

## Acute Appendicitis in Patients with Acute Leukemia

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*The decision to operate for abdominal pain in patients with leukopenia can be exceedingly difficult. Surgical exploration may be the only effective way to differentiate acute appendicitis from other causes, but it involves considerable risk of infectious complications due to immunosuppression. Leukemic patients, who presented significant RLQ pain, had been indicated for operation, despite having advanced disease or having had received chemotherapy or steroids.*

*Four adult leukemia patients, complicated by acute appendicitis, were reviewed. Two patients were in induction chemotherapy, one receiving salvage chemotherapy due to relapse and the other was in conservative treatment. Two patients were acute myelocytic leukemia (AML), one had acute lymphocytic leukemia (ALL), and the other had aleukemic leukemia. All patients underwent appendectomy and recovered without complication. Our experience supports the theory that the surgical management of appendicitis in acute leukemia is the most effective way, in spite of leukopenia.*

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**Key Words:** Acute leukemia, Appendicitis

### INTRODUCTION

At present, advanced leukemic chemotherapy and improved general supportive care have led to prolonged survival of patients with acute leukemia. With the prolonged survival, there are increasing complications related to the disease process and to the chemotherapy used to treat the disease<sup>1)</sup>. The prolonged survival has resulted in an increasing frequency of acute abdominal pain such as appendicitis, in conjunction with the tendency of the necrotizing enteropathy of the ileum, appendix or cecum<sup>2,3)</sup>. Diagnosis or surgical consultation may be delayed because typical signs and symptoms of acute intra-abdominal infection sometimes

are deficient in leukemic patients<sup>4)</sup>. So the decision to operate for abdominal pain in patients with leukopenia can be exceedingly difficult. Surgical exploration may be the only effective way to differentiate acute appendicitis from other causes of abdominal pain.

Appendectomy is accepted as the treatment of choice for presumed uncomplicated appendicitis also in patients with acute leukemia<sup>5)</sup>.

We present 4 cases of acute appendicitis in adult leukemia, one of them was periappendiceal abscess.

### PATIENTS

There were men and one woman ranging in age from 22 to 71. Two patients were AML, one ALL, and the other had aleukemic leukemia. Two patients developed symptoms during induction chemotherapy, one during salvage chemotherapy, and the other was in conservative treatment

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**Table 1. Signs and Symptoms and their Relationship to the Status of Leukemia**

Case	Status of leukemia	Signs and Symptoms	Duration of Sx.
1	Induction (ALL*)	RLQ+ pain, fever*	1 day, 3 weeks*
2	Induction (AML**)	RLQ pain and tenderness, fever	1 day
3	consolidation (AML)	Nausea, vomiting, diarrhea RLQ pain and tenderness with rebound Rovsing sign(+)	1 day
4	conservative (aleukemic)	RLQ pain and tenderness	

\*RLQ: right lower quadrant    \*ALL: acute lymphocytic leukemia    \*\*AML: acute myelogenous leukemia

**Table 2. WBC counts, Pathologic findings and Chemotherapeutic agents before Onset of Symptoms**

Patient	WBCs*/cu mm (% PMN**)	Pathologic findings	Chemotherapeutic agents
1	1500( 2%)	Suppurative inflammation Periappendiceal abscess	Daunorubicin, vincristine and Prednisolone
2	500( 8%)	Gangrenous inflammation Leukemic infiltration	Daunorubicin, L-asparaginase Vincristine and Prednisolone
3	600( 0%)	Suppurative inflammation	Mitoxantrone and Etoposide
4	2200(13%)	Suppurative inflammation	Conservative treatment

\*WBCs: white blood cells    \*\*PMN: polymorphonuclear cell

because of poor performance status and old age. Preoperative CBC was absolute granulocytopenia in all patients and relative thrombocytopenia, except one. Preoperative and intraoperative infusion of blood and platelets were required for three patients.

Table 1 lists the patients with their signs and symptoms presented at the onset of appendicitis.

Laboratory tests, pathologic findings, and chemotherapeutic agents shown in Table 2.

One of the four patients received prednisolone (12 mg/day) together at the onset of appendicitis, and one received steroids in previous chemotherapy.

**CASE REPORTS**

**Case 1**

The patient, a twenty-two-old woman with acute lymphocytic leukemia, had induction chemotherapy, with intravenous vincristine (2mg, weekly), adriamycin (45mg/M<sup>2</sup>×3days) and oral prednisolone (60mg/M<sup>2</sup>, daily). A week later, fever and right lower quadrant pain developed, but she denied diarrhea, nausea and vomiting and there was no rebound tenderness. Radiography of the small bowel revealed no pathological findings. On complete blood count, leukocyte count was 1500/mm<sup>3</sup>, with 29% of neutrophils, 62% of

lymphocytes %, 7% of monocytes. The hemoglobin was 7.8 mg/dl, hematocrit 22.8%, platelet 68,000/mm<sup>3</sup>. Liver function test (SGOT and SGPT) was three to five times higher than normal and hepatitis B virus surface antigen (HBsAg) was negative. Blood cultures were negative at three times. Bone marrow aspiration revealed a remitted state of ALL.

As appendicitis was suspected, explosive laparotomy was done immediately. The appendix was perforated and had abscess formation. Biopsy results showed acute suppurative inflammation with periappendiceal abscess formation, but there was no evidence of leukemic involvement. After surgery, the patient made an eventful recovery.

**Case 2**

The patient, a thirty-three-year-old man, who was diagnosed as hybrid leukemia which further defined AML, had induction chemotherapy, intravenously vincristine (2mg, weekly), adriamycin (45mg/M<sup>2</sup>×3days), L-asparaginase (6000 IU/M<sup>2</sup>×12days) and oral prednisolone (60 mg/M<sup>2</sup>×four weeks). On the fifth day, sudden spiking fever, RLQ pain and tenderness developed. On complete blood count, leukocyte count was 700/mm<sup>3</sup>, 83% of lymphocytes, 10% of neutrophils, 7% of band forms.

Operation was performed and biopsy results

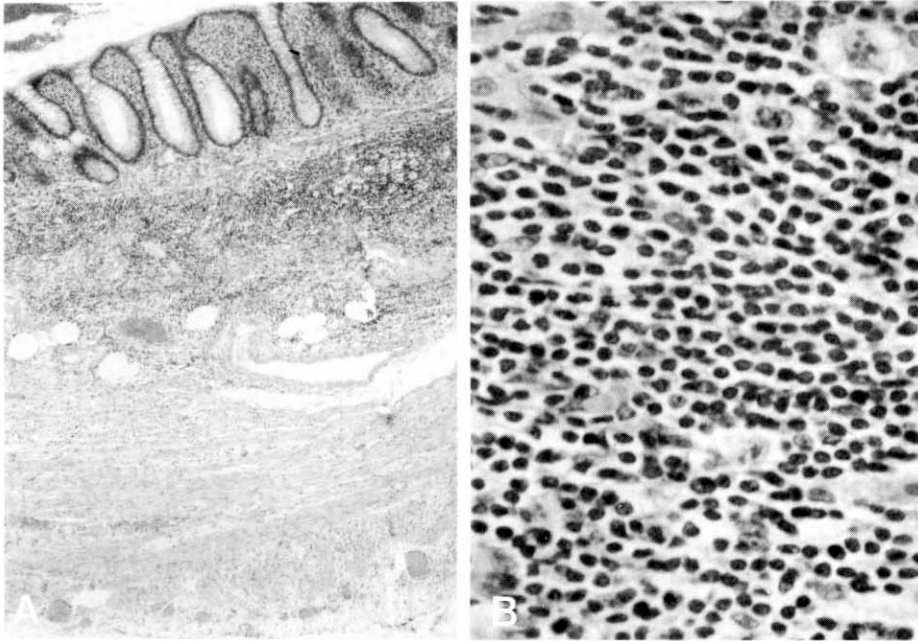


Fig. 1. Case 1. Appendix biopsy: Infiltration of mononuclear cells, lymphocytes and monocytes in the subserosal and mucular layer, suggesting reactive appendicitis (A: H and E, Original magnification,  $\times 100$ , B: H and E, Original Magnification,  $\times 400$ ).

were acute gangrenous inflammation and leukemic infiltration of the appendix.

### Case 3.

The patient, a twenty-nine-year-old man with acute myelogenous leukemia (M1), admitted for salvage chemotherapy due to relapse, received scheduled mitoxantrone ( $10\text{mg}/\text{M}^2 \times 5$  days) and etoposide ( $100\text{mg}/\text{M}^2 \times 5$  days). On the twelfth day, he complained of RLQ pain with fever, RLQ rebound and positive Rovsing sign. On complete blood count, leukocyte count was  $700/\text{mm}^3$ , with 98% of lymphocytes, 2% of monocytes. Hemoglobin was  $10.0\text{ mg}/\text{dl}$ , hematocrit 27.5%, platelet  $47,000/\text{mm}^3$ . Ultrasonographic findings were regional ileus in RLQ, but not visualized appendix. Operation was performed immediately and biopsy result was acute inflammatory change. No surgical complications were noted.

### Case 4.

The patient, a seventy-one-year-old man with aleukemic leukemia, had not received chemotherapy due to poor performance status and old age, and supportive care was done for a year. He

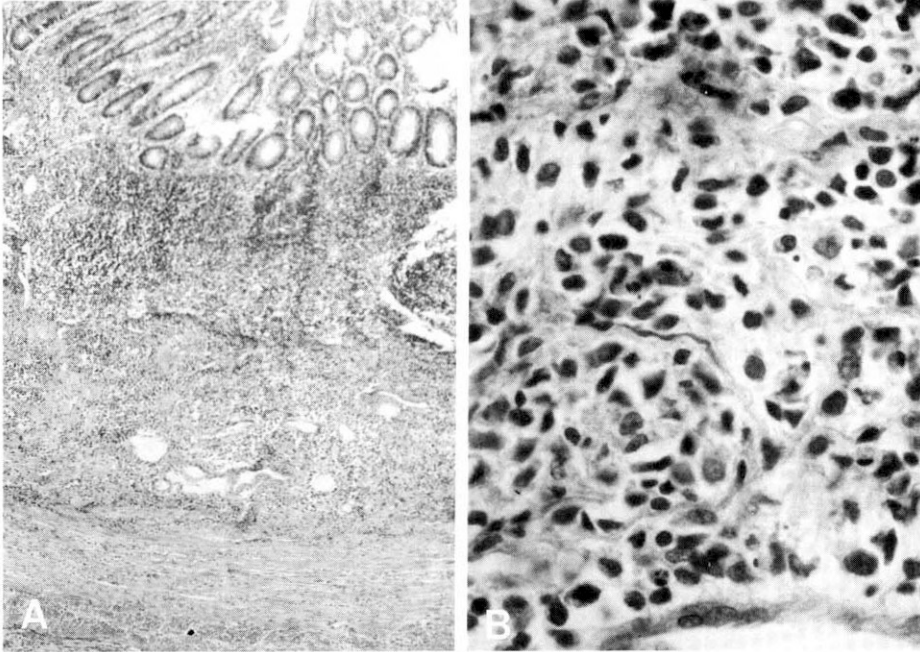
complained of sudden onset of RLQ pain and tenderness and was operated on under the diagnosis of acute appendicitis. The biopsy resulted in acute suppurative inflammation.

## DISCUSSION

Now that aggressive chemotherapy and advanced general supportive care improve survival, more patients with leukemia are likely to present intra-abdominal disease, not necessarily related to the underlying hematologic malignancy, which may require surgical intervention. The disease is more commonly reported in children, but is being increasingly reported in adult patients<sup>1)</sup>.

It is thought that chemotherapy may damage the gastrointestinal tract by destroying the rapidly dividing mucosal cells which, when coupled with neutropenia, allows bacterial invasion of the bowel wall. The invasive infection leads to necrosis of various layers of the bowel wall. The process has a predilection for the terminal ileum and cecum, but any segment of the bowel can be involved<sup>6,7)</sup>.

Intra-abdominal disease in leukemic patients seems to be most frequently associated with the



**Fig. 2.** Case 2. Appendix biopsy: Acute gangrenous inflammation and leukemic infiltration with immature leukemic cells (A: H and E, Original Magnification,  $\times 100$ , B: H and E, Original Magnification,  $\times 400$ ).

use of cytosine arabinoside and anthracycline<sup>8</sup>), although it has been reported following a variety of other chemotherapeutic regimens. Our patients had received adriamycin, etoposide, mitoxantrone and vincristine.

The diagnosis of acute appendicitis may also be complicated by chemotherapeutic agents, whose effects may mask the signs and symptoms or whose toxic effect may mimic the acute surgical abdomen<sup>9,10</sup>, and differential diagnosis is so difficult that a necrotizing enteropathy of the ileocecal lesion not limited to the appendix may occur. Diagnosis of neutropenic colitis, termed typhilitis, without pathologic examination is speculative and the differentiation from appendicitis is unclear. Typhilitis and appendicitis appear to be equally common in young leukemic patients with right lower quadrant pain and signs of peritoneal irritation. The preoperative differentiation between these two problems is difficult and one cannot be secure in recommending nonoperative treatment. The role of surgical management in appendicitis is clear, the role of surgical therapy in typhilitis is less well defined<sup>11</sup>.

Several investigators<sup>10-12</sup>) have pointed out the

difficulty in diagnosing intra-abdominal catastrophes. Signs suggesting an acute abdomen, such as abdominal pain, nausea, vomiting and melena, are frequent in leukemic patients and are also frequent symptoms of antileukemic drug toxicity. In addition, the frequent use of steroids may mask serious surgical complications. All of our patients had RLQ pain and tenderness, but had not peritoneal irritation signs and symptoms, for example, rebound tenderness, nausea and vomiting, except for one. We think that the typical signs and symptoms of acute appendicitis are not present due to severe neutropenia.

Preoperative barium enema study may be helpful in differentiating appendicitis from other entities but any rectal manipulation such as colonoscopy or contrast enemas are contra-indicated in severely neutropenic patient<sup>13</sup>). Alexander et al<sup>14</sup>) reported characteristic echogenic thickening of the bowel mucosa on ultrasonography to be helpful in the diagnosis of the disease process. We performed ultrasonography in two cases, but did not find abnormalities in the appendix.

Zeulzer and Flatz<sup>12</sup>) indicated that the success of surgical procedures in patients with acute leu-

kemia and surgical complications depends on the presence of hematological remission.

Appendectomy is also accepted as the treatment of choice for presumed uncomplicated appendicitis in patients with acute leukemia, but the management of perforative appendicitis with abscess formation remains controversial<sup>4)</sup>. The decision to operate for abdominal pain in patients with leukopenia can be exceedingly difficult. Vaughan et al<sup>15)</sup> advocated close surveillance, early surgical consultation and early operative intervention in patients with acute leukemia and intra-abdominal complications, even in the presence of granulocytopenia and thrombocytopenia. Surgical exploration may be the only effective way to differentiate acute appendicitis from other causes, but it involves considerable risk of infectious complications due to immuno-suppression<sup>4)</sup>. This principle may be correct as a general rule, but is not always true in individual instances. Leukemic patients who presented significant right lower quadrant symptoms and signs of peritoneal irritation had sufficient indications for operation, despite having advanced disease or having received chemotherapy or steroids<sup>9)</sup>. Our patients underwent appendectomy as soon as the diagnosis was suspected, although they had not peritoneal irritation signs. When needed, infusions of red blood cells, platelets and antibiotics were given, but granulocytes infusion was not given. The role of broad spectrum antibiotics has contributed significantly to the support of the patient during the postoperative period until marrow recovery occurs, and is probably the reason for the increasing proportion of patients who survive and recover from surgery<sup>16)</sup>.

Although occurring infrequently, appendicitis is associated with a high mortality rate in leukemic patients<sup>17)</sup>. In a recent review of the results of the intra-abdominal operations in cases of acute and chronic leukemia, the overall surgical mortality was 29%, and the difference between mortality associated with emergency procedures and with elective operations (55% vs 8%) was statistically significant<sup>15)</sup>. All of our patients were operated on as an emergency procedure, and all patients recovered without considerable complication.

## CONCLUSION

In this review, four patients with acute leukemia developed acute appendicitis, and appendectomy

was performed on three of them and appendectomy and removal of periappendiceal abscess was performed on one. Although the symptoms and signs are mild and not typical, early diagnosis and surgical intervention is the effectively way of dealing with acute appendicitis in acute leukemia.

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