

**Research Article**

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# Acute Abdomen and its Outcomes in Children with Acute Leukemia: A Single Center Experience

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## Abstract

**Background:** Acute abdominal conditions such as tiftitis, acute appendicitis and intussusception can be found in the follow-up of children with leukemia. In this study, we examined our patients with leukemia diagnosed with acute surgical abdomen in terms of clinical findings, prognosis and treatments, and we aimed to show that the results were satisfactory with good management in these patients.

**Materials and methods:** In this retrospective study; 9 patients who underwent surgery due to acute abdomen in our Pediatric Hematology-Oncology clinic between July 2016 and January 2021 were examined retrospectively. The patients were under treatment according to the Berlin-Frankfurt-Munich protocol risk groups. The diagnosis of acute abdomen was made with clinical, laboratory and radiological findings.

**Results:** Seventh of the patients were diagnosed as ALL, two were AML. Five of patients were girls and four were males. Two of patients were operated due to perforated tiftitis, tree for unperforated tiftitis, tree for acute appendicitis, one was operated due to intussusception respectively. A second operation was required due to the delayed wound healing in one patient. Apart from this, no complications were seen.

**Conclusion:** Acute appendicitis has been reported with a frequency of 0.5-4.4%, tiftit 2.6-10% in different studies in pediatric patients with hematologic cancer. Although the complications and mortality rates of surgery in these patients are higher than the immune system intact patients, early diagnosis, broad-spectrum antibiotics, antifungal use, appropriate liquid electrolyte and blood product support can be performed successfully.

**Keywords:** Childhood; Acute leukemia; Acute abdomen; Surgery.

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Acute abdominal conditions such as typhlitis, acute appendicitis, and invagination may be encountered in the follow-up of pediatric patients with acute leukemia. Abdominal pain, vomiting, fever, swelling in abdominal examination, tenderness, are considered when one or more of the defensive findings are present, and the diagnosis is supported by radiological imaging methods. Tiflitis, also known as neutropenic colitis or iliocolic syndrome, is a gastrointestinal system infection characterized by inflammation of the iliocolic region and ascending colon, usually observed in cancer, immunodeficiency or bone marrow transplant patients. The primary treatment of Tiflitis is conservative, and surgical treatment is required in case of complications or worsening of the picture [1,2]. Appendicitis is localized inflammation of the appendix, and unlike typhlitis, its treatment is primarily surgical [3]. Another cause of acute surgical abdomen is intussusception, which is an important cause of intestinal obstruction, especially in the young child age group; It occurs when a proximal bowel segment enters the lumen of the more distal bowel. Reduction is performed with different techniques, surgery is performed in selected patients, non-operative treatment with different types of enema reduction techniques, and operative treatment by laparotomy and laparoscopy, [4]. Making the decision of surgery in patients with leukemia is not as easy as patients with a healthy immune system due to the increased risk of complications and death. In these patients, rapid diagnosis, broad spectrum antibiotics, aggressive treatment with the use of antifungal in selected patients, and liquid electrolyte and blood product support are vital. In this study, we examined our patients with leukemia who were operated for acute surgical abdomen in terms of clinical findings, prognosis and treatment strategy.

### Materials and methods

In our study, nine patients who underwent surgery for acute abdomen among 208 acute leukemia patients who were followed up between July 2016 and January 2021 in the Pediatric Hematology-Oncology Clinic of our hospital were analyzed retrospectively. The patients were divided into risk groups and treated according to the Berlin-Frankfurt-Munich child protocol. Acute surgical abdominal diagnosis was made with clinical, laboratory and radiological findings. The age, gender, type and risk group of leukemia, recently used chemotherapy agents, clinical signs and symptoms, laboratory and radiological findings, treatments and results of the patients were recorded. As the imaging method, standing direct abdominal radiography (X-ray), ultrasonography (USG) and / or Computed Tomography (CT) were used. The criterion for appendicitis was accepted as appendix diameter > 6mm on USG or CT, unresponsive to compression and increased echogenicity in the surrounding mesenteric area, criteria for typhlitis was the measurement of cecal or terminal ileum thickness thicker than 3mm [3].

Acute surgical abdomen was observed in eight (0.04%) of our patients treated with leukemia within a four-year period. Among these patients, 7 patients were being treated for Acute Lymphoblastic Leukemia (ALL) and 2 patients for Acute Myeloid Leukemia (AML). 4 of the patients were female and 5 were male. The median age was 5,9 years (range: 1.5-15 years). Five of the patients were receiving induction and the other three were receiving consolidation therapy. Cytarabine was used most frequently in 6/9 patients among the chemotherapy agents taken in the last 15 days. In the clinical findings of the patients, 6/9 of the patients had fever, 5/9 had abdominal pain, 5/9 had vomiting, and all patients had abdominal tenderness and defense findings. In the examinations done just before the operation, the platelet count of 4/9 patients was <50000/mm<sup>3</sup> and 4/9 of them were very severe neutropenic (neutrophil count <200/mm<sup>3</sup>). Platelet + number median absolute neutrophil (ANC) median perioperative 0.25 x 10<sup>9</sup>/L (range: 0-0.21 x 10<sup>9</sup>/L), Platelet median 56 x 10<sup>9</sup>/L (range 7-523 x 10<sup>9</sup>/L). He gave hyponatremia (123 mmol/l) in one patient and hypopotasemia (2.7 mmol/l) in one patient. C reactive protein (CRP) was median 161 mg/L (limit: 71-313 mg/L).

Abdominal X-ray was performed as imaging method in all patients, both USG and CT scans were performed in 5/9 patients, USG for 2/9 and CT imaging for 1/9 patients. 3 of the patients perforated typhlitis, 3 unperforated typhlitis; 3 of them were diagnosed as acute appendicitis that could not be perforated, and 1 was diagnosed with invagination. Abdominal CT findings of the 11-year-old unperforated typhlitis case are displayed in (Figure 1). The direct abdominal radiography of the 2-year-old unperforated typhlitis case is displayed in (Figure 2). Except for 3 patients with unperforated typhlitis, open surgery was performed in tiflitis. Also in intussusception case open surgery was performed. In these unperforated tiflitis and appendicitis laparoscopic operation was performed. Broad-spectrum intravenous antibiotic treatment was given on average (mean) 14.8 days (limit: 10-19 days). Antifungal therapy was added to antibiotic therapy in 4 patients. One patient was given both granulocyte and pentaglobulin treatment in addition to the treatments because of deep neutropenia, fever and poor general condition. *Sterptococcus haemolyticus* was grown in the blood culture of one patient. Erythrocyte suspension was given to 3 patients and thrombocyte suspension to 5 patients during the perioperative period. Supportive treatment of two patients was performed with fluids with high sodium and potassium concentration. Inflammation, induration and enlargement of the appendix in laparoscopic appendectomy procedure of case 2 is displayed (Figure 3).

Eight patients who underwent surgery underwent surgery as soon as they were diagnosed with laparotomy, and three were confirmed with appendicitis and two were diagnosed with typhlitis. One patient required a second operation due to the problem of wound healing. Apart from this, there were no complications in the follow-up of any patient and their chemotherapy was resumed.

The demographic characteristics of the patients, diagnosis, risk groups, preoperative laboratory findings, and the last 15 chemotherapies they received are summarized in (Table 1).

**Table 1:** Demographic characteristics of the patients, diagnosis, risk groups, preoperative laboratory findings, last 15 days chemotherapy regimens.

Case No	Age Range(years)	Gender	Diagnosis	Risk group	Last 15 days chemotherapy regimens	Surgery Procedure	Imaging Test
1	15	Famale	ALL	HRG	Dexamethasone	Perforated Typhlitis	X ray, CT
2	7	Male	AML	SRG	Cytarabine, Etoposide, Idarubicin	Acute Appendicitis	X ray, USG
3	14	Famale	AML	SRG	Cytarabine, Etoposide, Idarubicin	Perforated Typhlitis	X ray , USG, CT
4	7	Famale	ALL	MRG	Methotrexate, Mercaptopurine	Acute Appendicitis	X ray, USG
5	6	Male	ALL	HRG	Cytarabine, Mercaptopurine	Acute Appendicitis	X ray, USG
6	1,5	Male	ALL	HRG	Cytarabine, Vincristine, Daunorubicin, Prednisolone	Intussusception	X ray, USG, CT
7	11	Male	ALL	HRG	Cytarabine, Vincristine, Daunorubicin, Prednisolone	Unperforated Typhlitis	X ray, USG, CT
8	2	Famale	ALL	MRG	Cytarabine, Vincristine, Daunorubicin, Prednisolone	Unperforated Typhlitis	X ray, USG, CT
9	3	Famale	ALL	MRG	Cytarabine, Vincristine, Daunorubicin, Prednisolone	Unperforated Typhlitis	X ray, USG, CT

ALL: Acute Lymphoblastic Leukemia AML: Acute Myeloblastic Leukemia SRG: Standart Risk Group, MRG: Median Risk Group, HRG: High Risk Group, USG: Ultrasonography, CT: Computed Tomography.

The lab findings, antimicrobial treatments, and supportive treatments of the patients during the perioperative period are summarized in (Table 2).

**Table 2:** Patients' perioperative lab findings, antimicrobial treatments, supportive treatments.

Hasta No	Preoperative ANC/ PLT (x 10 <sup>9</sup> /L)	Preoperative Na/ K (mmol/ L)	Preoperative CRP mg/dL	Antimicrobial Agents	Antimicrobial treatment period	Intravenous transfusions
1	20/ 52	139/ 5.1	236	Meropenem, Amikacin, Teicoplanin, Caspofungin	16	
2	10/ 49	134/ 3,3	203	Meropenem, Amikacin, Metronidazole, Caspofungin	15	TS
3	10/ 70	133/ 3.4	71	Siprofloksasin, Teicoplanin, Amikacin, Metronidazole, aspofungin	13	TS
4	312/ 95	133/ 4,1	111	Cefepime, amikacin	10	
5	0/ 15	136/ 2,7	313	Meropenem, Amikacin, Teicoplanin, Caspofungin, Metronidazole	19	GS, TS
6	40/ 63	127/ 4,7	119	Meropenem, Vancomycin, Amikacin, Caspofungin	15	
7	60/23	129/3,6	68	Meropenem, Amikacin, Metronidazole, Clindamycin	14	ES,TS
8	15/89	126/3,4	156	Meropenem, Amikacin, Metronidazole, Caspofungin, lindamycin,	18	ES,TS
9	50/65	129/3,9	102	Meropenem, Amikacin, Metronidazole, Clindamycin,	14	ES,TS

ANC: absolute neutrophil count; PLT: Platalatel; CRP: C-reactif pretein; TS: Trombocyte uspansion; ES: Eritrocyte suspansion; GS: Granulocyte suspansion.

## Discussion

Acute typhlitis and appendicitis are the most common gastrointestinal complications requiring surgery in childhood leukemia, and the frequency has been reported in studies of 1.7–6.7% and 0.5–4.4%, respectively [5-10]. In fact, since the frequency is less than the general population, especially appendicitis cases in patients with hematologic cancer have generally been reported as case reports or single-center studies [3,7,9]. Tiflit is observed relatively more frequently in cancer or neutropenic patients than appendicitis and childhood cancers. It is mostly observed in leukemia and lymphomas [5]. However, unlike typhlite appendicitis, it is primarily defined as an infection, not a surgical condition, except for perforation, necrosis or uncontrolled GIS memory, conservative management with antibiotics is fundamental [3,5,11]. Intussusception is very rare among acute gastrointestinal complications in these patients. In a large study of 800 patients with acute leukemia, gastrointestinal complications were observed with a frequency of 2%, among them intussusception was observed,

while in another study, acute GIS complication rate was 5.6%, while intusseption was not observed at a rate of 0.3% [12,13]. In our study, invagination was the least common complication of gis requiring surgery in our patients; acute app%, perforated typhlite and invagination% respectively.

If there are signs of peritoneal irritation such as abdominal pain, especially right lower quadrant, vomiting, abdominal distension and accompanying tenderness and defense, one should be alert for the diagnosis of acute abdomen. However, since patients with childhood malignancies receive chemotherapy, vomiting and abdominal pain are frequently observed in these patients, especially corticosteroids and anthracyclines are known to have gastrointestinal side effects [14]. In addition, typical localized pain and peritonitis findings may not always appear clearly due to neutropenia, or corticosteroids may suppress these findings [3]. Therefore, it is not always easy to diagnose in these patients. In our study, findings of typhlitis were missed in two patients, and these two patients had to be operated due to perforations. With

early diagnosis, it is possible to come out without complications and with less damage.

Acute appendicitis is usually caused by the obstruction of the lumen by fecaloids and sometimes by swelling LAPs secondary to infections. Another situation that should be kept in mind in patients with leukemia is extramedullary involvement of the appendix, although very rare cases were reported in the literature [15,16]. There was no leukemic involvement in the pathological examination of the appendix, either in our patients. In our study, we did not see any complications in 2 ALL and 1 AML patients operated for acute appendicitis, and uneventful recovery was 100%. This was similar to other studies in the literature. Young kim et al. Reported 6 uneventful recovery and 1 complicated but complete recovery out of 7 patients operated for acute appendicitis. Similar results were found to be 100% in a study involving 5 ALL and 1 AML patients, including 1 Burkitt lymphoma [3,8]. In studies published in previous years, they reported uneventful recovery as 60% and 64%, and mortality rates as 20% and 7.1%, respectively, in leukemia patients operated for acute appendicitis [7,17]. All patients with appendicitis in our study recovered without complications. One of the cases was very severe neutropenic. Due to the accompanying signs of fever and hypotension, the patient was given granulocyte suspension and pentaglobulin iv treatment in addition to intensive antimicrobial therapy.

Although the mechanism of typhlitis is not known exactly, the opinion is that it emerges with the translocation of bacteria from the damaged intestinal mucosa weakened by chemotherapy. Its classical triad is fever, neutropenia, and abdominal pain [1]. A noticeable symptom in Typhlitis is diarrhea. Hobson et al. argued that diarrhea and fever above 38.5 C were seen in typhlitis rather than appendicitis, while 87.5% of patients with typhlitis detected fever in their population, they did not detect fever in any of the appendicitis cases. They found the frequency of diarrhea to be 75% in typhlitis cases [8]. Chirletty et al also emphasized the importance of diarrhea in typhlitis [19]. In our population, 2 (50%) of four patients diagnosed with typhlitis had diarrhea and all had fever exceeding 38.2 C. In our cases with appendicitis, 2 (66%) of three patients had fever. Diarrhea was not present in any of our patients with appendicitis. Early aggressive antibiotic treatment is life-saving in Typhlitis, if the diagnosis is missed and treatment is delayed, it may have fatal consequences due to sepsis. Adding Granulocyte Stimulant Factor G-CSF to the treatment is recommended in some appropriate cases [1,11].

It is not as frequent as appendicitis and typhlitis in pediatric patients with intussusception leukemia, it has been reported very rarely [21]. Usually observed pathological changes are leukemic infiltration, infection, bleeding and necrosis. Intestinal hypomotility due to vincristine has been underlined as a cause of intussusception in these patients [12]. Our patient was receiving induction therapy and had received vincristine treatment within the last week. We thought it was due to the foreground vincristine. However, in the ongoing process, we continued the treatment of vincristine, one of the essential drugs, and we did not experience any complications. For acute appendicitis, the National Cancer Institute, the American Academy of Pediatrics, the American College of Radiology recommend USG as the initial imaging method in pediatric patients [22,23]. In a study comparing USG and CT in the diagnosis of acute

app, USG alone had sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), of 81, 88, 92.6 and 71.6%, respectively, when combined with CT scan in select cases, the sensitivity, specificity, PPV and NPV of combined USG + CT scan were 96%, 89%, 93% and 93.5% respectively [24]. In the study of Stephen et al., 268 (94.7%) of 283 pediatric patients who underwent appendectomy were pathologically confirmed. The sensitivity of the computed tomography (CT) scan was 94.6%, and the positive predictive value was 95.6% [25]. CT gold is standard imaging in patients with suspected typhlitis, typical findings, intestinal wall thickening, intestinal dilatation, and pneumatosis. Characteristic findings on USG are defined as circumferential wall thickening with predominant submucosa [18]. USG, which is a useful and simple method, and CT findings are guiding in the diagnosis of intussusception [26,27]. While all of our three patients diagnosed with acute appendicitis were diagnosed by USG only, CT imaging was performed in both patients with typhlitis. Both USG and CT imaging was performed in our patient with a diagnosis of intussusception.

The classic treatment of appendicitis is surgical intervention and appendectomy, but the optimal treatment method for immunocompromised patients is still controversial. Some authors primarily recommended conservative therapy rather than surgery. Surgery is recommended when symptoms aggravate after neutrophil count increases or while under conservative therapy [28]. However, in these patients who were given single conservative therapy, recurrence of right lower quadrant pain without any evidence of appendicitis during febrile neutropenia attacks after chemotherapy and a median time of 14 days for complete resolution of the findings on USG were reported [9]. We performed early surgery on our patients and achieved successful results. We think that late full recovery and the risk of perforation and recurrence are important handicaps in conservative treatment.

## Conclusion

Although surgical or conservative treatment methods can be chosen in acute abdominal cases in these immunocompromised patients with a high risk of death and serious disease, the important point is timely differentiation. If there are signs of peritoneal irritation such as abdominal pain, especially right lower quadrant, sensitivity defense, radiological imaging should be performed rapidly. Even if they are highly pancytopenic, supportive therapy and surgery results are satisfactory in these patients.

## What is known

- Acute abdominal conditions such as typhlitis, acute appendicitis, and intussusception may be encountered in the follow-up of pediatric patients with acute leukemia.
- Abdominal pain, vomiting, fever, swelling in abdominal examination, tenderness, are considered when one or more of the defensive findings are present, and the diagnosis is supported by radiological imaging methods.

## What is new

- In these patients, rapid diagnosis, broad spectrum antibiotics, aggressive treatment with the use of antifungal in selected patients, and liquid electrolyte and blood product support are vital.



- In this study, we examined our patients with leukemia who were operated for acute surgical abdomen in terms of clinical findings, prognosis and treatment strategy.

## Declarations

**Publication statement:** This paper have been presented as oral presentation in Hematology, Tranfusion and Cell Therapy journal online with doi: <https://doi.org/10.1016/j.htct.2021.10.1009>.

**Ethical committie:** Consent for publication have been taken from the patients' parents. Patient's parents gave informed written consent for their personal or clinical details along with any identifying images to be published in this study. According to limited number of patients ; Ethics approval and consent to participate have not been taken from Health Sciences University.

**Ethics statement:** Research Ethics Approval: Human Participants have been taken from Health Science Univercity ethical committie.

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**Authors' contributions:** Author Huseyin Avni Solgun and et al. have read and approved the manuscript.

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