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CGH Education Practice: A young woman with gallstone pancreatitis and abnormal liver tests: When is ERCP needed?

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Clinical scenario

A 39 year-old Caucasian female with past medical history only significant for allergic rhinitis and irritable bowel syndrome presented to the emergency room with acute onset of diffuse abdominal pain accompanied by subjective fevers and chills and nausea and vomiting. The total duration of the episode was 5 hours. The pain reached a subjective zenith approximately 30 min prior to presentation, precipitating her ER visit, but since that point in time, she noted that her pain was diminishing. The patient denied any significant changes to her diet or trauma to the abdomen. She has never had these symptoms before. The patient denied any history of abdominal surgeries. The patient denied any family history of pancreatitis, cystic fibrosis, inflammatory bowel disease or GI cancers. She was G2P2. On examination, the patient was in moderate distress with the following vital signs: temperature of 98.6°, pulse of 110 beats per minute and blood pressure of 100/76 with SAO₂ = 99% on room air. Mild scleral icterus was noted. She was tachycardic and tachypneic but her respiratory exam was notable only for dullness at the bases. On abdominal examination, bowel sounds were present but diminished, guarding was noted in the RUQ and exquisite tenderness diffusely was present over the entire abdomen. No rebound was present, but a Murphy's sign was noted. No stigmata of cirrhosis were noted. The patient was alert and oriented x 3, though she was insistent on immediate administration of pain medications.

Screening laboratory findings featured a serum lipase of 1044 U/L, and amylase of 458 U/L, ALT of 91 IU/L, AST of 81 IU/L, alkaline phosphatase of 199 U/L and total bilirubin of 1.5. A metabolic panel was within normal limits except for a CO₂ of 15. WBC was 12,000, hemoglobin was 14.2 and platelet count was 344.

Bedside abdominal ultrasound was performed by the emergency room staff and interpreted as demonstrating a gallbladder with cholelithiasis, but no choledocholithiasis. The common bile duct was noted to be dilated to 14 mm. The pancreas was poorly visualized. A CT scan of the abdomen was obtained afterwards, confirming cholelithiasis with a thin-walled gall bladder, a dilated CBD at approximately 15mm, and evidence of peripancreatic inflammation localized to the head and body of the pancreas without a fluid collection.

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The emergency room physician suggested that the patient should be evaluated and scheduled for an emergent ERCP, stating that the patient is “obstructed” and at high risk for developing cholangitis. As the GI consultant, if and at what point should an ERCP be performed?

The problem

The clinical problem centers on the risks and potential benefit of therapeutic ERCP in a patient presenting with acute pancreatitis most likely arising from biliary obstruction, which is frequently transient, as in this case. In almost all instances of acute gallstone pancreatitis, passage of a gallstone from the gallbladder into the common bile duct leads to transient obstruction distal to the introitus of the pancreatic duct. This event leads to stasis and retrograde flow of the contents of the biliary tree, including pancreatic zymogens¹ (some have postulated that multiple passages of gallstones leading to multiple events of transient obstruction are what trigger downstream inflammation²). Local inflammation adjacent to the obstruction causes further obstruction. If this mechanical obstruction is not relieved in a timely fashion, mucosal damage and further inflammation in three distinct areas along the biliary tract may occur: at the area of the obstruction, in the pancreas, and in hepatocytes at the most proximal points of the biliary system; clinically, this pathophysiology is reflected in the presence of RUQ abdominal pain with a Murphy’s sign, elevation of serum pancreatic enzymes and a rise to greater than three times the upper limit of normal of the liver associated enzymes. Local inflammation at the site of obstruction (triggered by mucosal injury from the offending gallstone) not only leads to the cascade of cytokine release, but also the acidification of biliary contents. It is theorized that local acidification of the bile leads to activation of pancreatic zymogens, thus causing further damage to the biliary tree, pancreas and hepatocytes as proteolysis and lipolysis occur. Further tissue damage leads to an exponential activation of cytokines which, if severe enough, can lead to multi-system organ failure, even in the absence of an offending infection. The relatively high pressure gradient within the biliary system normally protects against the development of cholangitis. However, when stasis occurs as a result of obstruction, infection, as a result of the entry of flora from the gut, can be dramatic, leading to multi-organ failure and death if no therapeutic maneuvers are undertaken.

ERCP with sphincterotomy and stone extraction has been shown in multiple studies to significantly reduce the morbidity and mortality in the setting of cholangitis due to retained stones in the biliary system. The concept underlying this practice is the early alleviation of biliary stasis so that the cascade of local inflammation and subsequent mucosal damage can be terminated as quickly as possible before local necrosis and systemic multi-organ failure can occur.

However, the indication for ERCP is not so clear when a patient presents with chemical pancreatitis with associated abnormalities in liver associated enzymes, and continued abdominal pain without any obvious choledocholithiasis, as in the present case. Should ERCP be performed in all such patients, to ensure clearance of the CBD? Or, can ERCP, and its associated risks, be safely avoided with conservative management? Many groups have studied the question, but the use of ERCP ultimately lies in the clinical judgment of the treating gastroenterologist.

The case against early ERCP without evidence of cholangitis: The evidence

Four total randomized clinical controlled trials (RCT) of adult patients presenting with gallstone-associated pancreatitis comparing ERCP with sphincterotomy within 72 hours of presentation have been performed²⁻⁵. In the first, 121 patients from a single center were randomized to receive ERCP². Sphincterotomy was only performed if biliary stones were seen. In this seminal study, no difference in mortality was seen, but a small, but significant, reduction in complications was noted in the early ERCP group. Secondary analysis revealed that the

entirety of this effect could be accounted for in the reduction in complications in those patients with “severe” pancreatitis as defined by a Glasgow score greater than or equal to 3. When patients with mild to moderate pancreatitis were analyzed, no differences were seen in terms of morbidity or mortality. A second group in Hong Kong observed no difference in measures of local or systemic pancreatitis or mortality in the early ERCP (within 24 hours of admission) and conservative management arms of their study³. However, this group was able to find a significant reduction in the rate of biliary sepsis in the urgent ERCP group among those patients who were predicted to have severe pancreatitis as delineated by modified Ranson’s Criteria. Folsch and colleagues⁴ confirmed the absence of benefit of early ERCP (within 72 hours of admission) with mild to moderate acute gallstone-associated pancreatitis. The most recent contribution to the subject further confirmed the above studies and conclusions⁵.

A Cochrane meta-analysis of the first three RCTs showed benefit of early ERCP if performed in patients with severe gallstone-associated pancreatitis (mortality OR = 0.27, 95% CI = 0.14 to 0.53)⁶. In no other subgroups of patients with gallstone pancreatitis was any significant benefit observed compared to conservative management.

Areas of Uncertainty

There are multiple classifications used to define severity in pancreatitis (summarized in Table 1). However, there has been no study systematically comparing each of these metrics in terms of outcomes with or without ERCP. In the four RCTs aforementioned, the Glasgow scale, CT severity index, and a modified Ranson’s criteria were used—there was no single system uniformly applied. It appears that severity as defined by any of these scales could serve to screen for patients who would benefit from early ERCP, but no clear evidence exists to suggest that this may be the case.

There has yet not been a head-to-head trial of benefit of ERCP performed within 24 versus 72 hours of presentation among patients with severe pancreatitis. While 3 of the four of the RCTs studied early ERCP with performance within 72 hours of admission, head-to-head comparison of benefits of earlier intervention can not be accomplished with the published literature.

Published Guidelines

The AGA institute published its technical review on acute pancreatitis within the past year⁷. In this paper, ERCP is recommended to be urgently performed “when acute cholangitis has complicated acute biliary pancreatitis (about 10% of patients)” and when “clinical or radiographic features suggest a persistent common bile duct stone”. Further, early ERCP, as defined as execution within 48–72 hours of the onset of illness, should be considered “when biliary pancreatitis is severe or is predicted to be severe (based on APACHE II, Ranson’s criteria, or modified Glasgow criteria).” Finally, it should also be mentioned that cholecystectomy is indicated “as soon as possible”, but no further than 4 weeks after discharge.

Recommendations

Our approach to acute gallstone pancreatitis is summarized in Figure 1. First, supportive care and resuscitation, including aggressive fluid administration, should be started as early as possible. Once initiated, additional tests can then be performed to confirm the etiology of the patient’s acute pancreatitis. If the clinical presentation is consistent with acute cholangitis, urgent ERCP should be performed; in our practice, we perform ERCP for acute cholangitis within 24 h of presentation dependent upon a number of clinical factors. Early ERCP (within 24–48 h) is performed in patients who have evidence of choledocholithiasis.

Finally, we also consider performing early ERCP if the patient's clinical course becomes unstable or deviates from the expected clinical course. While these patients may be identified by a number of metrics set forth in the literature (see Table 1), it appears that the most reliable evaluation test is a seasoned clinician's.

For the particular patient in this case, we would begin conservative management with supportive care and consideration of antibiotics, but would not perform an ERCP. The elevations in serum pancreatic enzymes and the CT findings suggestive of peri- and intra-pancreatic inflammation are supportive of the diagnosis of pancreatitis. Despite the dilated CBD, the CT and US do not demonstrate persistent choledocholithiasis. The elevated total bilirubin, the dilated CBD, cholelithiasis, and the diminishing abdominal pain suggest resolution of choledocholithiasis. Careful consideration of bilirubin elevations should be undertaken as Gilbert's may not be known beforehand. However, in a few patients, choledocholithiasis will not be detected despite both imaging studies. Therefore, serial serum liver associated enzyme and pancreatic enzyme tests are performed. If stone passage has occurred and there is no persistent CBD stone, one would expect a steady decline in the laboratory abnormalities accompanied by a decrease in the CBD diameter. If there is persistent or episodic pain, or the laboratories do not resolve as expected, then ERCP should be considered as choledocholithiasis can not be ruled out. For some patients who are felt to have a low probability of a retained CBD stone, an intra-operative cholangiogram may be obtained. In selected patients with a low or intermediate risk for a retained CBD stone, endoscopic ultrasound may provide the necessary information without the risks associated with ERCP.

Further evidence against early ERCP in this patient is the lack of any ominous predictive markers. While the patient has exactly 2 SIRS criteria, we suspect that these are due to pain from mild inflammation and that with minimal pain management, these would quickly resolve. Using other measures, this patient has a CT severity score of 3, a Ranson's criteria score < 3, and a Glasgow score < 3. These scores are not an absolute substitute for clinical examination and judgment, but such objective evidence supports the decision against ERCP in this particular patient.

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Figure 1.
Algorithm for the management of gallstone pancreatitis.

Table 1
Metrics utilized to predict severity in patients with pancreatitis

I. SIRS criteria

Positive when 2 or more of the following are met:

- 1 Temperature >38°C or <35°C
- 2 Heart rate >90 beats/min
- 3 Respiratory rate >20 breaths/min or PaCO₂ <32 mmHg
- 4 WBC >12,000 cells/mm³, <4000 cells/mm³, or >10 percent immature (band) forms

II. CT severity score⁸

Grade

A: Normal pancreas	1 point
B: Pancreatic enlargement	2
C: Pancreatic or peripancreatic inflammation	3
D: Single peripancreatic fluid collection	4
E: 2 or more fluid collections or peripancreatic air	5

Necrosis

< 30%	2
30–50%	4
>50%	6

CT severity index (= Grade + Necrosis)

Score	Morbidity	Mortality
0–3	8%	3%
4–6	35%	6%
7–10	92%	17%

Severe pancreatitis defined as > 5

III. APACHE II

Can be calculated at: <http://www.sfar.org/scores2/apache22.html> Variables: Temperature, Mean arterial pressure, heart rate, respiratory rate, A-a gradient/ PaO₂, serum HCO₃, pH, Na, K, Cr, hematocrit, WBC, Glasgow coma score, age.

IV. Ranson's criteria

Present on Admission: (one point for each)

- Age > 55 years
- Blood Glucose > 200 mg/dl
- Serum LDH > 350 IU/L
- AST > 250 IU/L
- WBC > 16,000/ul

Developing During the First 48 Hours:

- Estimated fluid Sequestration > 600 ml
- Arterial Oxygen saturation < 60 mm Hg
- Serum Calcium < 8 mg/dl
- Hematocrit fall greater than 10%
- Base deficit > 4 meq/L
- BUN increase > 8 mg/dl

Score is total number of points at either presentation or over 48h.

Score > 3 is defined as severe pancreatitis

Ranson score of 0–2

Ranson score of 3–5

Ranson score of >5

Minimal mortality
10%–20% mortality
>50% mortality, high morbidity

V. Glasgow score (Modified)

Finding at any time during 1st 48 hours

1. Age	
> 55 years	1 points
<= 55 years	0
2. Serum albumin	
< 3.2 g/dL	1
>= 3.2 g/dL	0
3. Arterial pO ₂ on room air	
< 60 mm Hg	1
>= 60 mm Hg	0
4. Serum calcium	
< 8 mg/dL	1
>= 8 mg/dL	0
5. Blood glucose	
> 180 mg/dL	1
<= 180 mg/dl	0
6. Serum LDH	
> 600 U/L	1
<= 600 U/L	0
7. Serum urea nitrogen	
> 45 mg/dL	1
<= 45 mg/dL	0
8. WBC count	
> 15,000 per L	1
<= 15,000 per L	0

Modified Glasgow prognostic criteria = SUM (points for all 8 parameters)

Interpretation:

If score ≥ 3 , severe pancreatitis likely.

If score < 3 , severe pancreatitis is unlikely.

VI. Atlanta Classification of Acute Pancreatitis

Criteria for severe acute pancreatitis - one or more of the following:

- 1 Ranson score on admission ≥ 3 (or during the first 48 hours)
- 2 APACHE II score ≥ 8 at any time during course
- 3 presence of one or more organ failures
- 4 presence of one or more local complications

Organ failure includes

- 1 shock (systolic blood pressure less than 90 mm Hg)
- 2 pulmonary insufficiency ($\text{PaO}_2 \leq 60$ mm Hg on room air)
- 3 renal failure (serum creatinine > 2 mg/dL after fluid replacement)
- 4 gastrointestinal bleeding, with > 500 mL estimated loss within 24 hours
- 5 DIC (thrombocytopenia and hypofibrinogenemia and fibrin split products)
- 6 severe hypocalcemia (≤ 7.5 mg/dL)

Local complications include:

- 1 pancreatic necrosis
 - 2 pancreatic abscess
 - 3 pancreatic pseudocyst
-