

Rethinking the Spectrum of Biliary Disease: Incipient Cholecystitis, an Intermediate Clinical Entity Between Biliary Colic and Acute Cholecystitis – A Case Series

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Abstract

Biliary disease is among the commonest and costliest diseases of the digestive system with an estimated 15% prevalence of gallstones in the United States population. While cholelithiasis may often remain asymptomatic, some patients eventually progress to biliary colic and acute cholecystitis. Both biliary colic and acute cholecystitis present with right upper quadrant pain, with pain persisting for greater than six hours in acute cholecystitis. Acute cholecystitis is thought to be an inflammatory process, with the development of fever and leukocytosis. In addition, acute cholecystitis is also characterized by typical findings of inflammatory processes on ultrasonography and cystic duct obstruction on cholecystography. However, a subset of patients presents with an intermediate clinical picture, with prolonged abdominal pain suggestive of acute cholecystitis, but a negative ultrasonography exam. This case series presents three patients with such a clinical presentation, who had abdominal pain with tenderness and a negative ultrasound but where cholecystography revealed cystic duct obstruction. The authors therefore propose a new hypothetical clinical entity, “incipient cholecystitis,” to characterize these individuals. We suggest that patients with similar intermediate clinical presentation should not be labeled as biliary colic alone, as they may have an accelerated rate of progression to acute cholecystitis. We suggest that future studies are needed in this specific subset of the population, to further investigate this accelerated progression which is not seen in the “typical” or “classic” indolent biliary colic. This will enable clinicians to characterize their risk of progression, as we feel that these patients may benefit from aggressive initial management and early surgical intervention, in stark contrast to “benign” biliary colic, which can be managed conservatively, with an interval cholecystectomy.

Keywords: Biliary Disease; Biliary Colic; Acute Cholecystitis; Pathophysiology; Definition

Abbreviations: RUQ: Right Upper Quadrant; CBC: Complete Blood Count; CMP: Comprehensive Metabolic Panel; ED: Emergency Department

Introduction

Biliary disease is among the commonest and costliest diseases of the digestive system. An estimated fifteen percent of population in the United States have gallstones [1]. With more than one-third of the population being obese, along with no expected changes in the Western diet, this number is expected to increase even further [2]. While patients with gallstones can be asymptomatic, some will eventually go on to develop biliary colic, which in and of itself is considered a relatively benign condition. The most common serious complication of biliary colic is acute cholecystitis, which can be seen in up to ten percent of patients within seven years of initial diagnosis [3].

Pain in both biliary colic and acute cholecystitis is classically located in the right upper quadrant or epigastrium and may be associated with nausea and vomiting [4]. The pain in biliary colic classically lasts for up to an hour before eventually subsiding with the entire

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episode usually lasting no longer than six hours [4]. Gallbladder contraction against a transiently obstructed cystic duct increases pressure within the gallbladder, which subsequently manifests as pain. When the gallbladder relaxes, pressure decreases and the pain lessens [5]. By contrast, the pain in acute cholecystitis is typically more prolonged and persistent, lasting at least longer than six hours. Pain in this instance, occurs from a prolonged obstruction of the cystic duct leading to gallbladder inflammation and the classic symptoms and signs associated with inflammation [5]. Biliary colic, in theory, should not have fever, leukocytosis or abdominal tenderness, as there is no inflammation. Diagnosis of acute cholecystitis can be suggested by ultra-sonographic findings of gallstones with either gallbladder wall thickening or pericholecystic fluid or with non-visualization of the gallbladder during cholecystography. Biliary colic, in contrast, should have visualization of the gallbladder during cholecystography along with no presence of gallbladder thickening or edema on ultrasound [6]. Management of biliary colic focuses solely on pain control and a referral for a prophylactic cholecystectomy to prevent future episodes or complications [7, 8]. In great contrast, acute cholecystitis, beyond pain control, necessitates hospitalization for intravenous fluids, antibiotics and bowel rest along with an urgent cholecystectomy [9,10].

We suspect that the transition from biliary colic to acute cholecystitis is characterized by certain clinical characteristics which constitute an intermediate or overlap state. The aim of this case series is to describe the clinical features associated with this intermediate entity, which we label as “incipient cholecystitis”. Appropriately identifying this clinical entity will enable clinicians to correctly identify individuals presenting as “biliary colic” but who in fact, have characteristics suggestive of an impending cholecystitis and as such, may benefit from an early surgical intervention.

Case Presentations

Patient 1

A 46-year-old Hispanic female presented to the hospital with abdominal discomfort, nausea, and vomiting. Patient had a known history of gallstones, dating back two years, when she was evaluated for back pain and found to have incidental cholelithiasis. She reported being completely asymptomatic for the past two years. She subsequently presented to the hospital with 48 hours of abdominal discomfort and nausea. Initially, she described the pain as acute, severe, epigastric, with a band-like radiation to the right upper quadrant (RUQ) associated with nausea, vomiting, chills that lasted for fifteen minutes. She reported that while the pain improved, it never resolved since the onset of pain. She continued to experience abdominal discomfort with intermittently worsening nausea and episodes of non-bloody emesis for hours leading to her seeking medical attention. On admission, patient was afebrile, hemodynamically stable. Laboratory findings yielded a complete blood count (CBC) and comprehensive metabolic panel (CMP) within normal limits. Ultrasound of the RUQ was positive for large gallstones within the gallbladder, without pericholecystic fluid or gallbladder wall thickening. Due to persistence of pain, a cholecystography was performed and revealed cystic duct obstruction. She was placed on bowel rest and started on intravenous fluids and antibiotics. She subsequently underwent a laparoscopic cholecystectomy the following morning and was discharged from the hospital in good health. The surgical pathology revealed an inflamed gallbladder.

Patient 2

A 22-year-old obese Caucasian female presented to the hospital with intermittent right upper quadrant abdominal pain for the past three days. Although she reported to having three episodes of pain daily, lasting up to fifteen minutes at a time, her pain never completely resolved between the episodes. Her pain was described as pressure-like, radiating to epigastric region and shoulder, and 8/10 in severity, worsening postprandially associated with subjective fevers and nausea without vomiting. On admission, she was afebrile, hemodynamically stable with an abdominal exam revealing RUQ tenderness. A CBC and CMP were within normal limits. A RUQ ultrasound revealed cholelithiasis without presence of gallbladder wall thickening or pericholecystic fluid. Due to persistence of pain and subjective fevers, a cholecystography was ordered and revealed cystic duct obstruction. She subsequently underwent a laparoscopic cholecystectomy the following afternoon. She tolerated the procedure well and was discharged within 24 hours post-operatively. Surgical pathology later confirmed an inflamed gallbladder.

Patient 3

A 34-year-old Caucasian male presented to the hospital with complaints of RUQ abdominal pain of 24 hours in duration. He reported that this was the second episode of such pain. First episode was two days prior when he presented with a sudden onset of colicky RUQ pain and was evaluated at the emergency department (ED) with ultrasonography and diagnosed with cholelithiasis-associated biliary colic. Given resolution of symptoms in the ED, patient was discharged with follow up for an elective cholecystectomy. However, patient returned to the ED two days later with recurrence of stable, constant, severe, non-remitting pain of 24 hours. He described the pain as sudden in onset, located in the RUQ, radiating towards the mid-sternum, sharp, 10/10 in intensity and associated with diaphoresis but he denied fever, nausea or vomiting. Upon admission, patient was afebrile, hemodynamically stable with a leukocytosis of 14,600 and otherwise unremarkable CBC and CMP. Repeat RUQ ultrasound again revealed cholelithiasis without gallbladder distention, wall thickening or edema. Due to persistence of symptoms along with leukocytosis, a cholecystography was performed and revealed cystic duct obstruction. A surgical intervention was recommended to the patient, however patient was reluctant to agree to surgery and left the hospital against medical advice (AMA). A follow-up correspondence with the patient revealed he ultimately underwent a cholecystectomy within days of presentation.

	Biliary Colic	Patient 1	Patient 2	Patient 3	Acute Cholecystitis
Total Duration of Pain	< 6 hours	48 hours	72 hours	24 hours	> 6 hours
RUQ tenderness	Absent	Present	Present	Present	Present
Fever	Absent	Absent	Subjective	Absent	Present
Leukocytosis	Absent	Absent	Absent	Present	Present
RUQ US	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis, Thickened GB Wall, Pericholecystic Fluid, Distended GB
HIDA Scan	Negative	Cystic Duct Obstruction	Cystic Duct Obstruction	Cystic Duct Obstruction	Cystic Duct Obstruction
Surgery	Elective	Early	Early	Left AMA	Early
Pathology	Negative	Inflamed GB	Inflamed GB		Inflamed GB

Table 1: Rethinking the Spectrum of Biliary Disease: “Incipient Cholecystitis”.

Discussion

The authors of this case series believe biliary colic and acute cholecystitis should be viewed as a continuous spectrum of gallstone related biliary tract diseases, with a possible intermediary clinical entity, which we label as “incipient cholecystitis”. These three clinical cases had atypical presentations which did not fit the classic descriptions of biliary colic or acute cholecystitis. The three cases all presented with RUQ abdominal pain and ultrasonographic findings of cholelithiasis and were initially diagnosed by our hospital house staff as biliary colic. However, the patients in the three cases all had persistence of prolonged RUQ abdominal pain lasting at least more than 24 hours, a finding which would be atypical of biliary colic. Moreover, second patient’s pain was associated with subjective fevers and third patient’s pain was associated with leukocytosis; both findings atypical of biliary colic. The initial RUQ ultrasounds interestingly did not reveal signs of any ongoing inflammation: no distended gallbladder, thickened gallbladder wall or pericholecystic fluid.

While no single or combination of findings can establish or exclude a diagnosis with certainty to avoid additional testing, we believe the persistence of prolonged RUQ abdominal pain with or without fever or leukocytosis should raise suspicion of possible impending or early cholecystitis. These patients, as shown in the three cases, benefited from further imaging studies in the setting of discordant clinical presentation and initial ultrasound. All three patients’ cholecystography’s revealed non-visualization of the gallbladder with cystic duct obstruction, a finding which would suggest impending cholecystitis. Furthermore, these patients underwent surgery and were found to have inflamed gallbladders on surgical pathology.

The main purpose of this case series is to identify select patients whose clinical presentation does not meet the clinical findings of biliary colic or acute cholecystitis. Instead, we raised the importance of considering a new clinically relevant entity, labeled as “incipient cholecystitis,” a hypothetical intermediary entity between the classic biliary colic and acute cholecystitis. We believe that patients presenting with 1) RUQ abdominal pain lasting more than six hours, 2) with abdominal tenderness on examination, 3) with or without other features of inflammation (fever or leukocytosis) and 4) cholelithiasis with the absence of ultra-sonographic evidence of cholecystitis should be termed “incipient cholecystitis” rather than biliary colic (Table 2).

1. Right Upper Quadrant Abdominal Pain lasting more than six hours
2. Abdominal Tenderness on Examination
3. +/- Features of Inflammation: Fever or Leukocytosis
4. Cholelithiasis with Absence of Ultrasonographic Evidence of Cholecystitis

Table 2: Proposed Criteria for “Incipient Cholecystitis”

In our small case series, such individuals were found to have cystic duct obstruction on scintigraphy and subsequently required urgent surgery, as opposed to interval cholecystectomy. By comparison, literature reveals a 10% risk of these patients with biliary colic eventually developing acute cholecystitis over the next seven years [3]. The patients in our case series had a considerably more acute course of disease.

RUQ ultrasound can detect acute cholecystitis with more than 85% sensitivity and specificity [11]. The proposed criteria could be used to identify a subgroup of patients who may potentially be having an impending cholecystitis with negative ultrasound findings of inflammation. From a pathophysiological standpoint, non-visualization of the gallbladder on cholecystography may precede the development of ultrasonography features of cholecystitis [6]. The initial event leading to cholecystitis is thought to be from a prolonged cystic duct obstruction, which is readily detected by cholecystography [6-11]. This is subsequently followed by contraction of the gallbladder against an obstructed outlet, with associated cholestasis and subsequent release of cytokines leading to gallbladder inflammation [5-12]. The inflammation is then reflected on the ultrasound. Gallbladder distention is expected to occur early in the course of the disease as a result of ongoing bile production in the setting of decreased outflow [5-12]. In our series of patients, gallbladder distention was not reliable in ruling out acute or impending cholecystitis. We are unable to account for this finding, we hypothesize that due to possible variable rates of bile production, not all patients may develop ultrasonographically evident distention by the time of clinical presentation [5- 12].

Conclusion

This proposed entity would identify patients who have unexplained prolonged biliary colic-like pain lasting more than six hours with or without possible associated fever or leukocytosis and negative ultrasound findings of gallbladder inflammation. The authors suggest that this phenotype should be distinguished from biliary colic in future studies, in order to determine the natural history and course of this presentation. It is our suspicion that “incipient cholecystitis” will have a higher rate of short term progression to acute cholecystitis as compared to the relatively indolent nature of biliary colic. This phenotype, in our belief, represents patients who have shown a predisposition to developing acute cholecystitis. If larger studies can confirm this suspicion, this would have important implications for clinical practice. These patients would then be managed similarly to acute cholecystitis, with hospitalization and aggressive intervention. Timely intervention and treatment, the authors hope, will result in a significant reduction in morbidity for our patients.

The aim of this series is to present three cases with clinical features which are separate from those of biliary colic and acute cholecystitis, all of whom benefited from early surgical intervention. Future studies are required to determine if this high risk phenotype is indeed “incipient cholecystitis” and would therefore possibly benefit from an early intervention.

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Conflict of interest

There are no financial interests or any conflicts of interest declared.

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