

ORIGINAL ARTICLE

Acute acalculous cholecystitis: challenging the myths

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*Department of Surgery, National University Hospital, Yong Loo Lin School of Medicine, Singapore***Abstract**

Background: Acute acalculous cholecystitis (AAC) is traditionally known to occur in critically ill patients, following cardiac surgery, abdominal vascular surgery, severe trauma, burns, prolonged fasting, total parenteral nutrition, or sepsis, and is believed to have a worse prognosis as compared with acute cholecystitis associated with stones. Our observation of *de novo* presentation of AAC in several outpatients in the absence of critical illness or predisposing factors prompted us to undertake this study. The aims of the present study were to examine the prevalence of AAC patients in the outpatient setting in our hospital, to identify associated risk factors and to assess the clinical course and outcome of these patients. **Patients and methods:** All patients who had a cholecystectomy (laparoscopic or open surgery) for acute cholecystitis at National University Hospital from January 2001 to May 2005 were reviewed from a prospectively maintained database. The demographic characteristics, clinicopathologic features, operative parameters, postoperative course, and histopathology of the patients were reviewed. **Results:** Eleven of 133 patients with acute cholecystitis fulfilled the criteria for the diagnosis of AAC. Patients' ages ranged from 30 to 69 years (mean 52.39 years). All these patients presented as outpatients. None of the patients had any critical illness predisposing to AAC. The mean age was slightly less in the AAC group as compared with the remaining patients with acute cholecystitis (52.39 years vs 55.22 years, $p = 0.54$). There was male predominance in the AAC group (male:female = 9:2). The time from admission to surgery, operative procedure, operative time, and postoperative stay were not statistically different from the remaining patients with acute cholecystitis. **Discussion:** AAC can occur in young and middle-aged healthy individuals, the presentation is no different from acute calculous cholecystitis, the prognosis is good if diagnosed and treated early.

Key Words: *acute acalculous cholecystitis, early treatment, morbidity, prognosis***Introduction**

Acute acalculous cholecystitis (AAC), i.e. inflammation of the gallbladder without evidence of calculi or sludge, comprises 2–15% of all cases of acute cholecystitis [1,2]. AAC is traditionally known to occur in critically ill patients, following cardiac surgery, abdominal vascular surgery, severe trauma, burns, prolonged fasting, total parenteral nutrition, or sepsis [3–7]. AAC is believed to have a more fulminant course, frequently associated with gangrene, perforation, and empyema, as well as significantly higher morbidity and mortality [2]. Moreover major cardiovascular disorders, complicated diabetes mellitus, autoimmune disease [8,9] and AIDS [10] have all been recognized as possible predisposing factors for AAC. There are a few reports of *de novo*

AAC in the outpatient setting, especially without the traditionally observed predisposing factors.

We have observed the *de novo* presentation of AAC in several of our patients in the absence of acute illness or predisposing factors, which prompted us to undertake this study. The aims of the present study were to examine the prevalence of AAC patients in the outpatient setting in our hospital, to identify associated risk factors, and to assess the clinical course and outcome of these patients.

Patients and methods

All patients who had a cholecystectomy (laparoscopic or open surgery) for acute cholecystitis at the National University Hospital from January 2001 to May 2005 were retrospectively reviewed from a prospectively

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maintained database. Patients were considered to have AAC if all of the following criteria were met: (1) radiological imaging studies failed to demonstrate stones or sludge in the presence of acute cholecystitis, (2) intraoperative confirmation of inflamed gallbladder and absence of stones or sludge in the gallbladder, and (3) postoperative pathologic examination confirmed the diagnosis of acute cholecystitis in the absence of biliary calculi. The demographic characteristics, clinicopathologic features, operative parameters, postoperative course, and histopathology of the patients were reviewed.

Results

A total of 133 patients with acute cholecystitis underwent cholecystectomy for acute cholecystitis at the National University Hospital from January 2001 to May 2005. Eleven patients fulfilled the criteria for the diagnosis of AAC. Patients' ages ranged from 30 to 69 years (mean 52.39 years). There were nine men and two women with AAC. The comorbid conditions, presenting symptoms and signs in the group with AAC are listed in Table I. There were five patients with no comorbid conditions and four patients had more than one comorbid condition. All of these patients presented as outpatients and none had developed AAC while hospitalized. None of the patients had any critical illness predisposing to AAC. The most common presenting feature was right upper quadrant abdominal pain and no patient had associated cholangitis. Only three patients had fever at presentation; however, three more patients developed fever after hospitalization. Nine patients had leukocytosis, and the most common biochemical abnormality was elevated lactate dehydrogenase (LDH). Levels of bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase were normal in all 11 patients. Ten patients had abdominal ultrasound, and acute cholecystitis was diagnosed in eight patients. Two patients had computed tomographic (CT) scan, which showed cholecystitis in one. One patient had no imaging study and was operated on clinical grounds of acute abdomen, and one patient, despite a normal CT scan, underwent a diagnostic laparoscopy which showed gallbladder gangrene. The latter patient had torsion of the gallbladder at the neck causing ischemia.

Table I. Comorbid conditions and presenting symptoms and signs in AAC.

Comorbid condition	n	Symptoms/signs	n
Diabetes mellitus	2	Right upper quadrant pain	8
Hypertension	5	Epigastric pain	4
Asthma	1	Generalized abdominal pain	2
Paraplegia	1	Nausea/vomiting	6
Peripheral vascular disease	1	Fever	3
Coronary artery disease	1	Septic shock	1

Five patients underwent laparoscopic cholecystectomy and six had open cholecystectomy, including two patients who had conversion to open surgery. The mean operative time was 101.36 min (60–150 min) and the mean postoperative stay was 5.5 days (2–10 days). There were no major postoperative complications in any of the patients and there was no mortality in this series. Two patients who underwent open cholecystectomy had prolonged ileus and wound infection. The comparison of demographic and perioperative characteristics in patients with AAC and acute calculous cholecystitis showed no significant difference; however, there was a preponderance of male patients in the AAC group (Table II).

The bile or blood cultures from two patients with AAC grew *Klebsiella pneumoniae* and *Escherichia coli* from one patient. The remaining eight patients had negative cultures. The histopathology in the patients with AAC revealed gangrenous cholecystitis in four patients, acute suppurative cholecystitis in four, patchy acute inflammation with mural microabscesses in two, and nonspecific inflammatory cell infiltration in one patient.

Discussion

AAC, which comprises approximately 10% of all cases of acute cholecystitis, is a well recognized but still poorly understood entity. Traditionally, AAC is known to occur in patients with chronic debilitating diseases, superimposed critical illness, trauma, or major burn injury. Although previous reports two decades earlier [1,2] have consisted almost exclusively of critically ill patients, reports in the last decade [11–13] demonstrated increasing *de novo* presentation of AAC in the absence of acute illness or traumatic injury. Recent reports have documented that 77–90% of patients developed AAC at home without evidence of acute illness or trauma [12,13]. In this study, the incidence of AAC was 8.3%, which is similar to

Table II. Comparison of demographic and operative characteristics of patients with AAC and calculous cholecystitis.

Characteristic	Acalculous cholecystitis (n=11)	Calculous cholecystitis (n=122)	p value
Gender (male:female)	9:2	62:60	0.057*
Age (mean) (years)	52.39	55.22	0.54†
LC	5	61	0.936*
OC	4	38	
Converted	2	23	
Time from presentation to operation (h)	32.72	45	0.28†
Operative time (min)	101.3	98.9	0.79†
Postoperative stay (days)	5.5	4.5	0.33†

LC, laparoscopic cholecystectomy; OC, open cholecystectomy.

*Fisher's exact test.

†Student's *t* test.

previous reports of AAC. However, all the patients in this study had AAC as outpatients and none had any acute predisposing illness.

The age of onset has been a subject of discussion in previous reports of AAC and was reported to be more common in the sixth decade [12,13] as compared with acute cholecystitis, which is more common in the fourth and fifth decades. However, in this series the mean age of patients with AAC was 52.39 years, which is lower than those with routine acute cholecystitis, with a mean age of 55.2 years. Parthivel et al. have previously described AAC in four patients without predisposing factors. Seven patients in our series were below 60 years age and two were in their thirties. AAC has been described to have a male preponderance in previous studies [2,11], which was also observed in our study.

In the series by Savoca et al. [11], 83% of the patients had significant underlying medical problems and 72% had evidence of underlying vascular disease. Most large series have observed that AAC occurs in medically compromised patients. In this series five patients had no comorbid condition. The most common comorbid condition in the remaining patients was hypertension (five patients), which is consistent with the recent series [11,13,14]. Hypertension may predispose to microangiopathy, which has been proposed to have a role in the development of AAC [15]. The most common presenting complaint in this series was right upper quadrant pain and it seems that the presentation of AAC is no different from routine acute calculous cholecystitis. Only three patients had fever at the time of presentation, which may be indicative of the early presentation of the patients. However, in critically ill patients, postoperative patients, and post trauma patients the presentation may not be classical and AAC should be considered in these settings with clinical findings of sepsis with no obvious source [14]. Most patients in this study had a diagnosis of acute cholecystitis confirmed on abdominal ultrasound, which has a high sensitivity and specificity, is relatively inexpensive, and can be performed easily [16]. Hepatobiliary scintigraphy, which is used when the diagnosis is difficult, was not deemed necessary in any of the patients in this series.

The operative time, the length of postoperative stay, and mean time from admission to operation in this series of AAC were comparable to calculous acute cholecystitis. Four patients had open surgery, two patients had conversion to open surgery following laparoscopic attempt, and the remaining patients had laparoscopic cholecystectomy. There were no major postoperative complications and no mortality in this series. The operative outcomes of AAC may be no different compared to routine acute cholecystitis if patients present as outpatients, have no major comorbid illness, and are operated relatively early in the course of illness. The poor prognosis of AAC in the

earlier series may be attributable to the poor physiologic states of the cohort of patients and not solely due to inflammation in the absence of stones in the gallbladder. Four patients had gangrenous gallbladders (36%) and none had perforation. From previous studies it appears probable that diagnostic delay is one of the factors responsible for the development of gallbladder gangrene. With a diagnostic delay of 36.9 ± 5.1 h a 28% incidence of gangrenous gallbladders was noted in the series by Savoca et al. [11]. However, factors other than diagnostic delay may have a role to play [17].

The most commonly postulated theories regarding pathogenesis of AAC are bile stasis with resultant change in chemical composition, sepsis, and ischemia. In critically ill patients AAC results from gallbladder ischemia, which may be secondary to shock from hypovolemia and/or sepsis. Experimental animal studies causing ischemia and reperfusion of the gallbladder have emphasized the potential role in the pathogenesis of AAC [18]. Dillon et al. [19] demonstrated that inhalation of the constituents of cigarette smoke condensate (tar) resulted in the prompt development of AAC and pneumonitis with thrombus formation in pulmonary vessels, using an *in vivo* canine model.

This study shows that the traditional beliefs regarding AAC are unfounded. AAC is known to occur in outpatients and it seems that the incidence is on the rise based on the published literature. Whether this represents changing epidemiology of the disease from critically ill patients to relatively healthy subjects, pattern of reporting (earlier studies may have focused on critically ill patients), or true increase in the incidence of AAC in outpatients is subject to further debate. AAC can occur in young and middle-aged healthy individuals, the presentation is no different from calculous cholecystitis, the prognosis is good if diagnosed and treated early. Although the pathogenesis of AAC remains elusive it is time to challenge the traditional myths.

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