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Acute Appendicitis in Patients with Leukemia: A Dilemma in Diagnosis and Surgical Treatment

*Chen Wang, Han-Zhang Huang, Yu-Jun Yu, Yu He and Shao-Liang Han**

Department of General Surgery, Wenzhou Medical University, China

Abstract

Acute appendicitis in patients with leukemia is rare, which mainly complicates leukemic involvement of appendix or associates with cases of relapse of the disease. Therefore, it is a challenge to make correct diagnosis and treatment of appendicitis. The clinical and surgical data of 23 leukemia patients with acute appendicitis were analyzed retrospectively. There were 15 male and 8 female, with median age of 25.6 years old (ranging: 15 to 44 years). The underlying disease was 5 acute leukemia and 18 chronic leukemia. The main symptoms were abdominal pain (100%), fever (87.0%), vomiting (44.4%), diarrhea (13.0%) and abdominal distension (21.7%). The median WBC count <2 × 10^9/L at the time of diagnosis was in one case, between 1 to 2 × 10^9/L in 4, <5 × 10^9/L in 4; and the median platelet count <20 × 10^9/L was in one case, <50 × 10^9/L in 8, and >50 × 10^9/L in 14; Hb>60 g/L was in 17 cases, and <60g/L in 6. All 23 patients received surgery, 17 with open appendectomy and 6 with laparoscopic appendectomy. A high index of suspicion must be kept when leukemia patients have right lower quadrant abdominal pain, and an early surgery is an effective treatment option for leukemia patients with appendicitis.

Keywords: Appendicitis; Leukemia; Neutropenia; Appendectomy

Introduction

Appendicitis is the most common acute abdomen that necessitates emergent abdominal surgery in both adult and children, and the diagnosis of acute appendicitis usually depends on abdominal pain, nausea and vomiting, and typical clinical manifestations [1-2]. However, appendicitis in patients with leukemia is a rare condition, which mainly complicates leukemic involvement of appendix or associates with cases of relapse of the disease [3-6]. The nonspecific clinical presentation, which is easily confusing with the symptoms following leukemia and/or chemotherapy for this disease, to make a correct diagnosis of appendicitis in patients with leukemia is challenging [5-9]. It has been reported that the incidence of appendicitis in patients with leukemia is low (0.5% to 1.5%), and most patients may present with vague, nonspecific symptoms, resulting in delay of diagnosis, which may result in perioperative complications and death [3-9]. Until now, only a few series of appendicitis in patients with leukemia have been reported, and not too much experience has been demonstrate to the surgeon. Therefore, we collected and analyzed the clinical and follow-up data of 23 cases of appendicitis in patients with leukemia, in order to improve the level of diagnosis and treatment.

Materials and Methods

Patients characters

The study was approved by the Institutional Review Board of Wenzhou Medical University. The 23 leukemia patients with appendicitis were diagnosed and treated in between January 1995 and December 2016 at the First Affiliated Hospital of Wenzhou Medical University, China. The patients' records were retrospectively reviewed for the patient's age, gender, underlying disease, clinical hematologic status at the onset of symptoms and signs, laboratory and imaging data, treatment and outcomes. Appendicitis was diagnosed based on clinical presentation, imaging study, laboratory study and histological findings. The Ultrasound (US) or Computed Tomography (CT) criteria for the diagnosis of appendicitis included an overall diameter of the appendix >6 mm and increased echogenicity of the surrounding mesenteric tissues with or without free fluid or abscess in the right lower quadrant of the abdomen.

Diagnosis of leukemia

The diagnosis and classification of leukemia was made by two hematologists who blind to this study according to FAB classification and its criteria [10], based on repeated complete blood

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Correspondence:
Shao-Liang Han, Department of General Surgery, Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China,
E-mail: slhan88@yeah.net

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counts, blood smears, and a bone marrow examination following observations of the symptoms. Sometimes, blood tests may not show that a person has leukemia, especially in the early stages of the disease or during remission. A lymph node biopsy can be performed to diagnose certain types of leukemia in certain situations.

Perioperative management

Preoperative treatment consisted in the following measurement: (1) blood transfusion: entire blood and packed red blood cells were indicated in cases with Hemoglobulin (Hb) <90 g/L; (2) transfusion of platelets and its derivatives: indicated in cases with thrombocyte (Plt) <20 × 10^9/L; (3) prophylactic administration of broad-spectrum antibiotics: the 3rd generation of cephalosporin was applied; (4) prophylactic administration of steroid for avoiding adrenal crisis caused by surgery, such as hydrocortisone 100 mg intravenously injected 30 min before operation, because most chemotherapy regimen in treatment of leukemia have used a great amount of steroid; (5) application of Granulocyte Colony-Stimulating Factor (G-CSF) 300 μg daily until neutrophil recovery and antithrombin III, if necessary; (6) intravenous immune globulin: because of sepsis with abnormal levels of antithrombin III, D-Dimer, fibrinogen degradation products and fibrinogen.

Results

The clinical features and presentations

There were 15 male and 8 female, with the male to female ratio of 1.9:1. The median age at the time of the diagnosis of appendicitis was 25.6 years old, ranging from 15 to 44 years. The underlying leukemia of this group, included 3 Acute Lymphocytic Leukemia (ALL), 2 Acute Myelogenous Leukemia (AML), 5 Chronic Lymphocytic Leukemia (CLL) and 13 Chronic Myeloid Leukemia (CML). Of the 5 acute leukemia patients, 2 patients had just completed remission induction chemotherapy, 2 patients were receiving maintenance chemotherapy and the other patient had completed delayed intensification chemotherapy (Table 1). Three of 5 patients with acute leukemia developed acute appendicitis during the period of neutropenia that occurred in intensive chemotherapy, and other 2 patients with acute leukemia developed acute appendicitis during the period of neutropenia that occurred after consolidation chemotherapy, respectively. All the patients displayed abdominal pain (100%), and other symptoms included high fever (>38.5°C) proceeding before abdominal pain in 20 patients (87.0%), nausea and vomiting in 10 patients (44.4%), diarrhea in 3 patients (13.0%) and abdominal distension in 5 patients (21.7%). On physical examination, all patients (100%) had limited direct tenderness in right abdominal quadrant, 16 patients (69.6%) had rebound tenderness in right abdominal quadrant, and 7 patients (30.4%) showed signs of diffuse peritoneal irritation (Table 2).

Laboratory examination and imaging study

The median White Blood Cells (WBC) count at the time of diagnosis was less than 2 × 10^9/L in one case, between 1 to 2 × 10^9/L in 4 cases, less than 5 × 10^9/L in 4 cases, and WBC elevated (greater than 10 × 10^9/L) in the other 14 cases, and the non-elevation of WBC was found in all acute leukemia and some chronic diseases cases. The median platelet (Plt) count at the time of diagnosis was less than 20 × 10^9/L in one case, <50 × 10^9/L in 8 cases, and >50 × 10^9/L in 14 cases. Hemoglobin (Hb) greater than an equal 60 g/L was in 17 cases, and less than 60 g/L in 6 cases. C-reactive proteins were above normal levels in 4 of the 17 patients, but the others were not checked. Lactate dehydrogenase increased in 13 patients and normal in other 10. Abdominal ultrasound revealed swollen appendix in 18 cases, abdominal inflammatory mass in 5 cases. On the preoperative abdominal CT scan, 7 patients were tentatively diagnosed with acute appendicitis without appendicolith, 5 patients were tentatively diagnosed with acute appendicitis with appendicolith and 11 patients were tentatively diagnosed with periappendiceal abscess due to appendicitis (Table 2).

Table 1: The clinical characters of 23 acute appendicitis patients with leukemia.

Age (year)	Mean 25.6 range (15-40)
Gender	Male: Female =15: 8
Underlying disease Acute leukemia (n=5) Chronic leukemia (n=18)	 ALL: AML=3:2 CLL: CML=5: 13
Phase of acute leukemia Remission Maintenance intensification	 2 2 1

ALL: Acute Lymphocytic Leukemia; AML: Acute Myelogenous Leukemia; CLL: Chronic Lymphocytic Leukemia; CML: Chronic Myeloid Leukemia

Table 2: The clinical presentation of acute appendicitis in leukemia patients.

Items	Cases (%)
Symptoms	
Abdominal pain	23 (100%)
Fever	20 (87.0)
Nausea and vomiting	10 (44.4%)
Diarrhea	3 (13.0)
Abdominal distension	5 (21.7%)
Physical signs	
Tenderness in right abdominal quadrant	23 (100%)
Rebound tenderness in right abdominal quadrant	16 (69.6%)
Signs of diffuse peritoneal irritation	7 (30.4%)
Median White Blood Cells (WBC) at the time of diagnosis	
WBC<2 × 10^9/L	1 (4.3%)
Between 1 to 2 × 10^9/L	4 (17.4%)
Less than 5 × 10^9/L	4 (17.4%)
Greater than 10 × 10^9/L	14 (60.9%)
Median platelet (Plt) count at the time of diagnosis	
less than 20 × 10^9/L	1 (4.3%)
<50 × 10^9/L	8 (34.8%)
>50 × 10^9/L	14 (60.9%)
Hemoglobin (Hb) at the time of diagnosis	
greater than and equal 60g/L	17 (73.9%)
less than 60g/L	6 (26.1%)
Abdominal ultrasound	
Swollen appendix	18
Abdominal inflammatory mass	5
Abdominal CT scan	
Appendicitis without appendicolith	7
Appendicitis with appendicolith	5
Periappendiceal abscess due to appendicitis	11

Table 3: Postoperative complications of acute appendicitis in 23 patients with leukemia.

Items	Number of patients (%)
Wound infection	4 (17.4%)
Intra-abdominal abscess	1 (4.3%)
Wound bloody oozing	3 (13.0%)
Death secondary to intra-abdominal abscess and septicemia	1 (4.3%)

Surgical outcomes and postoperative complications

All 23 leukemia patients received surgery, 17 with open appendectomy and 6 with laparoscopic appendectomy. The postoperative pathology confirmed simple acute appendicitis in 4 cases (17.4%), acute suppurative appendicitis in 13 cases (56.5%) and acute suppurative appendicitis with perforation in 6 cases (26.1%).

On microscopy, all the cases were appendicitis with neutrophil infiltration, and 2 cases showed evidence of leukemic infiltration on hematoxylin and eosin stain and immunohistochemical study. Three patients (13.0%) complicated wound bloody oozing after surgery, 4 patients (17.4%) complicated with wound infection, and 2 patients (8.7%) with intra- abdominal abscess, which included 1patient (4.3%) who died of septicemia and death. The other 22 patients recovered within a period of 7 to 18 days after surgery (Table 3).

Discussion

It has been reported that the lifetime cumulative incidence rate of appendicitis in the general population is 9% [3-4], and the incidence rate of appendicitis in leukemia patients is 0.5% to 4.4% [5-9]. Besides the common etiology of appendicitis such as fecal blockage, the following underlying factors may correlate with the development of appendicitis, which delays accurate diagnosis: (1) leukemic involvement of appendix can compromise the structural integrity of the appendiceal wall; (2) Moreover, atypical presentations of appendicitis are common in immunocompromised patients due to underlying malignancy and ongoing chemotherapy; (3) early symptoms such as nausea, vomiting, abdominal pain, and diarrhea are non-specific and may be attributed to chemotherapy side-effects [4,12-19]. Wiegering et al. [13] reported on 5 patients who were diagnosed with appendicitis out of a group of 113 leukemia patients (4.4%). Alioglu et al. [14] reported on 2 patients who were diagnosed with appendicitis out of 118 leukemia patients (1.7%). In our study, 23 patients were diagnosed with appendicitis out of a group of 2408 leukemia patients, representing an incidence of 0.96%.

The diagnosis and differential diagnosis

In ordinary appendicitis, the pain usually begins from periumbilicus that shifts to the Right Lower Quadrant (RLQ), and appendiceal distension can lead to nausea and vomiting, eventual fever by continued inflammation. Typical tenderness, rebound tenderness and signs of peritoneal irritation are positive on physical examination. However, these signs may not be so evident in neutropenic or immune compromised patients [4-6,17-19]. Hobson, et al. [20] indicated that diarrhea and a high fever above 38.5°C are more characteristic of typhlitis than appendicitis. In this study, all the patients displayed abdominal pain (100%), and other symptoms included high fever (>38.5°C) proceeding before abdominal pain (87.0%), vomiting (44.4%), diarrhea (13.0%) and abdominal distension (21.7%). On physical examination, all patients (100%) had limited direct tenderness in right abdominal quadrant, 16 patients (69.6%) had rebound tenderness in right abdominal quadrant, and 7 patients (30.4%) showed signs of diffuse peritoneal irritation. Most patients with appendicitis had elevated White Blood Cell Count (WBC); however, it is rarely seen in acute appendicitis patients with leucopenia. That may lead physicians easily to miss these cases that had normal white blood cell count and leukopenic presentation [6,9,21]. In this study, The median WBC count at the time of diagnosis was less than 2×10^9/L in one case, between 1 to 2×10^9/L in 4, less than 5×10^9/L in 4, and WBC elevated (greater than 10×10^9/L) in the other 14, and the non-elevation of WBC was found in all acute leukemia and some chronic diseases cases.

Imaging study such as abdominal Ultrasonography (US) and Computed Tomography (CT) may be helpful in diagnosis of appendicitis. If ultrasonography is not diagnostic, MRI scanning may not be adequate for immunocompromised/myelosuppressed patients [4,22,23]. Although Hobson et al. [20] noted that the diagnostic accuracy of CT for appendicitis is only about 33%; Stroman et al. [24] reported that the sensitivity and overall accuracy of CT for appendicitis in immune competent patients was about 92% and 90% respectively. An abdominal CT scan revealed appendiceal wall thickening, sometimes with hypodense lesion, suggesting appendicitis with periappendiceal abscess formation. That is different from CT findings of typhlitis, which include right-sided colon wall thickening, pericolonic stranding, ascites, and cecal pneumatosis. On T2-weighted MRI images, the appendix appeared with a markedly hyperintense center, a slightly hyperintense thickened wall, and markedly hyperintense periappendiceal tissue. Moreover, in a study from Kirkpatrick [25] comparing enhanced CT with unenhanced MRI in patients with suspected appendicitis, the authors concluded that the accuracy of MRI was similar to that of enhanced CT. Hörmann et al. [26] used ultrasonography and Magnetic Resonance Imaging (MRI) in 45 immunocompetent children with clinically suspected acute appendicitis, the correct diagnosis rates were 40% and 100%, respectively. In this study, abdominal ultrasound revealed swollen appendix in 18 cases, abdominal inflammatory mass in 5. On the preoperative abdominal CT scan, 7 patients were tentatively diagnosed with acute appendicitis without appendicolith, 5 patients were tentatively diagnosed with acute appendicitis with appendicolith and 11 patients were tentatively diagnosed with periappendiceal abscess due to appendicitis.

Surgical policy and treatment

How to treat acute appendicitis in patients with leukemia remains controversial. Medical treatment can be effective if the pathogenetic mechanism is cecal inflammation-induced periappendicitis instead of luminal obstruction. Response to antibiotics should be considered first before proceeding with surgery in some cases [27]. Although successful conservative management has been reported[28], the majority require surgery to avoid life-threatening complications in immunocompromised/myelosuppressed patients with leukemia [3,6,9,12,13,16,17]. Several reports have showed safety and efficacy of surgical intervention in appendicitis in patients with leukemia, and operative management may also shorten the length of hospital stay and decrease the mortality compared to non-operative management [3,6,9,12,16,17]. Leukemia patients with acute appendicitis need early surgery, because of delayed surgical management usually leads to high rate of surgical mortality [9,12,17]. Nowadays, laparoscopic appendectomy has been recognized as the operation of choice for appendicitis. A prospective randomized study of laparoscopic *vs.* open appendectomy for complicated appendicitis concluded that the laparoscopic approach is safe and that operation time, hospital stay, and rates of wound sepsis, reoperations, and readmissions did not differ between the 2 approaches [9,29-31]. Kim et al. [9] reviewed their experience with acute appendicitis in 7 Korean children with acute leukemia. Five of the 7 underwent laparoscopic appendectomy, and 2 underwent an open procedure. All experienced an uneventful recovery, but 1 in the laparoscopic group had an umbilical wound infection. Forghieri et al. [32] described their experience with 2 adult patients with hematologic malignancies (1 with multiple myeloma, the other with acute myeloid leukemia; M2) who developed acute appendicitis while neutropenic. Both surgical procedures started laparoscopically (one was converted to a minilaparotomy because of a gangrenous appendix) and each recovered uneventfully. In our study, all 23 leukemia patients received surgery, 17 with open appendectomy and 6 with laparoscopic appendectomy Three patients (13.0%) complicated wound bloody oozing after surgery, 4 patients

(17.4%) complicated with wound infection, and 2 patients (8.7%) with intra-abdominal abscess, which included 1 patient (4.3%) who died of septicemia and death. The other 22 patients recovered within a period of 7 to 18 days after surgery. Taken together, the clinicians should examine the patients carefully and maintain a high index of suspicion, when leukemia patients have right lower quadrant abdominal pain. The early surgical intervention may be the more effective treatment option for leukemia patients with appendicitis, with the help of early diagnosis.

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