Case report

Acute acalculous cholecystitis in hospitalized patients in intensive care unit: study of 5 cases

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ABSTRACT

Background: Acute acalculous cholecystitis (AAC) is an inflammation of the gallbladder with no evidence of gallstones. It occurs mostly in patients in intensive care units and is associated with several risk factors (fasting, parenteral nutrition, mechanical ventilation) leading to ischemia of the gallbladder wall.

Methods: This is a retrospective multiple cases study of five cases of AAC in patients hospitalized in the Medical Intensive Care Unit at Tahar Sfar Hospital in Mahdia over a 4-year period between January 2016 and December 2020.

Results: The mean age of our patients was 62.5 years (±8) with a male predominance (sex ratio 4/1). The mean Charlson comorbidity index was 4. Four patients were under invasive mechanical ventilation and total parenteral nutrition. Three patients were under vasoactive drugs. All patients had fever, the patient who was conscious presented with abdominal pain and vomiting with right hypochondrium tenderness, while two patients presented with abdominal bloating and bowel obstruction. All patients had a biological inflammatory syndrome, two patients had cytolysis, and only one patient had cholestasis. All patients had a thickening of the gallbladder wall greater than 3mm on ultrasound. Treatment was based on broad-spectrum antibiotic therapy followed by early (<72 h) cholecystectomy. Only one patient had postoperative peritonitis. All patients had gangrenous cholecystitis. Three patients died of multi-visceral failure.

Conclusion: This study, in spite of its small sample size, gave us an idea of patients at risk of developing this disease, on the difficulty of diagnosis and on the importance of surgical treatment.

1. Introduction

Acute acalculous cholecystitis (AAC) is an uncommon condition characterized by gallbladder inflammation in the absence of biliary calculi or sludge [1]. It represents 2%-14% of cases of acute cholecystitis [2, 3], with a higher prevalence among males. In spite of AAC can be diagnosed in patients without previous or concomitant comorbidities, it is usually associated with an underlying medical comorbidity [4]. Several predisposing factors including gallbladder epithelial ischemia and reperfusion injury, positive pressure ventilation, parenteral nutrition, and opioid use have been implicated [5, 6]. Although the precise mechanism is unknown, the most commonly postulated theories regarding its pathogenesis are bile stasis, sepsis, and ischemia of the gallbladder wall. Bile stasis may result in alterations of change in the chemical composition of bile, subsequently rendering the gallbladder mucosa susceptible to local injury. The role of ischemia in this process has been difficult to elucidate and etiologies of ischemia are multifactorial [7]. Due to its non-specific presentation, diagnosis of AAC is challenging, in fact symptoms and laboratory findings are unspecific and are likely to be masked in patients with critically ill diseases or neurological problem.

AAC can be diagnosed in children too, mainly associated to viral infections such as Epstein-Barr virus (EBV) and, thus, often associated to liver dysfunction as well [8]. Early detection and timely treatment are advocated in order to avoid a fulminant course of the disease and potential life threatening complications such as gangrene or perforation [7, 9]. In fact, Prognosis may depends on prompt diagnosis and active...
treatment [10]. Mortality rates may reach 90% in some study [11, 12, 13].

For patients with evidence of gallbladder gangrene or perforation, cholecystectomy is indicated as an aggressive immediate procedure to improve multi-organ failure [14]. For critically ill patients or those who are unfit for surgery, percutaneous cholecystostomy (PC) is recommended [2, 15, 16].

2. Methods

This is a retrospective, descriptive multiple cases study conducted in the Medical Intensive Care Unit of Tahar Sfar Hospital of Mahdia over a 4- year period extending from January 2016 to December 2019.

AAC was defined as acute cholecystitis (AC) in the absence of gallstones in the gallbladder or in the main bile duct on abdominal imaging studies or in Intraoperative Cholangiogram. A retrospective review of cases from our healthcare facility in this period was carried out. Demographic data, risk factors, clinical signs, complementary tests, intraoperative findings, and long-term consultation follow-up were collected.

Patients included in this study presented cholecystitis that acalculous character was confirmed during surgery after opening the gallbladder and sieving the bile. We excluded all patients with calculous cholecystitis or acalculous cholecystitis but with a main bile duct stone in Intraoperative Cholangiogram reflecting calcific migration from the gallbladder. AAC was diagnosed using abdominal sonography or computed tomography. Imaging studies were interpreted by an expert radiologist. All cases were confirmed by board-certified gastroenterologists or general surgeons based on clinical features and imaging findings. The date of diagnosis of AAC was defined as the day of abdominal imaging.

Demographic and clinical data were collected from the patients’ medical records. Variables such as age, sex, comorbidities including diabetes and cardiovascular disease, Charlson comorbidity index (CCI), cause of admission, Sequential Organ Failure Assessment (SOFA) score, interval from admission to diagnosis of AAC, treatment for AAC, historical findings, bacterial diagnosis, length of hospital and ICU stays, and mortality were collected. Additionally, red blood cell transfusion history, prior vasoactive drug, opioid use, total parenteral nutrition, and mechanical ventilation, which are known as a risk factors of AAC, were also collected.

Statistical analysis: Owing to the small number of patients, data are presented with descriptive statistics measures. Descriptive parameters were expressed as mean (± standard deviation). The different binary variables were expressed in number of cases.

The ethics comity approval was obtained (name of the ethics committee: ethics comity of Tahar Sfar Hospital, Institution: faculty of medicine of Monastir, Certificate number: CEM-2021-11-04).

Informed consent was obtained from all subjects and/or their legal guardian(s).

3. Results

In this period 148 patients were assessed for acute calculous or acalculous cholecystitis, the prevalence of AAC among all the patients developing acute cholecystitis is 3%.

Five patients were diagnosed with AAC after ICU admission during the study period. The patients’ mean age was 62.5 years. All patients were older than 50 years. Patients details are reported in Table 1 and Table 2.

All patients had gallbladder distension with a transverse diameter greater than 5 cm on ultrasound. Thickening of the gallbladder wall greater than 3 mm was found in four patients. The absence of gallstones was reported in all patients. Ultrasound Murphy’s sign was present in one patient.

Abdominal CT scan was performed in two patients; images showed gallbladder distension greater than 5 cm, gallbladder wall thickening greater than 3 mm and wall enhancement defect without the presence of calculus in these patients. One patient had perivesicular fluid infiltration and one patient had perivesical fluid imaging with subserosal edema.

According to Tokyo Guidelines, all patients were classified as Grade 3. Regarding the surgical risk assessment, all patients were classified ASA IV.

Probabilistic antibiotic therapy was subsequently documented by an antibioticogram performed on a bile sample after cholecystectomy. The combination Imipenem-Tigecycline was used in two patients. The following combinations: Cefotaxime-Metronidazole, Imipenem-Amikacin and Tygescycline-Colistin were used in one patient each.

We used the SOFA score to evaluate the evolution of our patients from the day of cholecystectomy to the 7th postoperative day. A decrease in the SOFA score was observed in patients with a favorable postoperative course. The average postoperative length of stay of our patients after cholecystectomy was 18 days ± 12. Only one patient had postoperative peritonitis. Three patients died due to multi-visceral failure (Table 3).

4. Discussion

The pathogenesis of AAC appears to be multifactorial: bile stasis, sepsis, and ischemia of the gallbladder wall are the most commonly postulated theories, but the precise mechanism is still unclear [3].

The gallbladder mucosa is susceptible to local injury when the chemical composition of bile is changed by the bile stasis [3]. Bile viscosity increasing intraluminal pressure and Ischemia resulting from hypotension or atherosclerosis has also been implicated as a possible cause. In most cases, hypovolaemia or sepsis are responsible for Gallbladder ischaemia. In fact, mediators released in response to systemic inflammation can induce inflammatory process in the gallbladder [12]. Additionally, in critically ill patients, sepsis and infection are frequently linked to cholestasis [7, 10] which is cytokine-mediated, and resulting from reaction to bacterial endotoxins [7]. Therefore, cholestasis, gallbladder ischemia, and systemic inflammation caused by pneumonia or any other sepsis could be responsible for the development of AAC in ICU patients [12].

In the series reported by Savoca et al. [1], underlying medical problems were present in 83% of patients and 72% of them had underlying vascular disease.

| Table 1. Baseline characteristics of the patients (n = 5). |
|---------------------------------|
| Age, years (mean ± SD) | 62.5 (±8) |
| Gender M/F | 4/1 |
| Comorbidities | |
| • Hypertension | 4 |
| • Diabetes | 3 |
| • Coronary artery disease | 3 |
| • Cerebrovascular disease | 2 |
| • Chronic obstructive airway disease | 2 |
| • Chronic kidney disease | 1 |
| Charlson comorbidity index | 4 |
| SOFA score in admission | 5, 6 |
| Interval from admission to diagnosis (days) | 9 (±7) |
| Abdominal pain | 1 |
| Vomiting | 1 |
| Bowel obstruction | 2 |
| T >38°C | 5 |
| Abdominal bloating | 3 |
| Tenderness of the right upper quadrant | 1 |
| Leukocyte >10³/μm³ | 17000 |
| CRP (mg/L) | 171 |
| ASAT >35 UI/L | 2 |
| ALAT >40 UI/L | 3 |
| Bilirubin total >20 mmol/L | 1 |
According to Hakala et al. [17]microcirculation disturbance could be an important factor in the pathogenesis of AAC. In fact, when it is compared to acute gallstone-associated cholecystitis, the capillary filling in AAC was poorer and more irregular.

Savoca et al. [1] reported 2 cases of AAC without any risk other than severe visceral atherosclerosis, suggesting that impaired mucosal resistance caused by visceral atherosclerosis could increase risk of AAC.

In the present study, all our patients had diseases associated with atherosclerotic vascular problems, such as hypertension, diabetes, cerebro-vascular accidents or coronary artery disease.

Some study reported an association between developing AAC and prolonged intensive care length of stay. In fact, Long ICU stay can be a result or a risk factor for developing AAC.

In our study the mean length of stay is 9 days, the same results were found by Laurila et al. [14]: for patients with AAC, the mean length of stay in the ICU was 8 days. This risk depends also on surgery indication; after cardiovascular surgery, the mean length of stay was 26 days [18]. In trauma patients, it was 13.2 days [19].

In fact, burns [20], cardiovascular surgery, or trauma [9, 21], are frequent with those patients. For Laurila et al. [14] operatively confirmed AAC are more frequent with severe illness, long ICU stay, multiple organ failure and infection.

Prolonged fasting and TPN, prior opioid or prior vasoactive drugs, and mechanical ventilation were frequently observed in patients who developed AAC in the ICU [10].

Clinical characteristics of AAC in the ICU have been reported by some studies but still nonspecific. Due to its variable presentation, diagnosis of AAC is challenging, in fact symptoms and laboratory findings are unspecific. In the present study abdominal pain was noted in only one patient, fever in only two patients. Therefore, the diagnosis of AAC has to be suspected, each time the patient is hospitalized in the intensive care unit for more than one week and has sign of indeterminate infection.

In matter of AAC, Ultrasound has high sensitivity and specificity of more than 90% [22], and it can be very useful not only in the early diagnosis of AAC but also in defining the treatment plans to be undertaken [23]. Images in ultrasound can be a distended gallbladder, a thickened wall, inflammation and pericholecystic fluid without any stones in the gallbladder [24]. Abnormal ultrasound findings could also be found in the gallbladder without having acalculous cholecystitis in critically ill patients [25], decreasing the specificity of ultrasounds.

Computed tomography (CT) imaging has the same sensitivity of ultrasound but lacks of specificity. Critically ill patients have a higher frequency of gallbladder abnormalities on CT compared with ultrasound.

In a retrospective study accounting 127 acalculous cholecystitis [26], 96% of critically ill patients had abnormal CT images: increased thickness, lack of enhancement of the gallbladder wall, subserosal edema, increased bile density, large perpendicular diameters of the gallbladder, gas within the gallbladder, ascites, peritoneal fat edema, and diffuse tissue edema. Finding gas in the gallbladder was the most specific finding for acalculous cholecystitis with specificity of 99.2% but a very low sensitivity of 11.1%. CT scan has a very good negative predictive value, effectively ruling out acalculous cholecystitis.

Imaging criteria for the diagnosis of acalculous cholecystis have been proposed in many study, such as a review from Barie and Eachempati [3]. The main CT images to search for are a distended gallbladder without any stones with a thickened or edematous wall.

Cholecystectomy is the treatment of choice for AAC. However, surgery is not always possible, in fact it depends on the patient’s condition especially that many of these patients are poor surgical candidates. For those patients, a PC tube placed by interventional radiology to secure gallbladder drainage can be used. This can be a temporary solution or a treatment option. As it has been suggested by a large retrospective study, for selected patients, PC can have a lower morbidity, fewer intensive care unit admissions, a decreased length of stay, and lower costs compared with open cholecystectomy [11] with a low overall rate of complications (around 2%) [27]. In addition, higher mortality rates could be linked to their conditions and not directly to the PC.

Transpapillary drainage through an endoscopic retrograde cholangiopancreatography (ERCP) has been used by some authors. Its success was variable and is associated with high recurrence rates [11].

The findings of this study must be seen in light of some limitations. First, it is a retrospective single-center study with a small number of patients included, so it may not reflect all critically ill patients in various hospital settings and second, the prevalence of AAC might be underestimated in our study. Larger prospective studies are recommended to assess more strong results.

5. Conclusion

Acalculous cholecystitis has non-specific presentation, its diagnosis is challenging. Symptoms and laboratory findings are unspecific and there are no clear diagnostic criteria.

Early diagnosis and timely treatment are very important in order to avoid complication such as perforation and sepsis.

In critical ill patient, the diagnosis of AAC should be advoked each time there is signs of infection and after eliminating common causes.

Ultrasounds and CT scan can be of a great help. A distended gall-bladder, a thickened wall, inflammation and pericholecystic fluid can be found. Gas in the gallbladder is the most specific finding for acalculous cholecystitis.

For patients with evidence of gallbladder gangrene or perforation, Cholecystectomy is the treatment of choice for AAC as an aggressive immediate procedure [10]. For critically ill patients or those who are unfit for surgery, percutaneous cholecystostomy (PC) is recommended [2, 19, 20].

Ethics approval and consent to participate

we have the approval of the ethics committee. All methods were performed in accordance with the relevant guidelines and regulations and have been performed in accordance with the Declaration of Helsinki.

Ethics comity approval

Name of the ethics comitee: ethics comity of Tahar Sfar Hospital.
Institution: faculty of medicine of monastir.
Certificate number: CEM-2021-11-04.

Consent for publication

Consent from all subjects and/or their legal guardian(s) for publication of identifying information/images in an online open-access publication.

Declarations

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The authors declare no conflict of interest.

Additional information

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Appendix

Table 2. Detailed laboratory findings

| Case | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|------|--------|--------|--------|--------|--------|
| Hemoglobin (g/dL) | 12.2 | 9.8 | 9.1 | 10.5 | 9.3 |
| white blood cell count (/mm3) | 15000 | 17500 | 12500 | 21800 | 20600 |
| neutrophil count (/mm3) | 12300 | 15100 | 12100 | 19600 | 18200 |
| Lymphocytes (/mm3) | 2400 | 2300 | 1100 | 1800 | 2200 |
| blood platelet (/mm3) | 172000 | 181000 | 190000 | 212000 | 126000 |
| CRP (mg/L) | 133 | 226 | 47 | 182 | 89 |
| creatinine (μmol/L) | 158 | 246 | 310 | 186 | 112 |
| Urea | 9.3 | 21 | 24 | 12 | 14 |
| Potassium (mmol/L) | 4.4 | 3.8 | 3.5 | 4.1 | 3.9 |
| sodium (mmol/L) | 144 | 133 | 134 | 132 | 142 |
| blood glucose (mmol/L) | 8.8 | 5.5 | 10.5 | 11 | 7.8 |
| AST (UI/L) | 19 | 10 | 155 | 32 | 182 |
| ALT (UI/L) | 46 | 18 | 162 | 20 | 91 |
| Total Bilirubin (μmol/L) | 16 | 19 | 18 | 15 | 38 |
| direct (conjugated) bilirubin (μmol/L) | 8 | 6 | 2 | 6 | 17 |

Table 3. Summary of patients with AAC in our study

| Case | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|------|--------|--------|--------|--------|--------|
| Age | 59 years | 70 years | 57 years | 74 years | 53 years |
| Gender | M | M | F | M | M |
| Comorbidities | Hypertension, Diabetes, Coronary artery disease, Atrial fibrillation | Hypertension, Diabetes, Coronary artery disease, Atrial fibrillation | Hypertension, Diabetes, Coronary artery disease, Atrial fibrillation | Hypertension, Chronic obstructive airway disease, Cerebrovascular disease | Chronic obstructive airway disease |
| CCI | 3 | 5 | 6 | 4 | 2 |
| Cause of admission | Heart failure | Pneumonia | Heart failure | Pneumonia | Pneumonia |
| SOFA score in admission | 9 | 1 | 5 | 5 | 8 |
| Interval from admission to diagnosis | 8 days | 22 days | 2 days | 16 days | 6 days |
| Clinical symptoms | Fever, Abdominal bloating | Fever | Fever, Abdominal pain, Vomiting | Abdominal bloating | - |
| Laboratory findings | BIS | BIS | BIS, Cytolysis | BIS | BIS, Cytolysis, Cholestasis |
| Antibiotics | Imipenem, Tigecycline | Imipenem, Tigecycline | Ceftriaxone, Metronidazole | Tigecycline, Colistin | Tigecycline, Colistin |
| Surgical approach | OC | OC | OC | OC | OC |
| Histological findings | Gangrenous | Gangrenous | Gangrenous | Gangrenous | Gangrenous |
| Bile culture | E.coli | Enterobacter | E.coli | Klebsiella | Klebsiella |
| Mortality | No | Yes | No | Yes | Yes |

BIS: biological inflammatory syndrome, OC: open cholecystectomy.
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