference in outcome due to gender, age, or diagnosis whether it was ALL or AML. A greater proportion of deaths was observed in patients with NE 38.3% (18/47) vs. those who had other types of intestinal complications 13.3% (4/30) as shown in Table 1. The univariable analysis using logistic regression revealed a trend towards worse outcomes in those patients who had NE episodes (*OR* 2.925, 95%*CI* 0.889–9.621, $P = 0.077$) compared to those who had other types of intestinal complications. Factors predictive of outcomes associated with the occurrence of either, of intestinal complication episodes as a whole, or episodes of NE, both in the univariable and multivariable analysis were shown in Table 2 and 3.

In multivariable analysis, the presence of abdominal tenderness was only marginally associated with a worse outcome in the group of intestinal complication episodes as a whole (*OR* 4.526, 95%*CI* 0.997–20.549, $P = 0.050$), and had a weak statistical significance in the group of NE episodes (*OR* 4.529, 95%*CI* 1.062–19.317, $P = 0.041$). Whereas, both hemodynamic instability, and longer duration of neutropenia revealed to be significantly predictive of a worse outcome in both of the two groups as were shown in Table 2 and 3.

TABLE 2 Factors predictive of outcome in intestinal complications as a whole in pediatric leukemia patients during induction chemotherapy using logistic regression analysis

Variables	*n*	Univariable[†]		Multivariable	
		***OR* (95% *CI*)**	***P***	***OR* (95% *CI*)**	***P***
Gender				Not included in the model	
Male	48	Reference			
Female	40	1.000 (0.379–2.635)	1.000		
Age (years)	88	1.052 (0.947–1.168)	0.345	Not included in the model	
Diagnosis				Not included in the model	
ALL	49	Reference			
AML	39	1.357 (0.516–3.572)	0.536		
Fever					
No	11	Reference		Reference	
Yes	77	3.574 (1.267–10.084)	0.016	1.001 (0.196–5.119)	0.999
Abdominal tenderness					
No	54	Reference		Reference	
Yes	34	7.111 (2.407–21.011)	<0.001	4.526 (0.997–20.549)	0.050
Hemodynamic instability[‡]					
No	60	Reference		Reference	
Yes	28	25.200 (7.039–90.215)	<0.001	17.625 (3.801–81.736)	<0.001
Absolute neutrophilic count ($\times 10^9$/L)	88	0.980 (0.513–1.873)	0.018	1.631 (0.611–4.350)	0.329
Duration of neutropenia[‡] (days)	88	1.263 (1.114–1.432)	<0.001	1.218 (1.019–1.455)	0.030
Bowel wall thickening					
No (≤ 3 mm)	43	Reference		Reference	
Yes (> 3 mm)	45	2.376 (0.986–5.725)	0.054	0.904 (0.187–4.362)	0.900

[†]Variables in the univariable analysis with a *P*-value arbitrarily set to $P = 0.1$ were included in the multivariable analysis. [‡]Hemodynamic instability and duration of neutropenia (in days) maintained their statistical significance in the multivariable analysis. *OR*, odds ratio; *CI*, confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

TABLE 3 Factors predictive of outcome in neutropenic enterocolitis episodes in pediatric leukemia patients during induction chemotherapy using logistic regression analysis

Variables	*n*	Univariable[†]		Multivariable	
		***OR* (95% *CI*)**	***P***	***OR* (95% *CI*)**	***P***
Gender				Not included in the model	
Male	32	Reference			
Female	26	0.703 (0.227–2.183)	0.543		
Age (years)	58	1.053 (0.929–1.193)	0.423	Not included in the model	
Diagnosis				Not included in the model	
ALL	25	Reference			
AML	33	1.270 (0.414–3.996)	0.664		
Fever				Not included in the model	
No	3	Reference			
Yes	55	2.432 (0.695–8.507)	0.164		
Abdominal tenderness[‡]					
No	26	Reference		Reference	
Yes	32	6.765 (1.686–27.135)	0.007	4.529 (1.062–19.317)	0.041
Hemodynamic instability[‡]					
No	32	Reference		Reference	
Yes	26	24.000 (4.679–123.099)	<0.001	17.023 (4.095–70.772)	<0.001
Absolute neutrophilic count ($\times 10^9$/L)	58	0.005 (0.000–0.420)	0.019	1.618 (0.615–4.254)	0.329
Duration of neutropenia[‡] (days)	58	1.233 (1.060–1.434)	0.007	1.215 (1.030–1.434)	0.021
Bowel wall thickening				Not included in the model	
No (≤ 3 mm)	14	Reference			
Yes (> 3 mm)	44	3.429 (0.680–17.291)	0.136		

[†]Variables in the univariable analysis with a *P*-value arbitrarily set to $P = 0.1$ were included in the multivariable analysis. [‡]Abdominal tenderness, hemodynamic instability and duration of neutropenia (in days) maintained their statistical significance in the multivariable analysis. *OR*, odds ratio; *CI*, confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

DISCUSSION

Typhlitis was most frequent in patients treated for acute leukemia.[16] During the induction phase of leukemia treatment; leukemic infiltration besides, the use of intensive chemotherapy, and the neutropenia preceding to treatment or resultant from it; one or more of these factors combining together may allow continuous bacterial invasion and colonization of the bowel wall with inflammation, ulceration, and possible necrosis and perforation.[9,17] In the present study, out of 77 patients who had episodes of intestinal complications; 47/77 (61.0%) of them were due to typhlitis, similarly to what was reported from the literature that typhlitis was the most frequent intestinal complication among patients with acute leukemias and particularly occurring in patients with AML.[4,17-20]

Out of all patients with acute leukemia who developed typhlitis in our study, patients with AML were 22/47 (46.8%) of them, despite that it has been known that AML 4 to 5 times less common than ALL and comprises only 15% to 20% in patients with acute leukemia aged less than 15 years.[21,22] Our results were consistent with those reported by Sloas et al[16] who found that 54% of their NE cases were in children with AML with a frequency that was significantly higher than that in patients with ALL (P = 0.00003).

In the present study, we didn't observe any statistically significant effect on the outcome in the multivariable analysis for each of age, gender, type of diagnosis, absolute neutrophilic count, and bowel wall thickening, that were consistent with the findings obtained from a retrospective study done in a developing country that entailed 231 episodes of enterocolitis conducted in pediatric patients with cancer treated at the Centro Infantil Boldrini in Brazil from 2003 to 2007.[20] Also, in a report from a retrospective study by McCarville et al[23] that involved 103 episodes of typhlitis in 94 patients treated at St. Jude Children's Research Hospital between 1990 and 2001, they found that age >16 years was the only demographic factor associated with the outcome in their study. Having no patients aged ≥ 16 years in our series precludes assessing this finding, where the mean age for those patients with typhlitis was 8.51 years (standard deviation = 4.71) in our study.

Fever occurred in 94.8% (55 of 58) of NE episodes in our study, a percentage that was slightly lower than 100% (11 of 11) in one study,[11] and higher than 84% (83 of 99) that was reported by McCarville et al[23] who concluded that the severity of typhlitis, as was assessed by the duration of the episode as a measure of outcome in their study, was correlated to the duration of neutropenia and the presence of abdominal tenderness. In our study, the presence of abdominal tenderness (*OR* 4.529, 95%*CI* 1.062–19.317, P = 0.041); and a longer duration of neutropenia (*OR* 1.215, 95%*CI* 1.030–1.434, P = 0.021), were found to be independently associated with worse outcome, a finding that was consistent with their results. Also, hemodynamic instability (*OR* 17.023, 95%*CI* 4.095–70.772, P < 0.001) as shown in our study was associated with a poorer outcome, a finding comparable to a study done by Starnes et al showed that hypotension at the onset of abdominal pain was associated with 80% mortality. At contrast, absolute leukocyte count did not correlate with mortality in their study.[12]

A non-significant trend (*OR* 3.429, 95%*CI* 0.680–17.291, P = 0.136) towards a worse outcome associated with intestinal wall thickening (> 3 mm) was only shown in the univariable analysis, and this was near to what has been reported by McCarville et al[23] that a bowel wall thickness of > 3 mm by ultrasound was significantly associated with the duration of typhlitis (P = 0.05), but not with a higher mortality rate. In line with that, Rizzatti et al[20] reported that intestinal wall thickening categorized as 3–5 mm, 5.1–10 mm, and > 10.1 mm in their study wasn't shown to correlate with mortality (P = 0.72), but a higher death rate (19.5%) was observed in the enterocolitis group with gut thickness > 10.1 mm. In contrast to studies conducted in children, Cartoni et al[24] reported that the degree of bowel wall thickening significantly correlated with the outcome of the patients with NE, where the mortality rate was 60% (12 of 20) among adult patients who had bowel wall thickness > 1.0 cm.

The mortality rate in our study from all complications was 28.6% (22 of 77), while for patients with NE was 38.3% (18 of 47); a finding for NE that despite being lower than that 45.5% (5 of 11) reported by Jain et al[14] and 59.1% (13 of 22) by Wade et al.[15] However, it was still higher than 20% reported by Altınel et al,[25] and also higher than 34% reported by Starnes et al.[12] The relatively high mortality rate in our study can be attributed to the fact that our study included a group of immunocompromised patients who were subjected to induction/re-induction phase of chemotherapy in whom severe myelosuppression due to the received intensive chemotherapy, and probably due to not achieving a remission from their primary disease till then.

In our study, abdominal tenderness and hemodynamic instability were associated with worse outcome that denotes the importance of early thorough clinical assessment in line with radiologic evaluation for proper early management in pediatric cancer patients with intestinal complications.

In Upper Egypt, typhlitis was the most encountered intestinal complication in pediatric patients diagnosed with acute leukemia during induction phase of chemotherapy. Aggressive use of systemic chemotherapy during the induction phase of leukemia treatment makes patients at risk for this potentially lethal intestinal complication. A

high index of clinical suspicion is warranted.

CONFLICT OF INTEREST

None.

REFERENCES

1. Bremer CT, Monahan BP. Necrotizing enterocolitis in neutropenia and chemotherapy: a clinical update and old lessons relearned. Curr Gastroenterol Rep. 2006;8:333-341.
2. Bow E, Marr K, Thorner A. Risk assessment of adults with chemotherapy-induced neutropenia. 2014. https://www.uptodate.com/contents/risk-assessment-of-adults-with-chemotherapy-induced-neutropenia. Accessed June 7, 2017.
3. Kirkpatrick ID, Greenberg HM. Gastrointestinal complications in the neutropenic patient: characterization and differentiation with abdominal CT. Radiology. 2003;226:668-674.
4. Portugal R, Nucci M. Typhlitis (neutropenic enterocolitis) in patients with acute leukemia: a review. Expert Rev Hematol. 2017;10:169-174.
5. Rodrigues FG, Dasilva G, Wexner SD. Neutropenic enterocolitis. World J Gastroenterol. 2017;23:42-47.
6. Salazar R1, Solá C, Maroto P, Tabernero JM, Brunet J, Verger G, 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.
7. Rotterdam H, Tsang P. Gastrointestinal disease in the immunocompromised patient. Hum Pathol. 1994;25:1123-1140.
8. Badgwell BD, Cormier JN, Wray CJ, Borthakur G, Qiao W, Rolston KV, et al. Challenges in surgical management of abdominal pain in the neutropenic cancer patient. Ann Surg. 2008;248:104-109.
9. Dietrich CF, Hermann S, Klein S, Braden B. Sonographic signs of neutropenic enterocolitis. World J Gastroenterol. 2006;12:1397-1402.
10. Shafey A, Ethier M-C, Traubici J, Naqvi A, Sung L. Incidence, risk factors, and outcomes of enteritis, typhlitis, and colitis in children with acute leukemia. J Pediatr Hematol Oncol. 2013;35:514-517.
11. Alioglu B, Avci Z, Ozcay F, Arda S, Ozbek N. Neutropenic enterocolitis in children with acute leukemia or aplastic anemia. Int J Hematol. 2007;86:364-368.
12. Starnes HF Jr, Moore FD Jr, Mentzer S, Osteen RT, Steele GD Jr, Wilson RE. Abdominal pain in neutropenic cancer patients. Cancer. 1986;57:616-621.
13. Moir CR, Scudamore CH, Benny WB. Typhlitis: selective surgical management. Am J Surg. 1986;151:563-566.
14. Jain Y, Arya LS, Kataria R. Neutropenic enterocolitis in children with acute lymphoblastic leukemia. Pediatr Hematol Oncol. 2000;17:99-103.
15. Wade DS, Nava HR, Douglass HO Jr. Neutropenic enterocolitis. Clinical diagnosis and treatment. Cancer. 1992;69:17-23.
16. Sloas MM, Flynn PM, Kaste SC, Patrick CC. Typhlitis in children with cancer: a 30-year experience. Clin Infect Dis. 1993;17:484-490.
17. Gray TL, Ooi CY, Tran D, Traubici J, Gerstle JT, Sung L. Gastrointestinal complications in children with acute myeloid leukemia. Leuk lymphoma. 2010;51:768-777.
18. Abramson SJ, Berdon WE, Baker DH. Childhood typhlitis: its increasing association with acute myelogenous leukemia. Report of five cases. Radiology. 1983;146:61-64.
19. Hsu TF, Huang HH, Yen DH, Kao WF, Chen JD, Wang LM, et al. ED presentation of neutropenic enterocolitis in adult patients with acute leukemia. Am J Emerg Med. 2004;22:276-279.
20. Rizzatti M, Brandalise SR, de Azevedo AC, Pinheiro VR, Aguiar Sdos S. Neutropenic enterocolitis in children and young adults with cancer: prognostic value of clinical and image findings. Pediatr Hematol Oncol. 2010;27:462-470.
21. Aquino VM. Acute myelogenous leukemia. Curr Probl Pediatr Adolesc Health Care. 2002;32:50-58.
22. Deschler B, Lübbert M. Acute myeloid leukemia: epidemiology and etiology. Cancer. 2006;107:2099-2107.
23. McCarville MB, Adelman CS, Li C, Xiong X, Furman WL, Razzouk BI, et al. Typhlitis in childhood cancer. Cancer. 2005;104:380-387.
24. Cartoni C, Dragoni F, Micozzi A, Pescarmona E, Mecarocci S, Chirletti P, et al. Neutropenic enterocolitis in patients with acute leukemia: prognostic significance of bowel wall thickening detected by ultrasonography. J Clin Oncol. 2001;19:756-761.
25. Altınel E, Yarali N, Isık P, Bay A, Kara A, Tunc B. Typhlitis in acute childhood leukemia. Med Princ Pract. 2012;21:36-39.

How to cite this article: Fouad ER, Morsy AM, Kamel HEM, Ali AM. Neutropenic enterocolitis in pediatric leukemia patients treated with intensive chemotherapy in Upper Egypt. Pediatr Invest. 2020;4:5-10. https://doi.org/10.1002/ped4.12174