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Case Report

Beyond conventions, medication-induced organ damage: exploring a case of gangrenous cholecystitis in a healthy young adult male on fluoxetine and amphetamines

Christina C. Sneed*, Martine A. Louis, Denis Gratsinsky, Kelly Cervellione

Department of Surgery, Flushing Hospital Medical Center, Flushing, New York, USA

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***Correspondence:**
Dr. Christina C. Sneed,
E-mail: csneed@sgu.edu

ABSTRACT

Acute cholecystitis occurs in 1 to 2% of patients with gallstones, with 2 to 20% progressing to gangrenous cholecystitis (GC). Within the realm of acute cholecystitis, GC presents itself as a formidable challenge, with a higher mortality rate (15 to 50%) compared to uncomplicated cholecystitis (3%) and elusive preoperative diagnosis. Traditionally observed among the elderly population burdened by comorbidities, GC's emergence in younger patients with no apparent risk factors sets the stage for intriguing exploration. Our case report involves a healthy young adult male on fluoxetine and amphetamines, introducing the potential of medication-induced ischemia leading to the development of GC.

Keywords: Acute cholecystitis, GC, Fluoxetine, Amphetamines

INTRODUCTION

Gangrenous cholecystitis (GC) is a serious complication of cholelithiasis where progressive vascular insufficiency results in ischemia, necrosis, and eventual perforation of the gallbladder wall. The most common causes of cholecystitis are gallstones, tumor, infection, bile duct blockage, or other severe illness that can damage blood cells and decrease blood flow. Within the realm of acute cholecystitis, GC presents itself as a formidable challenge, with a higher mortality rate (15 to 50%) compared to uncomplicated cholecystitis (3%) and elusive preoperative diagnosis.[1] Known risk factors of GC include male gender, advanced age, delayed surgery, cardiovascular disease (CVD), diabetes mellitus (DM), and leukocytosis.[2] Drug-induced cholestasis is uncommon, occurring in less than 20% of the elderly population in the United States, and even less so in younger patient populations; examples include certain antibiotics, immunomodulators, hormones, nonsteroidals (NSAIDs), anti-epileptics, antifungals, antipsychotics, and lipid-lower agents.[3] However, medication-induced vasoconstriction has been noted to cause organ ischemia in all ages. We present a healthy young adult male patient with epigastric and right upper quadrant (RUQ) pain and nausea within a few hours after amphetamine consumption, found on surgical exploration to have GC, and discuss the importance of medication effects in contribution to his disease formation.

CASE REPORT

GC is a serious complication of cholelithiasis where progressive vascular insufficiency results in ischemia, necrosis, and eventual perforation of the gallbladder wall. The most common causes of cholecystitis are gallstones, tumor, infection, bile duct blockage, or other severe illness that can damage blood cells and decrease blood flow. Within the realm of acute cholecystitis, GC presents itself as a formidable challenge, with a higher mortality rate (15 to 50%) compared to uncomplicated cholecystitis (3%) and elusive preoperative diagnosis. Known risk factors of GC include male gender, advanced age, delayed surgery,

CVD, DM, and leukocytosis. Drug-induced cholestasis is uncommon, occurring in less than 20% of the elderly population in the United States, and even less so in younger patient populations; examples include certain antibiotics, immunomodulators, hormones, NSAIDs, anti-epileptics, antifungals, antipsychotics, and lipid-lower agents. However, medication-induced vasoconstriction has been noted to cause organ ischemia in all ages. We present a healthy young adult male patient with epigastric and RUQ pain and nausea within a few hours after amphetamine consumption, found on surgical exploration to have GC, and discuss the importance of medication effects in contribution to his disease formation.

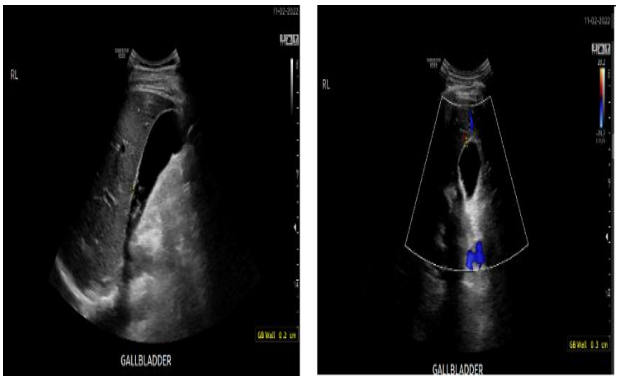

Figure 1: Gallbladder ultrasound findings sludge and multiple mobile gallstones in the gallbladder lumen, mild gallbladder distention, positive sonographic Murphy's sign, but no gallbladder wall thickening, no pericholecystic fluid, and no biliary dilatation.

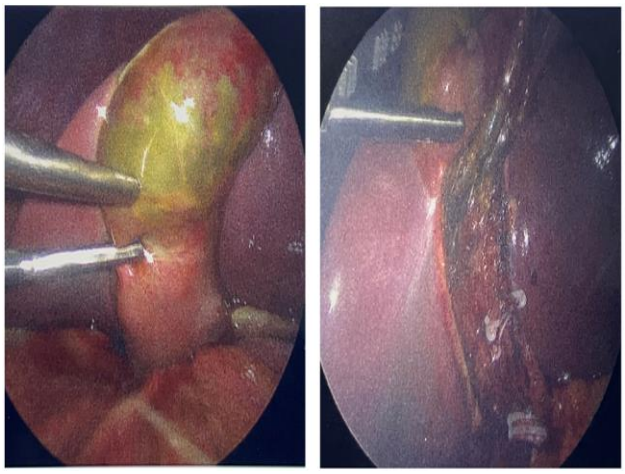

Figure 2: Intraoperative image of distended gangrenous gallbladder without perforation.

DISCUSSION

GC is a serious complication of cholelithiasis where progressive vascular insufficiency results in ischemia, necrosis, and eventual perforation of the gallbladder wall. The most common causes of cholecystitis are gallstones, tumor, infection, bile duct blockage, or other severe illness that can damage blood cells and decrease blood flow. Within the realm of acute cholecystitis, GC presents itself as a formidable challenge, with a higher mortality rate (15 to 50%) compared to uncomplicated cholecystitis (3%) and elusive preoperative diagnosis.[1] Known risk factors of GC include male gender, advanced age, delayed surgery, CVD, DM, and leukocytosis.[2] Drug-induced cholestasis is uncommon, occurring in less than 20% of the elderly population in the United States, and even less so in younger patient populations; examples include certain antibiotics, immunomodulators, hormones, nonsteroidals (NSAIDs), anti-epileptics, antifungals, antipsychotics, and lipid-lower agents.[3] However, medication-induced vasoconstriction has been noted to cause organ ischemia in all ages. We present a healthy young adult male patient with epigastric and RUQ pain and nausea within a few hours after amphetamine consumption, found on surgical exploration to have GC, and discuss the importance of medication effects in contribution to his disease formation.

Given the absence of common risk factors and findings, it is imperative to explore the potential role of medications in development of GC in our patient: Amphetamine-dextroamphetamine and fluoxetine, with more specific focus on amphetamines. Amphetamines introduce vasoactive amines into the system, exerting its effects through a multifaceted mechanism of action. By impeding the reuptake of norepinephrine, dopamine, and serotonin back into presynaptic neurons, as well as augmenting their release into the synaptic space, the drug elicits an elevation in catecholamine levels. Consequently, this surge in catecholamines triggers heightened sympathetic activity within the central nervous system (CNS). Subsequent cascades of responses ensue, involving beta-adrenergic agonistic reactions that encompass increased heart rate, stroke volume, and skeletal muscle perfusion. Simultaneously, the amplified alpha-adrenergic effects manifest through heightened vasoconstriction, elevated total peripheral resistance (TPR), hypertension characterized by elevated systolic and diastolic blood pressure, and enhanced respiratory stimulation.[5]

Amphetamine-induced organ dysfunction has been reported for years. Remarkable case reports have highlighted the occurrence of amphetamine-induced small bowel ischemia in a 33 year-old patient.[6] Similarly, a 2018 case report documented the diagnosis of septic shock, paralytic ileus, GC, and small bowel ischemia as a consequence of methamphetamine abuse in a 44 year-old. The repetitive exposure to catecholamines through amphetamines provokes a cascade of physiological responses, including hypertension, tachycardia, and vasoconstriction. These effects can give rise to vasospasm, thrombosis, and arterial dissection.[7] Consequently, the impact of amphetamine on the body may induce states akin to those seen in CVD or respiratory disease, potentially leading to ischemic events

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Acute acalculous cholecystitis (AAC) is characterized by gallbladder inflammation without the presence of gallstones. AAC often manifests in patients facing critical illness or enduring prolonged fasting or total parenteral nutrition (TPN). AAC can progress to a gangrenous state, carrying the risk of perforation due to stagnation of bile within the gallbladder, leading to increased intraluminal pressure, vasoconstriction, and subsequent ischemia. A retrospective study conducted from 2016 to 2020 shed light on 5 cases of ICU patients diagnosed with GC. Among these cases, 4 out of 5 patients were mechanically ventilated and receiving total parenteral nutrition (TPN), while all 5 presented with fever, abdominal pain, and vomiting. Remarkably, 100% of the patients exhibited ultrasonographic findings of gallbladder wall thickening exceeding 3 mm. Notably, 3 out of the 5 patients were also taking vasoactive drugs.[11] Consequently, the consideration of vasoconstrictive medications becomes pertinent in cases of gangrene associated with both calculous and acalculous cholecystitis.

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Less than 20% of cholecystectomies are performed in the young adult population (under 30 years of age). In one analysis of 178 young patients presenting with symptomatic gallbladder disease, 150 (84%) underwent cholecystectomy with a male to female ratio was 1 to 5.[12] A retrospective review was performed on a group of patients with preoperative diagnosis of acute cholecystitis who underwent LC from 2011 to 2015. Patients were classified on a grading scale as: (I) Symptomatic cholelithiasis, (II) Acute/chronic cholecystitis, (III) Gangrenous/necrotizing cholecystitis, or (IV) Gallbladder perforation or abscess. Of the 1,252 patients reviewed, 677 met inclusion criteria. Grade III (Gangrenous/necrotizing cholecystitis) occurred in 16% of patients. When applying the American association for the surgery of trauma (AAST) injury scoring scale to this set of patients, only 1% were grade III. Grade III patients in this study had a mean age of 52 years, 18% had LC converted to open, 28% had SIRS on admission, and length of stay in the hospital was a mean of 4.4 days.[13] Our patient was an otherwise healthy young adult male, who had only leukocytosis, with no risk factors, who was safely discharged 1 day postoperatively after a laparoscopic cholecystectomy.

Diagnosis of GC is difficult preoperatively. The Tokyo guidelines for acute cholecystitis 2018 (Tokyo 18) are used for patients with findings suspicious for acute cholecystitis to aid in early versus delayed management such as surgery, gallbladder drainage, and selection and duration of antibiotics. Grade II criteria include leukocytosis greater than 18,000/mm^3, palpable tender RUQ mass, duration of complaints greater than 72 hours, and marked local inflammation (GC, hepatic abscess, emphysematous cholecystitis, pericholecystic abscess, biliary peritonitis). Grade III criteria include hypotension requiring dopamine or norepinephrine, altered mental status, ratio of arterial oxygen partial pressure in mmHg to fractional inspired oxygen (PaO_2/FiO_2 ratio) less than 300, oliguria or creatinine greater than 2.0 mg/dL, prothrombin time and international normalized ratio (PT-INR) greater than 1.5, or platelet count (PLT) less than 100,000/mm3. Tokyo 2018 graded our patient as grade II (moderate) acute cholecystitis. Laparoscopic cholecystectomy is the surgical treatment of choice for grades II (moderate) and III (severe) acute cholecystitis. Grade I (mild) acute cholecystitis does not require urgent surgery, as it does not meet the criteria for grades II and III. Grade I (mild) is associated with a 1.1% mortality rate; grade II with 0.8%; grade III with 5.4%. Tokyo 2018 guidelines note the limitations in data for the decrease in mortality from mild (Grade I) to moderate (Grade II) acute cholecystitis, but there is significant increased mortality between Grades II and III, so early identification before reaching Grade III is important for the benefit of patients presenting with symptoms of acute cholecystitis.[4]

RUQ ultrasound is the preferred initial diagnostic test in suspicion of acute cholecystitis. In cases of GC, RUQ ultrasound and abdominal CT scan typically show gallbladder wall thickening, irregular or absent gallbladder wall, edema, and pericholecystic fluid collections.[2] A cross-sectional and retrospective exploratory study performed between 2012 and 2016 noted that gallbladder wall thickness greater than 4 mm was associated with a 3.8-fold increased probability of GC compared to thickness lesser 4 mm.[14] However, ultrasound has a lower diagnostic accuracy with a sensitivity of 81% compared to computed tomography (CT) (sensitivity 94%).[15] Laboratory findings of a high degree of leukocytosis is also characteristic for GC, with some studies reporting a WBC count greater than 15,000/mm^3 as a predictor for development of GC. AST, ALT, ALP, and total bilirubin are also elevated in most GC patients. Elevated liver function tests (LFTs) occur in GC due to gallbladder inflammation causing secondary necrosis of nearby hepatocytes.[2] Our patient had no gallbladder wall edema or pericholecystic fluid; his AST, ALT, ALP, and bilirubin were not elevated.

Urgent LC is the preferred surgical procedure for treatment of GC.[16] A 2019 study found an 8-fold increased risk of mortality in patients with GC compared to uncomplicated cholecystitis.[4] Conversion to open surgery is seen more so in cases of difficult dissection secondary to adhesions, bleeding complications, and difficult anatomy. Complications of GC include wound infection most commonly, followed by pulmonary complications and intra-abdominal abscess. Increased complications were seen in delayed surgery, so timing with urgent or emergent surgery for GC is an essential for optimizing morbidity and mortality in these patients. Mortality was found to be significantly lower in patients admitted to hospital and treated less than 24 hours after diagnosis, while patients who received delayed admission and treatment (greater than 54 hours) had a higher mortality association.[2] GC can also be treated with percutaneous cholecystostomy tube (PCT). PCT is considered a safer alternative for patients who are not good surgical candidates, such as critically ill patients, those with malignancy, gallbladder perforation, and biliary obstruction.[16] Regardless of procedural choice, medication review is an important step in the physician process of treatment planning in all patient populations.

CONCLUSION

In conclusion, this case report highlights the critical significance of a comprehensive approach to diagnosing patients. Acute cholecystitis should be considered in all patients presenting with acute onset RUQ and nausea, regardless of age, race, sex, etc. GC is difficult to diagnose preoperatively but is considered both a medical and surgical emergency, so a prompt and thorough patient history and physical exam are imperative for timing from onset of symptoms to diagnosis and treatment. While laboratory tests and imaging studies provide valuable insights, it is essential to recognize that a patient's history and physical examination are equally indispensable. This report serves as a reminder that physicians must remain vigilant and not solely rely on preconceived disease profiles. By avoiding stereotyping and embracing a holistic diagnostic mindset, physicians can prevent the potential for missed diagnoses and ensure timely and accurate treatment for their patients. Ultimately, this case underscores the vital role of the physician in synthesizing all available information to make informed and precise clinical decisions.

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