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Case Report

Atypical presentation of gangrenous cholecystitis: A case series

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ABSTRACT

Gangrenous cholecystitis (GC) is a serious complication of acute cholecystitis that has been associated with increased morbidity. Patient with GC can present with a wide variety of non-specific clinical, laboratory, and imaging characteristics, making the diagnosis challenging. This disease requires emergent treatment, which is why a quick and reliable diagnosis is essential for the wellbeing of the patient. The authors herein present a case of GC in a patient whose initial complaint was intractable hiccups, and provide a thorough review of the literature of cases of GC with atypical presentations.

1. Introduction

Acute cholecystitis is defined as inflammation of the gallbladder that is diagnosed based on clinical features and imaging [1]. Gangrenous Cholecystitis (GC) is one of the complications that may result from acute cholecystitis [2]. The incidence of GC varies between 10 and 40% of all patients presenting with acute cholecystitis [2]. It is an advanced form of acute gallbladder inflammation associated with high rates of complications and increased morbidity [3]. GC has been associated with a significantly higher mortality rate than uncomplicated cholecystitis, reported to be between 15% and 50% [4,5]. It is characterized by transmural acute inflammation and intramural abscess formation resulting in full-thickness necrosis and ulceration of the gallbladder secondary to sustained obstruction of the cystic duct [6]. Factors that have been previously reported to increase the risk of GC include male gender, age > 45, leukocytosis, cardiovascular diseases and diabetes mellitus [3].

Typically, patients present with symptoms of acute cholecystitis, with steady and severe right upper quadrant pain, that may radiate to the right shoulder or back. On physical examination, patients may be febrile, have an elevated pulse, and have muscle rigidity on examination [7]. Associated symptoms may include nausea, vomiting and anorexia. Patients frequently have voluntary and involuntary guarding on abdominal exam [8]. They classically present with leukocytosis (WBC > 13,000) with an increase in bands formation [9].

However, classic symptoms and abnormal laboratory work results are frequently not present in the elderly (> or = 65 years of age) presenting with cholecystitis [10]. A study by Parker et al. showed that 8 patients out of 168 had no abdominal pain [10]. Since some patients may present atypically, the preoperative diagnosis may become difficult. This is a case review of patients with atypical presentations of gangrenous cholecystitis. We also report on a patient who presented to the Emergency Department (ED) with a primary complaint of intractable hiccups without any classical symptoms of cholecystitis and was later diagnosed with gangrenous cholecystitis.

1.1. Objectives

The objective of this review is to report on a series of patients with atypical presentation of gangrenous cholecystitis. It also describes the case of a patient with gangrenous cholecystitis who presented to the ED of a tertiary care medical center with a chief complaint of hiccups.

2. Literature review and methods

A literature review of the published cases of atypical presentations of gangrenous cholecystitis was conducted using the following databases: Medline (1996 to 2018), Pubmed, Google Scholar, and Embase. The search terms included: “atypical or unusual or non-typical or uncommon”, “cholecystitis”, and “gangrenous cholecystitis”. The search

Abbreviations: mm Hg, millimeter of mercury; mg/dl, milligrams per deciliter; / cu·mm, per one cubic millimeter; $\times 10^3$, thousand; Afib, atrial fibrillation; ALT, alanine transaminase; AS, aortic stenosis; AST, aspartate transaminase; C, cholecystitis; CA, cancer; CBD, common bile duct; CKD, chronic kidney disease; CRP, C-reactive protein; CT, computed topography; DMII, diabetes mellitus II; ED, emergency department; ERCP, endoscopic retrograde cholangiopancreatography; GC, gangrenous cholecystitis; GERD, gastroesophageal reflux disease; GGT, gamma-glutamyl transferase; HTN, hypertension; ILD, interstitial lung disease; IU/L, international units per liter; N/V, nausea and vomiting; O2, oxygen; RUQ, right upper quadrant; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; SPS, statistical package for social sciences; T, temperature; WBC, white blood cell.

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yielded 6 published papers discussing the atypical presentation of gangrenous cholecystitis; describing a total of 7 cases. The study selection was accomplished through two steps. First, the literature was reviewed as a first step and then all case reports that describe patients of interest were included. Afterwards, full articles were obtained for all accepted studies. Excluded articles included those that do not discuss the presenting symptoms of acute cholecystitis or gangrenous cholecystitis, or articles in any language other than English. (Fig. 1)

Four tables summarize the published cases found in the literature review according to demographics, presentation, workup, imaging and treatment. Table 1 summarizes demographics and past medical history whereas Table 2 focuses on presenting symptoms, vital signs, and physical exam findings. Table 3 includes laboratory work results, antibiotic use and treatment; while Table 4 discusses imaging (ultrasound of right upper quadrant or CT abdomen). The tables serve as a quick reference for the currently available literature. All the cases described were eventually diagnosed with gangrenous cholecystitis and initially presented with varying chief complaints and characteristics.

To further describe the gathered data, the Statistical Package for Social Sciences (SPSS), version 24.0 was used. Descriptive statistics were summarized by presenting the mean and standard deviation for continuous variables (such as age) and number and percentage for categorical variables (such as gender). (Table 5.)

Table 1
Baseline characteristics of patients presenting to the Emergency Department.

Case		Age	Gender	Past medical history
Chaudhry et al.	[23]	78	Male	DMII
Occhionorelli S et al.	[24]	49	Male	DMII, Obese
Clerigo et al.	[25]	79	Female	DMII, HTN, Breast CA
Carmenate et al.	[26]	79	Male	HTN, Afib, Prostate CA
Dhira et al.	[6]	83	Male	Hypothyroidism, Hyperlipidemia, Osteoarthritis
Dhira et al.	[6]	75	Male	HTN, Hyperlipidemia
Crossley et al.	[27]	85	Female	ILD on O2, Immunosuppression on mycophenolate and prednisone, Severe AS, DM II, CKD stage 3, GERD, HTN, Hyperlipidemia

DMII = diabetes mellitus 2; HTN = hypertension; CA = cancer; Afib = atrial fibrillation; ILD = interstitial lung disease; O2 = oxygen; AS = aortic stenosis; CKD = chronic kidney disease; GERD = gastroesophageal reflux disease.

3. Case

A 78-year-old man with hypertension, hyperlipidemia and irritable bowel syndrome presented to the emergency department of a tertiary care medical center with worsening persistent hiccups of 5 days duration. He denied any history of abdominal pain, nausea, vomiting or diarrhea. The patient also denied any fever or chills, chest pain, cough or sputum production, and did not take any medications for his hiccups.

On presentation, the patient was hemodynamically stable with a body temperature of 36.3 °C, a blood pressure of 153/82 mmHg, pulse rate of 84 beats/min and a respiratory rate of 12 breaths/min.

Physical examination was unremarkable except for possible and non-reproducible mild right upper quadrant discomfort, without any guarding or rebound, and the Murphy sign was negative. Multiple pharmacological treatments were used in the ED including Diazepam (Valium), Promethazine (Phenergan), and Baclofen; however, there was no change in frequency of the patient's hiccups.

To investigate the etiology of the hiccups, a chest x-ray was done and showed clear lungs and normal diaphragms. His initial laboratory measurements showed an elevated white blood cells (WBC) count of 13,700/cu·mm with a left shift (83% neutrophils), elevated liver enzymes, with an alkaline phosphatase of 237 IU/L, GGT of 171 IU/L, AST (SGOT) of 86 IU/L, ALT (SGPT) of 65 IU/L. (Reference range: AST = 0–50 IU/L; ALT = 0–65 IU/L; Alkaline Phosphatase = 35–120 IU/L; GGT = 10–50 IU/L).

A CT chest/abdomen/pelvis showed significant gallbladder distension with gallbladder wall thickening and pericholecystic inflammatory changes suggestive of acute cholecystitis (Fig. 2). An ultrasound of the gallbladder showed findings that are consistent with acute gangrenous cholecystitis, with an overly distended gallbladder with a maximal diameter of 5 cm with significant wall thickening, a large amount of layering sludge and a minimal pericholecystic fluid. (Fig. 3)

The patient was given Piperacillin/Tazobactam intravenously, underwent an endoscopic retrograde cholangiopancreatography (ERCP) showing no evidence of common bile duct (CBD) stone, followed by a cholecystectomy.

The gallbladder pathology report showed a severely inflamed GB measuring 8.5 × 4.5 × 3 cm, with around 150 mL of pure pus inside

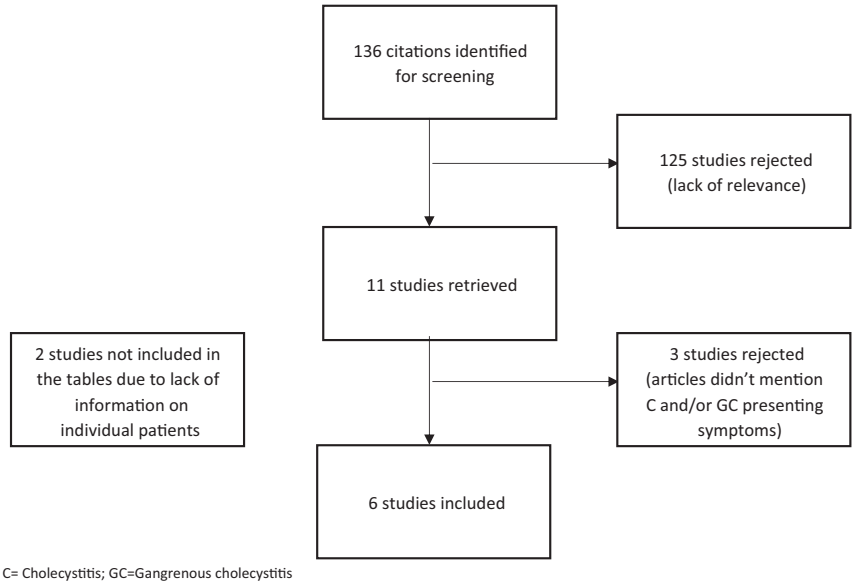

Fig. 1. CONSORT flow, study attrition diagram. C = Cholecystitis GC = Gangrenous Cholecystitis.

Table 2
Presentation of patients presenting to the Emergency Department.

Case		Presenting symptom	Vitals	PE	Murphy's sign
Chaudhry et al.	[23]	RUQ pain, N/V	Hemodynamically stable	RUQ tenderness	Sonographic murphy negative
Occhionorelli S et al.	[24]	RUQ pain	Hypertensive (200/100 mmHg) and tachycardia	Diffusely tender abdomen	NA
Clerigo et al.	[25]	N/V and malaise	Hemodynamically stable	Normal	Negative
Carmenate et al.	[26]	Hiccups, N/V, left hip pain, weight loss	Hemodynamically stable	Normal	Negative
Dhira et al.	[6]	N/V, malaise, dark urine	T = 37.8 °C	RUQ tenderness	Negative
Dhira et al.	[6]	Chest pain, abdominal discomfort radiating to the back	Hypertensive (220/102 mmHg)	Normal	Negative
Crossley et al.	[27]	Vague abdominal pain, low grade fever	Hemodynamically stable	RUQ tenderness	Negative[a]

N/V = Nausea and vomiting; RUQ = Right upper quadrant; T = Temperature; NA = Not applicable.
[a] Patient presented to the Emergency Department again 8 days after the first presentation with a positive Murphy's sign.

the GB. The serosa was smooth and shiny and the wall was 0.4 cm. The mucosa was ulcerated without cholesterolosis or stones.

Intra-operative bile fluid cultures grew Escherichia coli and *Klebsiella pneumoniae* that were resistant to piperacillin/tazobactam, and the patient was switched to ceftriaxone and metronidazole.

The patient's postoperative course was complicated by a phlegmon containing an air-fluid level and pockets of gas at the post-cholecystectomy surgical bed. No surgical intervention was done. However, the patient received a prolonged antibiotic therapy: ceftriaxone 2 g once daily and metronidazole 500 mg three times daily for a total course of 14 days. The patient's hiccups persisted post-cholecystectomy despite treatment with metoclopramide 10 mg every 8 h. Eventually, they self-resolved at day 5. The patient was discharged home 10 days post-cholecystectomy, with improvement in his condition, to continue his antimicrobial therapy.

4. Discussion

Gangrenous cholecystitis is a severe complication of acute cholecystitis, with persistent cystic duct obstruction causing vascular insufficiency that results in increased gallbladder wall tension [11]. This eventually leads to epithelial injury that enhances the development of gangrenous cholecystitis [12]. Moreover, phospholipases released from the damaged epithelium cell membranes cause an inflammatory reaction that causes ischemia and progressive worsening of the gallbladder wall, resulting eventually in necrosis and perforation [13-15]. Patients with a completely

Table 3
Laboratory values and treatment of patients presenting to the Emergency Department.

Case		WBC ($\times 10^3$)	CRP (mg/dl)	Liver enzymes (IU/L)	Amylase (IU/L)	Antibiotics	Treatment
Chaudhry et al.	[23]	23.7	14.8	Normal	30	Amoxicillin/clavulanic acid	Laparoscopic cholecystectomy
Occhionorelli S et al.	[24]	17.58	16.47	Normal	180	Moxifloxacin	Exploratory laparotomy and subsequent cholecystectomy
Clerigo et al.	[25]	15.47	5.1	Normal	3	Piperacillin/Tazobactam	Laparoscopic cholecystectomy
Carmenate et al.	[26]	<5	NA	Normal	NA	NA	Emergency percutaneous cholecystostomy and subsequent cholecystectomy
Dhira et al.	[6]	16.4	NA	Normal	NA	Ampicillin/Sulbactam	Laparoscopic cholecystectomy
Dhira et al.	[6]	5.4	NA	Normal	NA	NA	Laparoscopic cholecystectomy
Crossley et al.	[27]	32.82	NA	Normal	NA	NA	CT-guided percutaneous drainage

WBC = white blood cells; CRP = C-reactive protein; NA = not applicable; CT = computed topography; ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma-glutamyl transferase.
IU/L = international units per liter; mg/dl = milligrams per deciliter; /cu·mm = per one cubic millimeter; $\times 10^3$ = thousand.
^Liver Enzymes include Alkaline phosphatase, ALT, AST and GGT.
&Amylase Reference Range 10–120 IU/L; AST Reference Range = 0–50 IU/L; ALT Reference Range = 0–65 IU/L; Alkaline Phosphatase Reference Range = 35–120 IU/L; GGT Reference Range = 10–50 IU/L.

Table 4
Imaging results of patients presenting to the Emergency Department.

Case		Ultrasound	CT Imaging
Chaudhry et al.	[23]	Gallbladder shaped echogenic viscous fluid present in gallbladder fossa with posterior acoustic shadowing	Gallbladder slightly distended, and few small calcified stones. Small rim of fluid anterior to the surface of the liver's right lobe
Occhionorelli S et al.	[24]	Dark crescent beneath the diaphragm	NA
Clerigo et al.	[25]	NA	Gallbladder distension, wall thickening, densification of vascular bed, radiopaque calculation in infundibular region.
Carmenate et al.	[26]	NA	GC with pneumobilia and fluid collection around the anterior margin of the liver
Dhira et al.	[6]	Gallbladder dilation, wall thickness of 13mm with septations, CBD 7mm, sludge and stones	NA
Dhira et al.	[6]	Cholecystitis with an irregular gallbladder wall, no pericholecystic fluid, normal caliber CBD	Mild gallbladder distension, gallstones and pericholecystic fluid
Crossley et al.	[27]	Gallbladder distention, wall thickening with discontinuity, inspissated bile (sludge), and surrounding fluid collections	Gallbladder distension and CBD dilation[a]

CT = computed topography; NA = not applicable; CBD = common bile duct; GC = gangrenous cholecystitis.
[a] Patient presented to the Emergency Department again 8 days after the first presentation with CT showing gallbladder rupture.

Table 5
Descriptive statistics of patients with gangrenous cholecystitis.

Variables		n = 8
Age (years) mean ± SD		76 ± 11
Gender	Male, n (%)	6 (75)
	Female, n (%)	2 (25)
Diabetes mellitus, n (%)		4 (50)
Hypertension, n (%)		5 (62.5)
Hyperlipidemia, n (%)		4 (50)
Murphy's sign, n (%)		1 (14.3)
Hypertensive on presentation, n (%)		2 (25)
Febrile on presentation, n (%)		1 (12.5)
White blood cell count (/mm^3) mean ± SD		16.3 ± 9.1
C-reactive protein (mg/L) mean ± SD		12.1 ± 6.1
Abdominal pain, n (%)		4 (50)
Nausea and vomiting, n (%)		4 (50)
Antibiotic therapy given, n (%)	Moxifloxacin	1 (20)
	Piperacillin/Tazobactam	2 (40)
	Ampicillin/Sulbactam	1 (20)
	Amoxicillin/Clavulanic acid	1 (20)
Treatment, n (%)	Laparoscopic cholecystectomy	5 (62.5)
	CT-guided drainage	2 (25)
	Open Cholecystectomy	1 (12.5)
Fluid cultures, n (%)	*Escherichia coli*	3 (100)
	Klebsiella pneumoniae	1 (33.3)

gangrenous cholecystitis may present with negative Murphy's sign secondary to denervation from gangrenous changes [9].

We reviewed 7 cases extracted from 6 different papers, and the case described above, for a total of 8 cases. All patients included in this review suffered from gangrenous cholecystitis. We provide descriptive statistics of the cases for completion.

Patients included in this review were mostly males (75), and the average age was 76 years ±11. Half the patients had diabetes (50%) and hyperlipidemia (50%), whereas the majority had hypertension (62.5%). On presentation, only half the patients had abdominal pain and similarly only half had nausea and vomiting. Only one patient (12.5%) was febrile on presentation to the ED and 2 were hypertensive (25%); otherwise, all other patients were hemodynamically stable on presentation.

On physical examination in the Emergency Department, 6 patients had negative Murphy's sign (85.7%). As for the laboratory workup, the white blood cells count (WBCs) was elevated in 75% of the cases, with a mean of 16.3 ± 9.1/cu·mm. C-reactive protein (CRP) was only reported in 3 cases, with a mean of 12.1 ± 6.1 mg/L (normal range < 2.5). All cases, excluding the presented above, reported normal liver enzymes; however, no details were given on the values.

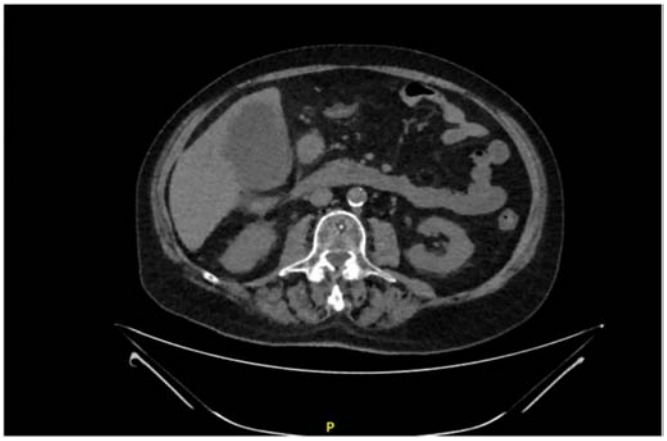

Fig. 2. Computed Topography (CT) showing signs of acute cholecystitis.

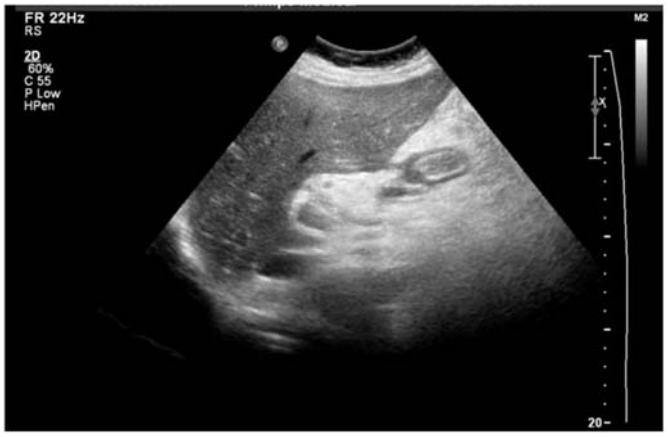

Fig. 3. Ultrasound of gallbladder showing acute gangrenous cholecystitis.

5 patients received antibiotics therapy (62.5%) - including Amoxicillin/Clavulanic acid (20%), Moxifloxacin (20%), Piperacillin/tazobactam (40%), and Ampicillin/Sulbactam (20%). 5 underwent laparoscopic cholecystectomy (62.5%), 1 underwent open cholecystectomy (12.5%), and 2 underwent percutaneous drainage (25%). Only 3 cases had fluid bacterial cultures results and all 3 showed *Escherichia coli* growth, whereas one also had *Klebsiella pneumoniae* growth.

3 cases had pathology results where 2 described areas of hemorrhage, one described necrosis and suppurative inflammation, and 1 described smooth and shiny serosa with ulcerated mucosa and 0.4 cm gallbladder wall thickness.

Only 1 case had postoperative complications, where the patient was found to have phlegmon containing air-fluid level and pockets of gas that resolved with antibiotic therapy and no intervention. Despite GC's high mortality rate [4,5], all 8 cases survived and were discharged after appropriate treatment.

All the above 8 cases presented to the Emergency Department with atypical symptoms. Moreover, the physical exam and laboratory workup were not specific to guide the diagnosis.

The classical symptoms that a patient with GC might complain of are those that point to acute cholecystitis, and include but are not limited to, right upper quadrant pain, nausea, and vomiting [8].

GC is considered to be a challenging diagnosis in the preoperative phase due to the nonspecific physical examinations and laboratory findings [9,11]. Some studies correlate the challenge to the fact that GC presents most commonly in older age, where atypical symptoms are likely and cause a missed diagnosis [9,11]. In our presented case, the patient's only presenting symptom was intractable hiccups. Hiccup is the sudden erratic diaphragmatic and intercostal muscles contraction followed by laryngeal closure [16]. Since hiccups have a neurological reflex arc consisting of peripheral and central midbrain pathways, patients with intractable hiccups are likely to have structural or functional irritation involving the reflex arc [17-19]. In our case, the patient's intractable hiccups were explained by the diaphragmatic irritation resulting from the gallbladder inflammation.

Contini, S., et al., reported that delayed admission was also an important criteria for developing GC [20]. However, a study done by Nikfarjam, M., et al., found that there was no difference in symptom duration prior to presentation in developing GC [7]. This suggests that developing GC is not related a progression in the severity of acute cholecystitis [7].

Risk factors that were found to correlate with the development of GC were male gender, older age > 70 years, diabetes mellitus II, hypertension, febrile on admission, elevated pulse, and muscle rigidity on physical exam [7]. There was no mention whether hyperlipidemia increased the risk of developing gangrenous cholecystitis. In our cases, 50% of patients had hyperlipidemia.

As for laboratory tests, the most specific for GC detection was considered to be a high degree of leukocytosis, as it correlates with the infection severity in the gallbladder wall [21]. A study done by Merriam et al. reported that WBC count > 17,000/mm^3 was a predictor for development of GC [13]. In the cases reported above, WBCs were elevated in 75%.

Regarding imaging, the study done by Bennett, G.L., et al. describes the expected radiological findings of GC. The hallmark of sonography of GC is the presence of heterogeneous or striated thickening in the gallbladder wall which is often irregular with pericholecystic fluid collections [22]. The presence of intra-luminal membranes representing desquamative gallbladder mucosa is considered a specific finding but is not very common [22]. Furthermore, a surgical series of patients with GC showed that 28% of patients had a sonogram that was not diagnostic of any inflammation, mainly due to the absence of Murphy's sign and a wall thickness of <3 mm [25].

CT findings most specific for acute gangrenous cholecystitis are gas in the wall or lumen, intraluminal membranes, irregular wall, and pericholecystic abscess [25].

Bennett, G.L., et al. also looked at the diagnostic capacity of CT scans and found a sensitivity, specificity, and accuracy of 91.7%, 99.1%, and 94.3%, respectively in acute cholecystitis, compared to 29.3%, 96.0%, and 64.1% respectively for acute gangrenous cholecystitis.

These findings support the fact that in our case series, most patients had signs of inflammation on imaging: mostly gallbladder distention and thickening (Table 4). However, it was not until the operative stage that some were diagnosed with gangrenous cholecystitis. This suggests that imaging modalities such as abdominal ultrasounds and CT scans are sometimes not helpful in reliably and confidently diagnosing gangrenous cholecystitis.

When it comes to predictors of mortality, the study done by Nikfarjam, M., et al. was unable to associate, using a multivariate analysis, any independent predictors of mortality in patients with gangrenous cholecystitis [7]. Moreover, there was no significant difference in the rates of postoperative complications and morbidity between cases of GC and cases of uncomplicated acute cholecystitis. However, previous studies have reported increased abscess formation, perforations, biliary peritonitis, increased conversion to open surgery and prolonged hospital stay for patients with GC [4,5,15,23,24]. In our review, almost all patients were discharged from the hospital with good outcomes and no complications. The exception was the patient described in our case report who developed a phlegmon with a fluid collection at the post-cholecystectomy surgical bed which was resolved with antibiotic therapy, without any surgical interventional.

5. Conclusion

Acute gangrenous cholecystitis is a possible complication of acute cholecystitis that may go unnoticed, resulting in surgical delays and worsening outcomes. It is a disease that requires emergent treatment which is why a quick and reliable diagnosis is essential for the wellbeing of the patient. Many factors have been correlated with GC, including a past medical history of DM or HTN, laboratory findings showing leukocytosis, and the presence of pericholecystic fluid, gallbladder distention or wall thickening on imaging. However, this disease can still present atypically without any specific symptom and there is no single clinical or laboratory finding or imaging modality that can help reliably diagnose the disease. We hope that this review sheds light on this important topic and helps physicians diagnose it more accurately.

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None

Authors' contributions

GAD, RS, IB, and SH were the main authors of this article, performed the literature review and wrote the manuscript. GAD and SH attended to the patient and followed up on his care in the tertiary care Emergency Department.

Ethical committee approval

NA.

Competing interests

The authors have no competing interests.

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