2 Pathophysiology and Diagnosis of Acute Calculous Cholecystitis

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2.1 Introduction

Gallbladder ailments have been affecting humans for thousands of years, as proved by the fact of gallstones found in Egyptian and Chinese mummies. In 1909, an Egyptian mummy was presented to the Museum of the Royal College of Surgeons in London, with a preserved liver and a gallbladder, containing 30 gallstones. The mummy came from Thebes and belonged to a twenty-first dynasty priestess (circa 1500 BC) and was donated by Dr. Elliot Smith, a well-known Egyptologist and anatomist. The gallbladder was described as "large and containing many spherical calculi" (1).

Alexander the Great is believed to have died on July 11,323 BC at age 34 due to peritonitis resulting from the perforation of an acute cholecystitis, fueled by alcohol consumption and abundant intake. In 1867, John Bobbs performed the first cholecystostomy on a 31-year-old lady who survived until the age of 77 in Indianapolis. Fifteen years later, Carl Langenbuch performed in Berlin the first cholecystectomy in a 35-year-old male patient (2).

Acute calculous cholecystitis (ACC) accounts for 3–11% of hospital admissions and carries a mortality of about 0.8% (3). ACC represents more than 90% of all cases of acute cholecystitis, the remaining include acalculous, xanthogranulomatous, and other variations of acute cholecystitis. The gold standard treatment of ACC is laparoscopic cholecystectomy, but its timing (early vs. delayed) is also a matter of discussion.

Although most patients with cholelithiasis remain asymptomatic for long periods, 1 to 4% of those patients per year suffer biliary colics (4, 5). ACC eventually may develop in about 20% of those symptomatic patients if left untreated (6). Nonetheless, most patients with ACC have had previous episodes of biliary colic pain; but for some, ACC may represent the initial episode. In some cases, ACC may coexist with choledocholithiasis, acute cholangitis, or acute biliary pancreatitis. Around 60% of patients with ACC are women; however, ACC develops more frequently in men and tends to be more severe (7). Patients suffering from diabetes are also more prone to develop ACC.

ACC represents the most frequent complication of patients with diagnosis of choledocholithiasis. Gallstone disease incidence is a major world health problem which undoubtedly is expanding. The best method to investigate the real incidence of biliary gallstones is screening ultrasonography, since it is far superior than autopsy findings and clinical diagnosis, which requires biliary symptoms only present in 20% of those individuals with gallstones. The frequency of cholecystectomy, mostly performed in a laparoscopic approach, has a very limited relationship to the prevalence of the disease and

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is more related to the surgeon's driven practice as well as patient access to surgical care (8). In developed countries, 10–15% of white adults carry gallstones. It is estimated that in the USA about 15% of the population are gallstone carriers, with a higher incidence in the Hispanic population than in non-Hispanics. In that country, 6.3 million males and 14.2 million women between 20 and 74 years have gallbladder stones (9). A very high prevalence has been described in American native Indians, such as the Pima group in Arizona. The same applies to original Indian populations in South America. The prevalence of gallstones in the Hispanic population of Latin America (Central and South America) is higher, similarly to native populations in the same areas. In these populations, genetic risk factors lead to lithogenic bile and gallstone early in life (less than 30 years) resulting in gallstone prevalence rates of more than 50% at 50 years of age in both men and women (10). In Europe, the Multicenter Italian Study on Cholelithiasis (MICOL) informed an overall incidence of gallstones of 18.8% in females and 9.5% in males (11). In south east Asia, the prevalence is lower, but usually located in the bile ducts and associated with parasitic infestations (12).

In the West, about 70% of gallstone carriers possess cholesterol gallbladder stones, with a cholesterol content of more than 50%, meanwhile 30% have black pigment gallbladder stones. In eastern Asia, there is a very high incidence of pigment stones lodged in the bile ducts and being responsible for causing severe cholangitis. Nonetheless, in these countries the incidence of cholesterol gallstones has been steadily increasing in the last years, presumably due to the changes in the diet.

Ethnicity is a major determinant of the following facts: cause of the disease, type of stone/s, and location in the biliary tract system. In developed countries, most of the gallstones (around 85%) are predominantly of cholesterol composition, where the remainder 15% are black pigment calculi, due to calcium bilirubinate. Cholesterol and black pigment stones are formed within the gallbladder lumen, but in the first case the starting point is represented by the liver production of supersaturated bile with cholesterol, which tends to precipitate in the gallbladder. The excess secretion of mucin together with an impaired gallbladder motility keep these crystals, aggregating to them other materials and turning them into macroscopic stones (13).

Gallstones may be classified according to their location and composition (Fig. 2.1, see Addenda). The location may be: extrahepatic (choledocholithiasis) where the stones may be present in the

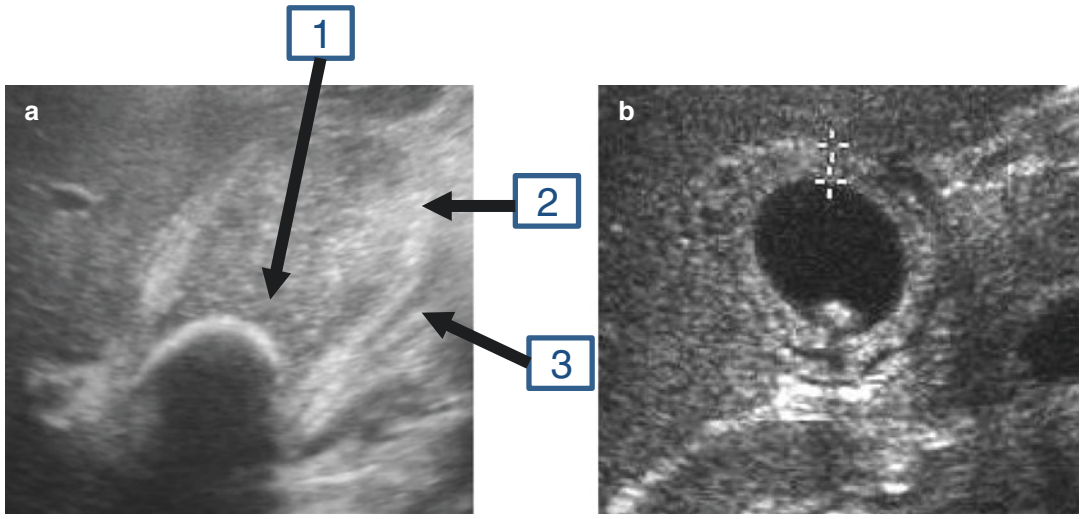

Fig. 2.1 (**a**): 1. Impacted gallstone + sludge. 2. Wall thickening. 3. Pericholecystic fluid. (**b**): Gallbladder wall with thickening of its layers and an impacted gallstone

gallbladder and/or in the common bile duct, or intrahepatic (hepatolithiasis). Stones in the common bile duct may be either primary (originated de novo in that conduct, and usually pigment stones) or secondary, due to migration from the gallbladder and, typically, of cholesterol. Black pigment stones also develop in the gallbladder, but consist of bilirubin polymers (calcium bilirubinate) and are typically associated with advanced age, liver cirrhosis, cystic fibrosis, and hematologic conditions with increased erythrocytes' destruction (sickle cell anemia, chronic hemolytic states).

Bile duct stones may originate in the gallbladder and get there due to migration or otherwise develop primarily in the biliary system. In the Western world, the risk of concomitant common bile duct stones, which migrate from the gallbladder, is estimated in 10–15% and is usually compounded by cholesterol. But choledocholithiasis may develop primarily due to strictures and subsequent inflammation and infection with the appearance of brown pigment stones. In southeastern Asia, pigment stones are predominant, composed by calcium bilirubinate, fatty acids, cholesterol, and mucin (glycoproteins primarily from bacterial biofilms). They tend to aggregate in the common bile duct or in the intrahepatic bile ducts. Infection by bacteria but mostly by parasites (*Clonorchis sinensis*, *opisthorchis species*, and *fasciola hepatica*) as well as stasis represent key factors (8).

Risk factors for gallstone formation are multifactorial (14):

- Constitutional: Represented by age, female gender, genetics, and ethnicity. These are not able to be changed or modified.
- Environmental or exogenous: Include the following factors, which represent modifiable conditions:
  - Dietary factors: Mostly linked with cholesterol gallstone formation, including high carbohydrate/high calories intake, high glycemic upload, low fiber intake.
  - Metabolic aspects: Also linked with cholesterol gallstone formation. Physical inactivity, diabetic or prediabetic conditions, obesity, nonalcoholic fatty disease.
  - Increased enterohepatic bilirubin circulation: Liver cirrhosis, Crohn's disease (both for cholesterol and pigmentary stones), ileal resections, and bariatric procedures (for pigmentary stones).
  - Underlying chronic disease: Cystic fibrosis, spinal cord injuries, some colon conditions are associated with increased risk of gallstones development.
  - Medications: Hormone replacements, octreotide, fibrates, calcineurin antagonists.
  - Alterations in the motility of the gallbladder.

2.2 Pathogenesis of Gallstones

2.2.1 Cholesterol Stones

Bile is a yellow-brown to dark green fluid whose composition is more than 90% water. Bile contains bile salts, cholesterol, and phospholipids as well as little amounts of proteins and inorganic salts. In humans, bile is produced by the liver and stored in a concentrated fashion in the gallbladder. It serves as a surfactant, emulsifying the lipids in the digestive tract. Bile salt anions are hydrophilic on one side and hydrophobic on the other, tending to aggregate around droplets of lipids to form micelles, with the hydrophobic sides towards the fat and the hydrophilic facing outwards.

The organization of cholesterol gallstones is the consequence of a failure in the homeostasis of cholesterol concentration in the bile. The increase in the liver production of biliary cholesterol has been considered the primary pathophysiologic defect in human cholelithogenesis, followed by abnormal secretion rates of bile salts and phospholipids and thus inducing the supersaturation of cholesterol in the gallbladder bile.

There are five primary defects which play a major role in the organization and formation of cholesterol gallstones (Table 2.1, see Addenda):

Table 2.1 Primary defects for cholesterol gallstone formation

Cholesterol gallstones
1. Genetic factors and lith genes
2. Liver cholesterol hypersecretion into bile
3. Alterations in the motility of the gallbladder
4. Rapid phase transitions of cholesterol in bile (with precipitation of cholesterol crystals)
5. Intestinal factors:
• increased absorption of cholesterol
• slow intestinal motility
• dysbiosis

2.2.1.1 Genetic Factors and Lith Genes

A genetic predisposition to gallstone formation seems to be clearly evident (15). The discovery of the lithogenic Lith 1 and Lith 2 genes in mice's chromosomes 2 and 19, respectively associated with quantitative trait locus (QTL) analysis—a powerful genetic study technique—confirmed the genetic role in alterations ending in gallstone formation.

Genome-wide association study (GWAS) has allowed the study in humans, leading to the discovery of two major variants: ABCG5-R50C and ABCG8-D19H, which have been associated with gallstones formation in German, Chilean, Chinese, and Indian populations (16). Nonetheless, less than 25% of the risk of cholesterol gallstones is determined by genetics (17).

2.2.1.2 Liver Cholesterol Hypersecretion into Bile

Although cholesterol secreted into bile recognizes its origin from liver synthesis, reverse cholesterol transport, and chylomicrons, the contribution of each pathway is not yet absolutely clear. Estrogens enhance the formation of cholesterol gallstones by stimulation of the liver synthesis and the production of cholesterol as well as the reduction in the production of bile salts. These mechanisms are the ones responsible for the higher prevalence of stones in females than in males.

2.2.1.3 Alterations in the Motility of the Gallbladder

The emptying of the gallbladder tends to be impaired before gallstones are detected, giving a clinical picture of biliary dyskinesia. This phenomenon is due to the fact of the absorption of large amounts of cholesterol by the epithelial cells of the gallbladder's wall from the supersaturated bile. Cholesterol in excess is transformed to esters and stored in the mucosa and lamina propria, originating changes in the sarcolemmal membranes with further disruption of cholecystokinin I receptors' signaling cascade as well as the alteration of the signal transduction mediated by G proteins (18).

2.2.1.4 Rapid Phase Transitions of Cholesterol in Bile (with Precipitation of Cholesterol Crystals)

The secretion of cholesterol into the bile depends on the balance of the liver's cholesterol input and output. Cholesterol crystal nucleation is considered the first and earliest step in cholesterol gallstone formation and depends on the relative amounts of cholesterol, phospholipids, and bile salts. Although cholesterol solubility in watery solutions is very little, the situation is completely different amidst gallbladder bile. This increase in solubility is due to the incorporation of cholesterol in mixed micelles, together with bile salts and phospholipids, the most representative being phosphatidylcholine.

Supersaturation of the bile occurs when either too much cholesterol or not enough bile salts and phosphatidylcholine molecules are secreted to permit the complete solubilization of micellar cholesterol. The cholesterol in excess may be stored in vesicles or in cholesterol crystals (19). The organization of these crystals is believed to happen from vesicles supersaturated with cholesterol, in the two following stages:

(a) Small unilamellar supersaturated vesicles tend to gather or fuse into larger multilamellar crystals (cholesterol crystal nucleation).
(b) Subsequent phase separation of cholesterol crystals (20).

Wang and Carey studied the cholesterol crystallization pathways and sequences in human gallbladder bile and were able to describe the

equilibrium bile salt, phospholipid, and cholesterol ternary phase diagram, which permits to predict the behavior of the three components when present in different proportions (21). Three factors strongly affect the balance of the bile salt–phospholipid–cholesterol ternary phase diagram, with potential alterations of the cholesterol crystallization: the bile concentration, the higher hydrophobicity of bile salts and the type phospholipids, and the composition of their acyl chains.

1. Intestinal factors: are represented by the increased absorption of cholesterol, a slow intestinal motility, and the alterations in gut microbiota.

The small bowel absorbs cholesterol from the diet intake and reabsorbs the cholesterol present in the bile, depending upon the expression of sterol transport proteins (16). Small and large bowel dysbiosis occurs in cholesterol gallstone patients and may be affected by toxins introduced with the food intake.

2.2.2 Pigment Stones

(a) Black pigment stones: Their primary component is calcium bilirubinate, while other components are calcium carbonate and calcium phosphate joined to mucin glycoproteins. In normal conditions, most bilirubin, the breakdown product of hemoglobin, is conjugated in the liver to bilirubin monoglucuronide and subsequently to water-soluble bilirubin diglucuronide, highlighting the fact that unconjugated bilirubin is poorly soluble in water. In case of hemolysis, biliary excretion of bilirubin is very much increased, with the risk of precipitation of calcium bilirubinate. This mechanism explains the high prevalence of these type of stones in chronic hemolytic disorders (22).

(b) Brown pigment stones: In contrast to the black, these are mostly developed in the lumen of the bile ducts. Their primary composition is calcium salts of unconjugated bilirubin and different amounts of cholesterol and proteins. They are associated with bile stasis and chronic bacterial infection of the bile ducts by *Escherichia coli*, *Bacteroides spp*, *Clostridium spp* and parasites like *Opisthorchis viverrini*, *Clonorchis sinensis*, *Ascaris lumbricoides* (Table 2.2, Addenda). Bacteria produce β glucuronidase, phospholipase A, and bile acid hydrolase which leads to an increase in the amounts of unconjugated bilirubin, palmitic and stearic acids, and unconjugated bile acids, which can join with calcium and thus form stones. Parasites may stimulate stone formation by the calcified overcoat of the parasite egg, which may serve as the nucleus of the future stone with the deposit of calcium bilirubinate (23).

Table 2.2 Factors for the formation of brown pigment stones

Genetic factors
Liver hypersecretion of bilirubin
Bile stasis
Bacterial infection

2.3 Pathophysiology of ACC

The primary cause of acute cholecystitis is obstruction. Of all individuals who have gallstones, only 1–3% will undergo an acute episode. Other obstructive causes include: primary tumors of the gallbladder or the biliary tract, polyps, parasites, metastatic tumors, or nodes in the vicinity of the gallbladder neck (24).

The extended gallbladder outlet obstruction by a stone is the initial and main factor leading to an ACC. The process corresponds to the physical obstruction of the gallbladder by a gallstone, which may be located at the neck or in the cystic duct. The following sequence of pathophysiologic steps is described in the production of an episode of ACC (Table 2.3, Addenda): the obstruction leads to distention and an increased gallbladder pressure, taking into account the fact that the progression to acute cholecystitis is determined by two main factors: (a) the degree of

Table 2.3 Steps in the development of calculous acute cholecystitis

Obstruction at the gallbladder's neck
↓
Increased endoluminal pressure
↓
Venous congestion, compromised blood irrigation, alterations in lymphatic drainage Ischemia of the mucosa
↓
Release of inflammatory mediators: prostaglandins I2 and E2
↓
Localized mucosal trauma
↓
Lysosome release of phospholipase
↓
Conversion of lecithin to lysolecithin
↓
Wall thickening + edema, vascular congestion and intramural hemorrhage
↓
Mucosal ulcers with focal areas of wall necrosis

obstruction and (b) the duration of the obstruction by the stone. Meanwhile the obstruction is partial and the duration short, the patient will most probably experience a biliary colic, but if the obstruction is complete and the duration long, an acute cholecystitis episode will develop. In this case, if the patient does not receive immediate treatment, the clinical picture will tend to progress and increase the severity of its evolution with a higher incidence of complications. The persistence of the obstruction leads to a sustained increase in the gallbladder endoluminal pressure, leading to venous congestion, a compromise in the blood irrigation, and the lymphatic drainage with mucosal ischemia. It is important to note that the inflammatory response and the release of its mediators (prostaglandins I2 and E2) generate the release of phospholipase from the lysosomes, which aids in the conversion of lecithin into lysolecithin, via enzymatic hydrolysis, within the supersaturated bile in the gallbladder lumen. Lysolecithin is a potent detergent and very harmful for the mucosa (25). The gallbladder wall may suffer from necrosis and gangrene, achieving a gangrenous or necrotizing cholecystitis.

Regarding the role of bacteria, this fact does not play neither an initial nor a major role in ACC, but it has been recognized that secondary infection may complicate up to 50% of the cases (26). Bacteria implicated in ACC are usually present in the bile before the onset of the disease, since bacterial growth is present in 20% to 70% of patients. They include:

(a) Gram negative bacilli (*Escherichia coli*, *Klebsiella spp*, *Enterobacter spp*).
(b) Gram positive cocci (*Enterococci*).
(c) Anaerobes (Bacteroides, *Clostridia spp*, *Fusobacterium spp*).

A major Achilles' heel is represented by the limitations of microbial cultures, situation that may be improved by the use of next-generation sequencing (27). The overgrowth of gas-producing bacteria within the gallbladder lumen may lead to emphysematous cholecystitis.

Histologically, infiltration of neutrophilic leukocytes, microabscesses, and secondary vasculitis will be the usual findings. Secondary bacterial infection, due to delay in diagnosis or inappropriate initial antibiotic treatment, may result in gallbladder empyema with accumulation of pus, perforation with localized or generalized peritonitis, and even sepsis (13). Other complications are liver abscess and intra-abdominal collections.

There are some specific forms of acute cholecystitis that need to be distinguished from ACC: (a) xanthogranulomatous, (b) emphysematous, (c) acalculous, and (d) torsion, due to inherent, acquired, and other physical causes.

2.4 Diagnosis of ACC

The diagnosis of ACC is based on the clinical presentation and imaging. Although ACC is a common disease for patients presenting in the Emergency Department, its diagnosis represents a major challenge for clinicians and surgeons, in order to decide the best treatment and management strategy. The cornerstone of a correct and precise diagnosis consists of the evidence of an acute inflamed gallbladder with stones in its

lumen, preventing the passage of bile to the cystic duct and the main biliary duct due to impacted calculi.

The diagnosis of ACC is based on the clinical presentation and physical examination, laboratory, and imaging studies. Nonetheless, the gold standard for diagnosis is the confirmation of the presence of a stone obstructing the gallbladder infundibulum or the cystic duct together with the pathological examination of the specimen, performed through a cholecystectomy, usually in a minimal invasive approach.

Most patients who present with ACC have symptoms of right upper quadrant pain, but many times the pain may be referred in different locations as well as irradiation. When the inflammation worsens, the pain tends to be localized in the right upper quadrant. The patients may also refer a history of biliary colic or dyspepsia or even a previous diagnosis of cholelithiasis, but sometimes the acute presentation is the initial one. Nausea, vomiting, and anorexia are usually described in the acute episode.

The most typical physical sign is the presence of abdominal pain, usually in the upper abdomen and the right upper quadrant. The examination may evidence tenderness or Murphy's sign in the right upper quadrant; this sign was described in 1903 as a sign of cholelithiasis (28). A palpable mass is usually present in about 25% of patients after more than 24 h of symptoms. In occasions, ACC can derive in sepsis and organ failure, usually when a gangrenous or emphysematous cholecystitis is present. The additional presence of choledocholithiasis should be ruled out, since this situation may preclude a somewhat different approach.

According to the Tokyo Guidelines 2013 (29), the diagnostic criteria are based on the following three aspects:

(a) Local signs of inflammation: (1) Murphy sign, (2) right upper quadrant mass/pain or tenderness.
(b) Systemic signs of inflammation: (1) fever, (2) elevated protein C, (3) elevated white blood cell count.
(c) Imaging findings, characteristic of acute cholecystitis.

Ultrasonography should be considered as the first option as imaging modality (30). The typical and pathognomonic findings include: thickening of the gallbladder wall (5 mm or more), pericholecystic fluid, and ultrasonographic Murphy's sign (abdominal tenderness when the probe is pushed against the right upper quadrant or the palpable gallbladder). The simultaneous presence of these three signs is definitive for the diagnosis of acute cholecystitis. Other findings include an enlarged and distended gallbladder, an impacted stone, and debris echo (Figs. 2.1 and 2.2, Addenda_2). According to a meta-analysis published by Shea et al. (31), the diagnostic capability of ultrasonography for acute cholecystitis achieves a sensitivity of 88% and a specificity of 80%.

Ultrasonography is also useful when an emphysematous cholecystitis is suspected since an irregular thickening of the gallbladder wall and imaging of a ruptured gallbladder may be noted.

The suspected diagnosis of ACC includes one item in (a) and one item in (b), meanwhile

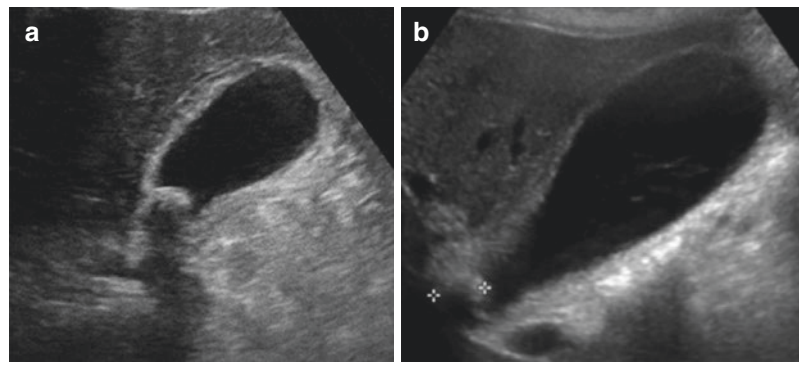

Fig. 2.2 (**a**): Distended gallbladder with impacted gallstone. (**b**): Distended gallbladder with impacted gallstone

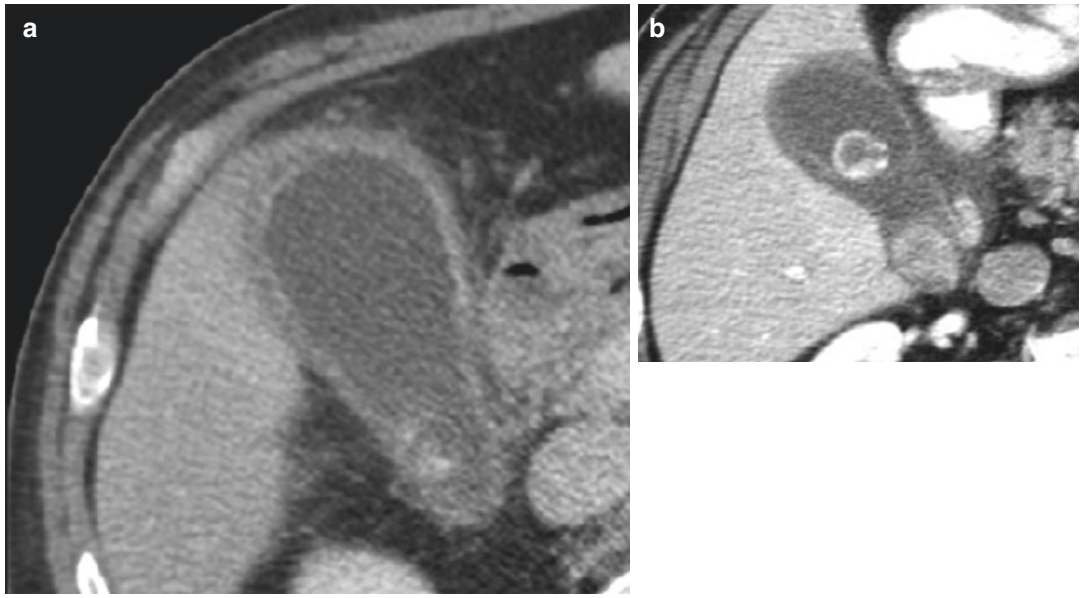

Fig. 2.3 (**a**): CT scan, showing a distended gallbladder with impacted gallstone. (**b**): CT Scan, with distended gallbladder with impacted stone and another one in its lumen

a definitive diagnosis of ACC includes one item in (a) and one in (b) plus (c). The level of serum bilirubin may be increased due to several factors: compression of the common bile duct by the inflamed infundibulum or the presence of contemporary common bile duct stones.

Some remarks should be added to these guidelines: some patients may present with few or minimal systemic symptoms and hence, underdiagnosed, and the use of protein C levels is seldom used for the diagnosis of ACC in many countries (32). From the point of view of laboratory tests, there are no specific ones for performing a diagnosis of ACC. The World Society of Emergency Surgery guidelines for ACC also recommend the use of clinical, laboratory, and imaging findings for the diagnosis (33).

Contrast-enhanced CT scans are usually not requested in the emergency setting, exception made in those conditions where a differential diagnosis needs to be ruled out. Some of the findings are: gallbladder distention, pericholecystic fat stranding, gallbladder wall thickening, subserosal edema, mucosal enhancement, transient focal enhancement of the liver adjacent to the gallbladder, pericholecystic fluid collections, pericholecystic abscess, gas collection within the gallbladder (Fig. 2.3, Addenda_2). It is recommended to rule out gangrenous cholecystitis (Fig. 2.4, Addenda_2) as well as emphysematous cholecystitis, where the main findings include gas in the wall or lumen, intraluminal membranes, irregular or absent wall, abscess/es, Fig. 2.5 Addenda_2 (30).

The use of magnetic resonance cholangiography maybe useful in the emergency setting to rule our common bile duct stones and hence, the chance of acute cholangitis. At a time, the use of HIDA scan (with 99 Tc-HIDA cholescintigraphy) was considered the most accurate test for the diagnosis of acute cholecystitis, with a sensitivity of 97% and specificity of 87% (34). The gallbladder was usually visualized within 30 min and the absence of the radiotracer uptake by 4 h was considered positive for cystic duct obstruction. Identification of the radiotracer in the pericholecystic space is suggestive of perforation. But since the availability of emergency ultrasound, HIDA scan is considered unnecessary.

The Tokyo Guidelines 2013 also collaborated in setting guidelines for establishing the severity of ACC in three grades (29):

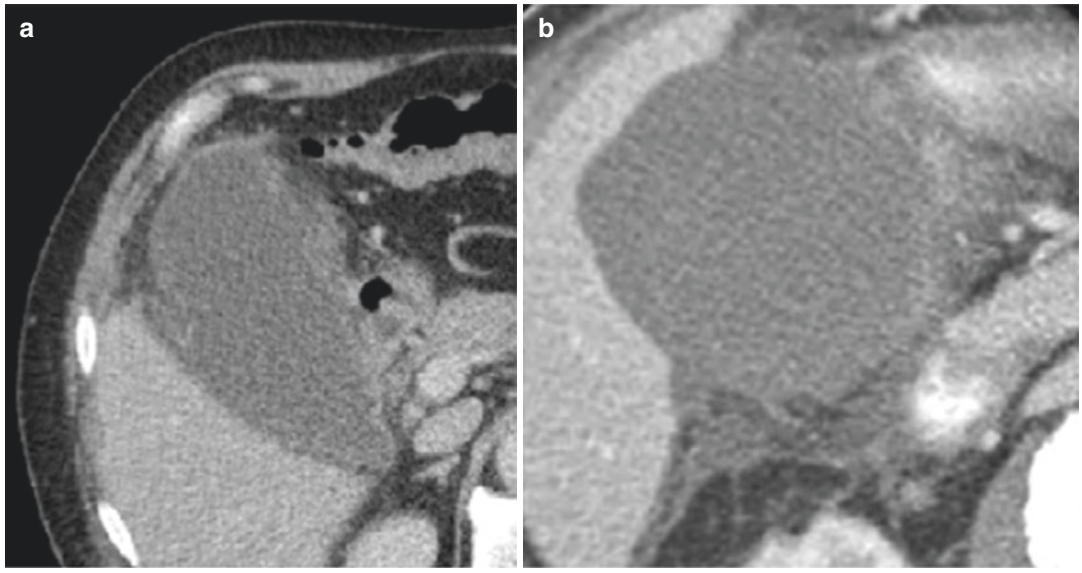

Fig. 2.4 (**a**, **b**): CT scan Gangrenous cholecystitis

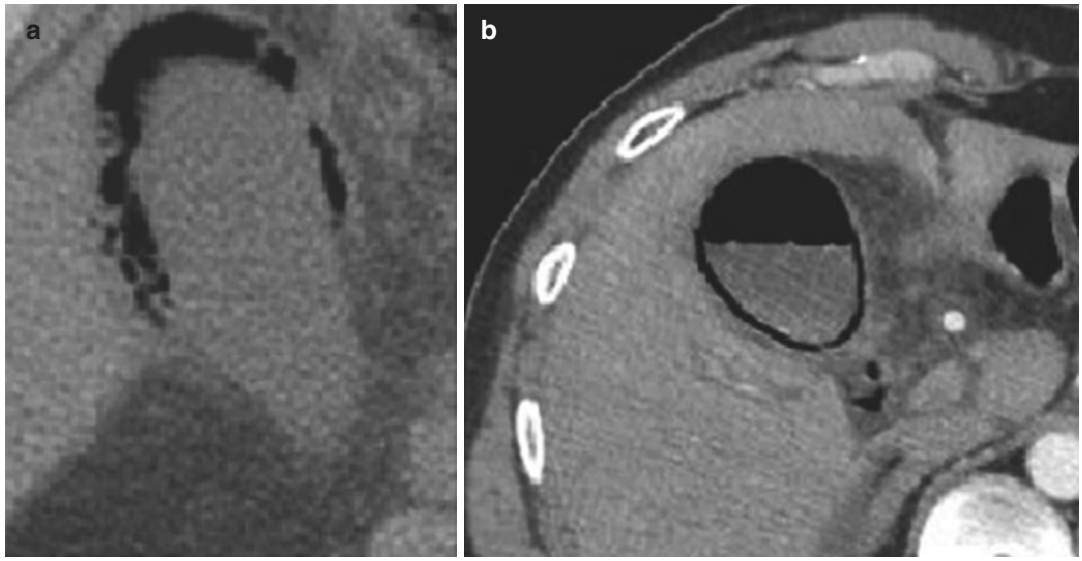

Fig. 2.5 (**a**, **b**): CT scan Emphysematous cholecystitis

- Mild (Grade I): Acute cholecystitis in a healthy individual with no organ dysfunction, mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.
- Moderate (Grade II): Acute cholecystitis in which the degree of acute inflammation is likely to be associated with increased operative difficulty in performing cholecystectomy (WBC > 18,000/mm^3, palpable tender mass, duration of complaints >72 h and/or suspicion of local complications gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis).

– Severe (Grade III): Associated with organ dysfunction (cardiovascular, neurological, respiratory, renal, liver, and hematologic) and mandating intensive care with respiratory and circulatory support.

There are other grading scales for severity of acute cholecystitis, such as the one proposed by the American Association for the Surgery of Trauma, based on anatomic variables using clinical, imaging, operative, and pathologic criteria to assess the severity of acute cholecystitis in 5 Grades, excluding physiologic parameters. Grade 1 corresponds to acute cholecystitis; Grade 2, gangrenous or emphysematous cholecystitis; Grades 3 to 5 describe gallbladder perforation with local contamination, abscess or fistula and generalized peritonitis, respectively (35, 36). The Parkland score relies solely on the intraoperative macroscopic findings (37).

Keypoints

- ACC may eventually develop in about 20% of symptomatic patients when left untreated.
- The primary cause of ACC corresponds to the physical obstruction of the gallbladder by a gallstone, which may be located at the neck or in the cystic duct.
- Bacterial infection does not play neither an initial nor a major role in ACC, but secondary infection may complicate up to 50% of the cases.
- The diagnosis of ACC is based on the clinical presentation and imaging, being ultrasonography the most widely used in the emergency setting.
- Contrast-enhanced CT is useful in clinical conditions where a differential diagnosis needs to be ruled out.

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