

## Acute Appendicitis in Neutropenic Patients with Acute Leukemia

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### Abstract

**Background:** In neutropenic patients with acute leukemia, acute abdomen which is usually attributed to typhlitis may be encountered. However, the diagnosis of acute appendicitis is rarely described or confirmed.

**Methods and Materials:** A retrospective study of acute appendicitis in adult patients with acute leukemia was conducted at the Riyadh Armed Forces Hospital between January 1991 and December 2002 and then the study was continued at King Faisal Specialist Hospital and Research Centre in Riyadh between January 2004 and December 2006.

**Results:** Acute appendicitis developed in three out of 408 patients with acute leukemia treated at both institutions. The incidence of acute appendicitis in adult patients with acute leukemia was 0.74%. Acute appendicitis was encountered during the neutropenic periods following the courses of cytotoxic chemotherapy given to control the leukemia. The three study patients were males and they presented with the classical clinical manifestations of acute appendicitis and they underwent successful appendicectomies. The radiological investigations were helpful in confirming the clinical diagnoses. Compared to the control group of patients, the study patients developed acute leukemia at a younger age and they also had higher rates of: infectious complications, relapse and mortality but lower rate of cytogenetic abnormalities and extramedullary disease.

**Conclusions:** The development of acute appendicitis in neutropenic patients with acute leukemia is an extremely rare event. The combination of the classical clinical manifestations as well as the compatible radiological features is essential diagnostically. Taking a decision to operate on these immunocompromised patients during the periods of severe pancytopenia is a real challenge to surgeons and hematologists. However, surgical intervention may be associated with long term complications such as relapse of the leukemia, infectious complications and decreased survival.

**Keywords:** acute lymphoblastic leukemia, acute myeloid leukemia, acute appendicitis, hematopoietic stem cell transplant

*Clinical Medicine Insights: Trauma and Intensive Medicine* 2010:3 1–7

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## Introduction

In patients with leukemia, the recent advances in therapy have led to an improved survival rate and to an increase in the incidence of clinical events requiring surgical intervention, such as acute appendicitis (AA).<sup>1</sup> In immunocompromised patients, the clinical manifestations of AA may occasionally be similar to those encountered in healthy individuals.<sup>2-7</sup> However, some studies have shown that some of these manifestations may be absent or atypical.<sup>6</sup>

Delays in the diagnosis of AA may lead to complications such as: perforation, infections and death.<sup>2,5,6</sup> Surgery has been shown to be an acceptable first line modality of treatment in patients with acute leukemia (AL) presenting with clinical features consistent with AA, as conservative medical management is usually unsuccessful.<sup>2,3,5,6</sup>

## Patients, Methods and Materials

Riyadh Armed Forces Hospital (RAFH) and King Faisal Specialist Hospital and Research Centre (KFSH&RC) in Riyadh are major tertiary care centers with specialty services including: intensive care, hematology/oncology and solid organ as well as hematopoietic stem cell transplantation (HSCT). A retrospective study of AA in adult patients with AL was initially conducted at the hematology ward and the HSCT unit at RAFH between January 1991 and December 2002 then the same study was continued at the leukemia and the HSCT units at KFSH&RC in Riyadh between January 2004 and December 2006. The records of adult patients with AL who developed AA during their treatment or follow up at both institutions (study group) were reviewed. Their results were compared to those of a control group composed of adult patients with similar backgrounds but never developed AA during their treatment or follow up at both hospitals. Only patients who developed clinical, radiological and histological features consistent with AA were included in the study. Patients with AL who developed acute abdomen due to other causes e.g. acute cholecystitis, acute pancreatitis, pseudomembranous colitis, typhlitis etc were excluded.

## Study patients

The study group consisted of 3 adult patients with AL. All the 3 study patients were males and their ages

ranged between 15 and 26 years with a median age of 20 years. Two patients had had acute lymphoblastic leukemia (ALL) and one patient had acute myeloid leukemia (AML).

## Control patients

The control group of patients consisted of all adult patients with AL treated at both institutions during the study period but never developed AA during their treatment or follow up. This group included 405 patients with various types of AL [205 AML, 187 ALL and 13 acute biphenotypic leukemia (ABL)]. There were 238 males and 167 females and their ages ranged between 14 and 75 years with a median age of 29 years.

Only one study patient (33.3%) had HSCT, while 162 control patients (40%) had HSCT. Both groups of patients received the same chemotherapeutic protocols to control their leukemias. They were also given the same HSCT conditioning protocols and the same immunosuppressive therapies.

## Results

A total of 408 patients with AL were treated at both institutions during the study periods specified previously. Only 3 adult patients with AL developed AA during their treatment at both institutions. The incidence of AA in adult patients with AL was 0.74%. Two study patients had ALL and one had AML. All the 3 study patients were young males (Table 1). All the study patients developed AA during the neutropenic periods following the courses of cytotoxic chemotherapy given to control their leukemias. They developed acute abdomen 2 to 3 weeks following the administration of chemotherapy. They all presented with the classical clinical manifestations of AA i.e. fever, sudden onset of abdominal pain, tenderness, guarding and rebound tenderness involving the right iliac fossa (RIF). The radiological investigations e.g. ultrasound and computerized axial tomography (CAT) scan of the abdomen were very helpful in establishing the diagnoses. The three patients were operated upon successfully after giving them enough supportive measures e.g. broad spectrum antibiotics and blood products (Table 2).

The first patient was found to have a perforated appendix as there was some delay in establishing the diagnosis of AA. However, the subsequent

**Table 1.** Details of the acute leukemia in the study patients.

Patient number	Age (years)	Sex	Type of acute leukemia	Number of courses of cytotoxic chemotherapy given	Number of relapses/response to chemotherapy	Infections encountered	HSCT	Status
1	15	Male	AML, M <sub>4</sub>	3	2 relapses, 1 before and 1 after surgery	Pseudomonal bacteremia	Done	Deceased
2	20	Male	T-cell ALL	4	1 relapse, after surgery	Culture-negative septic shock	Not done	Deceased
3	26	Male	Pre-B ALL	6	1 relapse, before surgery then refractory disease	MDR Pseudomonal bacteremia causing septic shock	Not done	Deceased

**Abbreviations:** ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplant; MDR, multi-drug resistant.

complications he encountered namely: bacteremia due to *Pseudomonas aeruginosa* (*P. aeruginosa*) and bleeding from the operation site were rapidly controlled. The diagnosis of AA in the second patient was rather prompt and he encountered no single complication post-operatively. The third patient was not only severely pancytopenic at the time of diagnosis of his AA, but also he was having refractory leukemia as well as bacteremia caused by a multi-drug resistant *P. aeruginosa*. Despite having a successful surgical intervention, he subsequently deteriorated due to having progressive uncontrolled AL and delayed recovery of his blood counts. The histology confirmed the presence of AA in the three study patients. However, no leukemic infiltration was seen in any of the 3 appendicular tissue samples.

None of the three study patients had chromosomal abnormalities or extramedullary disease at the presentation or during the relapse of their leukemias. All the 3 study patients received cytotoxic chemotherapy to control their hematological malignancies. They were given a median of 4 courses of chemotherapy per patient. All the study patients had relapses of their AL and in one of them the relapse was refractory to two salvage courses of chemotherapy. All the study patients developed infectious complications in the form of bacteremias and septic shocks. However, none of them developed candidemia or invasive aspergillosis. Follow up of these patients showed that the 3 study patients were dead at the end of the study period. The causes of death in these patients were progressive disease or

**Table 2.** Details of the acute appendicitis in the study patients.

Number of patient	Timing of the acute appendicitis	Blood counts at the presentation of appendicitis	Clinical manifestations	Radiological procedures and findings	Histology of appendix
1	2 weeks after re-induction chemotherapy for the first relapse	Pancytopenia	Fever, abdominal pain, tenderness and rebound tenderness in RIF, then guarding and palpable abdominal mass	Ultrasound: appendicular mass	Gangrenous appendicular mass with perforation of appendix
2	3 weeks after the second part of ALL induction course of chemotherapy	Pancytopenia	Fever, abdominal pain, tenderness and rebound tenderness in RIF	CAT scan: enlarged appendix with obstruction of appendicular lumen	Inflamed and enlarged appendix with luminal obstruction by fecolith
3	3 weeks after second line salvage therapy for the refractory relapse	Pancytopenia	Fever, diffuse abdominal pain, vomiting, tenderness, guarding and rebound tenderness in RIF	CAT scan: enlarged appendix with localized bowel wall thickening	Inflamed appendix and autolysis

**Abbreviations:** CAT, computerized axial tomography; ALL, acute lymphoblastic leukemia; RIF, right iliac fossa.



relapsed AL, although one patient had superadded septic complications.

The median age of the study group was lower than that of the control group of patients (20 versus 29 years). ALL was the predominant type of AL encountered in the study group (66.7%), while less than 50% of the control patients had ALL. Infections affected all the study patients, while 55.6% of the control group of patients developed infectious complications. The AL was more refractory to treatment in the study group of patients (33.3% vs. 5%). Extramedullary disease was not seen in the study patients but it was present in 11% of the control patients. The death rate was also higher in the study group of patients (100% vs. 33.6%). Interestingly, no cytogenetic abnormalities were seen in the study group while approximately 57% of the control group had chromosomal abnormalities. Also, the relapse rate of AL was much higher in the study group compared to the control group of patients (100% vs. 40%). The mortality in the study group was due progressive and relapsed leukemia in the 3 study of patients. On the other hand, infections caused death in one third of the control patients, while relapsing/refractory AL caused death in two thirds of the deceased patients (Tables 1 and 3).

## Discussion

The appendix may be involved by leukemia and other malignant disorders e.g. myeloid sarcoma, lymphoma and other primary as well as secondary neoplasms.<sup>7-11</sup> It may also be involved by other non-malignant conditions e.g. endometriosis, peritoneal endosalpingiosis, vasculitis and neural proliferation.<sup>8</sup> The appendix may become infected with certain organisms e.g. *Aspergillus* and *Candida*.<sup>12,13</sup> Furthermore, it may be duplicated or congenitally absent.<sup>8</sup> AA may be encountered at the presentation of AL or during the febrile neutropenic episodes following the courses of cytotoxic chemotherapy given to control the leukemia.<sup>2,4</sup> The clinical manifestation of AA in patients with malignant disorders include: fever; abdominal pain which may be vague, non-localized or localized to the right lower quadrant; abdominal distension; lack or presence of abdominal guarding; localised or generalised abdominal tenderness; rebound tenderness; diarrhea and dehydration.<sup>2-7</sup> It may be complicated by upper gastrointestinal hemorrhage, peritonitis, necrotizing

enterocolitis and rupture of the appendix leading to abscess formation, uncontrolled septicemia and death.<sup>3,6,11-17</sup>

Studies in healthy individuals have shown that clinical evaluation is still paramount to the management of patients with suspected AA before considering medical imaging.<sup>18</sup> Other studies in immunocompromised hosts have shown that it is often difficult to make an accurate diagnosis of acute abdominal conditions because symptoms and physical findings are often suppressed as a result of steroid or immunosuppressive therapy and that no preoperative factor can accurately differentiate neutropenic colitis (typhlitis) from AA on clinical grounds.<sup>3,19</sup> Various radiological methods, e.g. plain X ray, ultrasound and CAT scan, can be used to diagnose acute abdominal conditions and to detect potentially lethal complications.<sup>2,10,14-22</sup> Despite the recent advances in the diagnostic techniques, there is still 37.5% error rate in the ability to accurately diagnose appendicitis particularly in children.<sup>3,10</sup> CAT scan is considered the diagnostic tool of choice for confirming the diagnosis of AA and differentiating it from typhlitis in cancer patients. It is safe, reliable, accurate, non-invasive and has better sensitivity and specificity than ultrasound.<sup>6,20-22</sup> Typhlitis is the main differential diagnosis of AA in neutropenic cancer patients.<sup>6,19-21</sup> It presents with: fever, nausea, vomiting, right lower quadrant abdominal pain, guarding, rebound tenderness and tachycardia. The indications of surgical intervention in patients with typhlitis include: persistent and localised abdominal pain or guarding, lack of improvement with medical therapy, clinical deterioration and the development of an abdominal mass.<sup>6</sup> Despite the recent trend toward diagnosing right lower quadrant abdominal pain as typhlitis, which requires medical management, there are still instances where it is really appendicitis. So appendicitis must always be ruled out in leukemic patients presenting with right lower quadrant abdominal pain.<sup>3,6,10</sup> The incidence of sepsis at the time of presentation of AA or typhlitis is high i.e. about 53%. Coagulopathy and organ failure resulting from sepsis are the main preoperative risk factors. Post-operative morbidity is about 25% and the mortality is approximately 8%.<sup>3</sup> Gastrointestinal perforation is a surgical emergency and any delays in the diagnosis or in the management may be hazardous. However, in immunocompromised





Table 3. Shows details of the control group of patients.

Type of acute leukemia	Number of patients		Alive patients		Deceased patients		HSCT		Relapses		Refractory disease		Chromosomal abnormalities		Infections encountered								
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	CMV	No	%	Bacterial	No	%	Fungal	No	%
AML	205	50.6	151	73.7	54	26.3	97	47.3	53	25.9	9	4.4	117	57.1	36	17.6	74	36.1	9	4.4			
ALL	187	46.2	115	61.5	74	39.6	60	32.1	97	51.9	6	3.2	108	57.8	21	11.2	69	36.9	7	3.7			
ABL	13	3.2	5	38.5	8	61.5	5	38.5	6	46.2	5	38.5	7	53.8	2	15.4	5	38.5	2	15.4			
Overall numbers and percentages	405	100.0	271	66.9	136	33.6	162	40.0	156	38.5	20	4.9	232	57.3	59	14.6	148	36.5	18	4.4			

Abbreviations: HSCT, hematopoietic stem cell transplant; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CMV, cytomegalovirus; ABL, Acute biphenotypic leukemia; No, Number, %, Percentage.

individuals, the clinical signs of gastrointestinal perforation may be blunted.<sup>12,14,15,23</sup>

In neutropenic cancer patients with acute abdomen, the decision to operate can be exceedingly difficult.<sup>2,5,6</sup> Surgical exploration may be the only way to differentiate AA from other causes of acute abdomen e.g. typhilitis, despite the considerable risk of infectious complications due to profound immunosuppression.<sup>2,3,5,6</sup> Studies in patients with AL have shown that surgical management of AA, i.e. appendectomy, can be safely performed and is the most effective therapeutic modality despite having leukemia and neutropenia.<sup>2,5,6,21</sup> Therefore, patients with leukemia having significant right lower quadrant abdominal pain and signs of peritoneal irritation should be operated upon despite having an advanced disease or having had received cytotoxic chemotherapy or steroids.<sup>2,5,6,14</sup> In patients with malignant hematological disorders who present with acute abdomen experience has shown that prompt diagnosis and early surgical intervention with an adequate supportive care i.e. transfusion of blood products and administration of broad spectrum antibiotics can improve the immediate survival.<sup>1,17,23,24</sup> In such patients, urgent and early surgical intervention may occasionally become a life saving measure.<sup>2,5,6,25</sup> Even in neutropenic and thrombocytopenic individuals, major surgeries can be successfully performed with acceptable mortality and morbidity, provided experienced surgeons are involved and enough preparations are made.<sup>25</sup> The critical condition of the patient should not deter surgical management as delays in treatment usually lead to more complications and a higher mortality.<sup>2,5,6,23,25</sup>

Infections with a diverse group of organisms remain the leading causes of morbidity and mortality in patients with malignancy and in HSCT recipients despite the recent advances in the supportive care and despite the use of infection prophylaxis, growth factors and newly developed antimicrobial agents.<sup>26,27</sup> The main risk factors for infections in patients with malignant disorders are: uncontrolled malignancy, immunosuppressive and cytotoxic chemotherapy and immunological deficits including hypogammaglobulinemia and T-cell depletion. The risk of infection is directly related to the intensity and to the duration of cytotoxic chemotherapy and immunosuppressive treatment.<sup>28</sup> In surgically treated patients, infections caused by microorganisms such as *P. aeruginosa* and



non-albicans *Candida* are commonly encountered post-operatively.<sup>25</sup> These infections can be minimized by: taking enough infection control measures, using prophylactic antimicrobials, decreasing the magnitude of surgical trauma by resorting to laparoscopic approach whenever possible and optimizing the host immune response by maintaining homeostasis.<sup>25,29</sup> Studies have also shown that most patients with hematological malignancy subjected to major surgical procedures eventually die from relapses, infections or both. The reduced long term survival and the increase in the incidence of relapse in surgically treated patients may be due to alterations in cytokine metabolism induced by surgical trauma or the possible implantation of malignant cells in injured tissues as this may produce a nidus for relapse in the future.<sup>25</sup>

In our first patient, the initial impression was in favour of typhlitis, but as there was an evidence of clinical deterioration and as the abdominal ultrasound showed an appendicular mass, surgery was performed. Even after appendectomy and giving all the required supportive care, the patient developed further complications e.g. colonic tear causing abdominal hematoma and pseudomonal sepsis. The second patient had prompt diagnosis of his appendicitis and early surgical intervention and thus further complications were prevented. The third patient had an uncontrolled relapse of his leukemia in addition to pseudomonal sepsis at the time of the presentation of his acute abdomen. Despite having successful surgery and despite giving him full supportive care, he deteriorated further and eventually died because of uncontrolled disease and sepsis. Our patients with AL who were subjected to appendectomy had short survival due to relapsing leukemias and repeated infections. Despite including a relatively large number of patients with AL from two major tertiary care centers in Saudi Arabia, we acknowledge that the number of patients with AL who developed AA is rather small and we also acknowledge the limitations of retrospective studies.

## Conclusion

Patients with AL may develop AA during the neutropenic periods following the courses of chemotherapy given to control their hematologic malignancy. Appendicitis can be differentiated from typhlitis clinically and radiologically. Provision of adequate

supportive care facilitates successful surgical intervention. However, surgically treated patients may have decreased survival because of increase in the rates of leukemic relapse and infections caused by multidrug resistant organisms.

## Acknowledgements

We are grateful to all medical, nursing and technical staff who participated in the management of the patients presented at Armed Forces Hospital and King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia.

## Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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