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Pancreatobiliary Reflux Resulting in Pancreatic Ascites and Choleperitoneum after Gallbladder Perforation

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Key Words
Ascites · Cholecystitis · Pancreatitis, acute necrotizing · Peritonitis

Abstract
A 65-year-old man with chronic hepatitis C and no history of alcohol abuse was admitted to our liver unit for the recent development of massive ascites and presumed hepatorenal syndrome. In the preceding two weeks, he had received medical treatment for acute pancreatitis and cholecystitis. Abdominal paracentesis demonstrated a cloudy, orange peritoneal fluid, with total protein concentration 3.6 g/dl, serum-ascites albumin gradient 1.0 g/dl, and ratios of ascites-serum bilirubin and amylase approximately 8:1. Diagnostic imaging demonstrated no pancreatic pseudocysts. Ten days later, at laparotomy, acalculous perforation of the gallbladder was identified. After cholecystectomy, amylase concentration in the ascitic fluid dropped within a few days to 40% of serum values; ascites disappeared within a few weeks. We conclude that in the presence of a perforated gallbladder, pancreatobiliary reflux was responsible for this unusual combination of choleperitoneum and pancreatic ascites, which we propose to call pancreatobiliary ascites.

Introduction

Pancreatic ascites is a massive accumulation of peritoneal fluid with high protein (>3 g/dl) and amylase (>1,000 U/l) content, resulting from benign pancreatic disease [1]. It is an uncommon, but well recognized complication of acute and chronic pancreatitis, usually generated by leakage or rupture of a pancreatic pseudocyst communicating with the ductal system, but also the consequence of pancreatic ductal disruption after blunt

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abdominal trauma [2]. Here we present a case of pancreatic ascites associated with choleperitoneum after gallbladder perforation.

Case Report

A 65-year-old man with chronic hepatitis C and no history of alcohol abuse was admitted to our liver unit for the recent development of massive ascites and presumed hepatorenal syndrome. Two weeks earlier he had presented to the emergency department of another hospital for sudden severe postprandial epigastric pain, associated with vomiting, sweating, tachycardia, and dyspnea. Serum amylase concentration was 4,817 U/l (reference range 0–104 U/l), total bilirubin 2.5 mg/dl (reference range 0.3–1.2 mg/dl) and white blood cell count 15,760 cells/mm^3. A plain abdominal film showed moderate distension of the stomach and a few fluid levels in the small intestine. Abdominal ultrasonographic examination showed gallbladder distension with pericholecystic fluid collection; no biliary stones were visualized. The patient was admitted to a surgery ward for acute pancreatitis with cholecystitis, for which a decision was made in favor of conservative treatment. In the following days, an abdominal CT scan showed no evidence of biliary tract dilatation, while an enlarged pancreas with mild Wirsung duct dilatation, massive ascites, and hepatomegaly with irregular margins were noted. Later during the hospital stay, a magnetic resonance cholangiopancreatography was performed, demonstrating a distended gallbladder with thickened walls. Despite gradual and almost complete normalization of serum amylase concentration, the patient's clinical condition worsened steadily with progressive oliguria, and he was transferred to our unit.

The patient was in acute distress for intense pain, fatigued and cachectic, with tense ascites. A central venous catheter was inserted and a paracentesis was performed. Ascitic fluid was orange-colored and cloudy (**fig. 1**), with marked leukocytosis, and bilirubin and amylase concentrations far exceeding the corresponding values measured on the same day in blood (**table 1**). The serum-ascites albumin gradient was 1.0 g/dl. The patient's condition was considered too poor to sustain an endoscopic retrograde cholangiopancreatography, proposed in order to identify and treat a biliary fistula. Antibiotics, parenteral nutrition, terlipressin and albumin were started intravenously, with initial improvement of renal function. Cultures of ascites and blood turned positive for *E. coli*. On a new abdominal CT, pancreas morphology was reported as normal, without pseudocysts or duct dilatation. On the 11th hospital day, however, the patient developed frank peritonism, associated with sudden deterioration of liver function tests. A plain film of the abdomen showed generalized bowel distension with fluid levels but no evidence of free peritoneal air. Surgical exploration documented biliary peritonitis with gallbladder perforation; a cholecystectomy was performed, and the gallbladder was sent for pathologic examination (**fig. 2**). No biliary stones were present in the biliary tract, including the gallbladder, and the anatomy of the extrahepatic biliary tree was intact. Ascitic fluid amylase concentration dropped to normal within few days from surgery, and the patient was discharged in fair condition 30 days after his admission. At the last follow-up visit, 10 months later, he had fully recovered his usual body weight, showed no physical or ultrasonographic signs of ascites, and had platelet count and liver function tests within the normal reference range.

Discussion

To interpret this case, it is necessary to review both the clinical presentation of gallbladder perforation and the pathogenesis of pancreatic ascites. It is conceivable that, in our patient, both cholecystitis and acute pancreatitis originated from sphincter of Oddi dysfunction, a benign, noncalculous obstruction to the flow of bile or pancreatic juice through the pancreaticobiliary junction, that may be manifested clinically by pancreaticobiliary pain, pancreatitis, or deranged liver function tests [3]. Alternatively, they may have been caused by gallstone migration into the common bile duct, followed by spontaneous disimpact. In any case, acute pancreatitis resolved, whereas cholecystitis was complicated by localized gallbladder perforation, which must have been present for more than 10 days before surgery, since choleperitoneum with an ascitic fluid bilirubin concentration of approximately 33 mg/dl and an ascitic fluid/blood 8:1 ratio for bilirubin was documented at the diagnostic paracentesis performed on admission. Ascitic fluid

bilirubin concentrations above 6 mg/dl and ascitic fluid/serum bilirubin ratio greater than 1.0 are characteristic of choleperitoneum [4]. Perforation of the gallbladder has long been recognized as a cause of choleperitoneum [5]; it occurs in 3–15% of patients with cholecystitis and is associated with significant morbidity and mortality [6]. Its clinical picture and diagnostic imaging are often indistinguishable from those of acute cholecystitis. Therefore, the diagnosis of gallbladder perforation is rarely made before operative exploration, as it happened in this case.

Coming to pancreatic ascites, the driving force leading to accumulation of fluid in the peritoneal cavity in this rare condition (<3% of cases of ascites) is the leakage of protein-rich mesenteric lymph from an inflamed peritoneal surface. This peritoneal exudate is rich in vasoactive substances, proinflammatory mediators and activated lipolytic and proteolytic enzymes [7]. Typically, the ascitic fluid/serum ratio for amylase is 6:1, with absolute values often above 1,000 U/l. In contrast, in patients with cirrhotic ascites the capillarization of sinusoids and the increased hydrostatic pressure due to portal hypertension favor the formation of ascitic fluid with low protein content and serum-ascites albumin gradient, i.e. the value obtained subtracting albumin in the ascitic fluid from albumin simultaneously measured in the serum, >1.1 g/dl. In the present case, the combination of a serum-ascites albumin gradient below 1.1 g/dl, a total protein level >3 gm/l, and elevated ascitic amylase were diagnostic of pancreatic ascites. The absence of a pseudocyst and the rapid and complete resolution of pancreatic ascites after cholecystectomy suggest that spillage of pancreatic juice into the peritoneal cavity must have occurred via the perforated gallbladder, necessarily in the presence of pancreatobiliary reflux. Indeed, when systematically searched for, evidence of occult pancreatobiliary reflux is found in almost all patients with acute cholecystitis, both calculous and acalculous [8]. Pancreatobiliary and biliopancreatic refluxes result in several of various pathological conditions in the biliary tract and in the pancreas, including acute cholecystitis and acute pancreatitis, and do not have pancreaticobiliary maljunction as a necessary prerequisite [9]. Therefore, these refluxes are a reasonable explanation for the full clinical picture of this case, although in the absence of secretin-stimulating magnetic resonance cholangiopancreatography imaging [10], this conclusion remains speculative.

Finally, one might ask whether acalculos cholecystitis could have been favoured, in our patient, by the presence of liver disease (chronic hepatitis C). The literature is not conclusive regarding this specific issue. In a series of patients with end-stage liver disease and symptomatic gallbladder disease who underwent endoscopic stent insertion, acalcolous cholecystitis occurred in 2 out of 29 patients [11]. Diffuse lymphoplasmacytic acalcolous cholecystitis is a distinct form of chronic cholecystitis associated with primary sclerosing cholangitis [12], but not with liver disease of other etiologies. Gallbladder disease and fatty liver disease share similar predisposing factors, including obesity and insulin resistance, which play a well recognized role in hepatitis C, but these patients almost invariably present with gallbladder stones [13].

In conclusion, we propose to call pancreatobiliary ascites the combination of choleperitoneum with pancreatic ascites. The present case, of which we were not able to find other examples in the literature, reminds us of the difficulties in diagnosing gallbladder perforation preoperatively and of the importance of evaluating the results of ascitic fluid analysis with a correct, pathophysiology-oriented approach.

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Table 1. Hematologic and biochemical laboratory data

Variable	Reference range	On admission	Hospital day			
			3	8	10	15
White cells, per mm^3						
Blood	4,000–10,000	15,710	17,930	10,500	12,300	15,700
Ascites	N.A.	19,740	17,560	23,200	9,300	400
Total bilirubin, mg/dl						
Serum	0.3–1.2	4.2	31	4.9	3.5	1.7
Ascites	N.A.	32.6	14.1	6.5	5.1	N.T.
Amylase, U/l						
Serum	0–104	358	468	247	252	250
Ascites	N.A.	2,999	2,767	2,486	2,184	104
Total protein, g/dl						
Serum	6.4–8.3	6.3	N.T.	N.T.	N.T.	N.T.
Ascites	N.A.	3.6	N.T.	2.2	2.2	2.5
Albumin, g/dl						
Serum	3.4–4.8	2.7	N.T	2.7	1.8	3.1
Ascites	N.A.	1.7	N.T.	N.T.	N.T.	N.T.

N.A. = Not applicable; N.T. = not tested.

Fig. 1. Physical appearance of the ascitic fluid.

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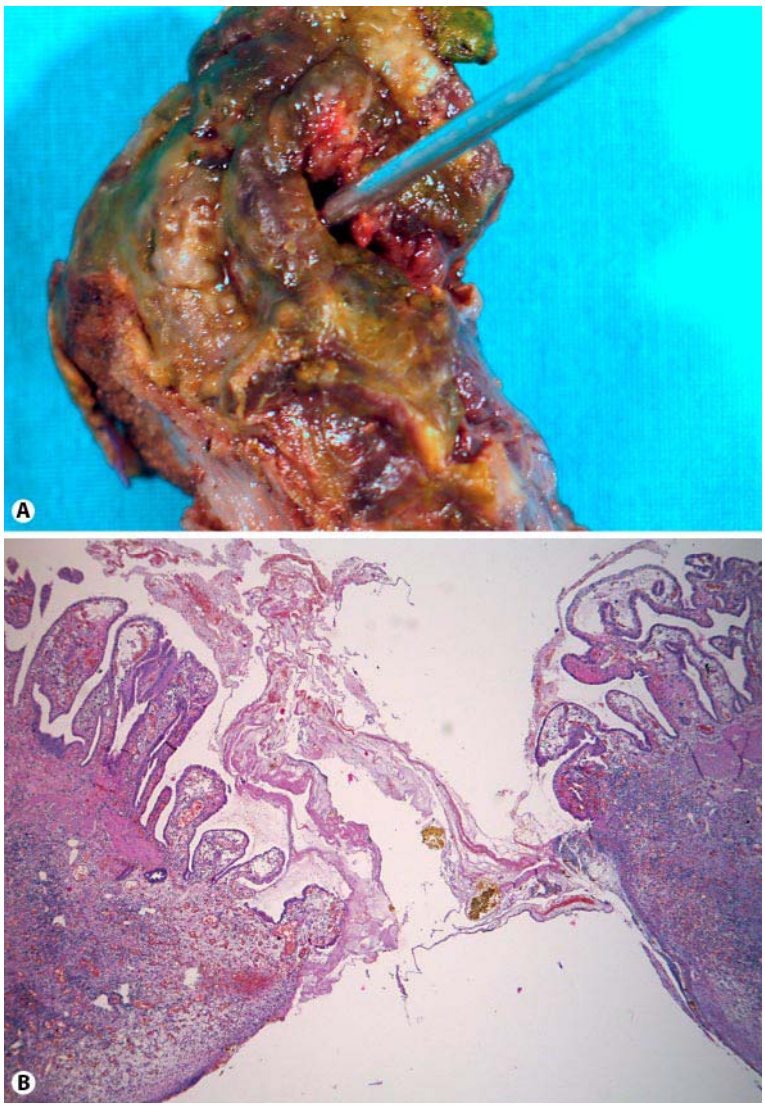
Fig. 2. Gross appearance of the gallbladder perforation (**A**) and microscopic features of mucosal ulceration with transmural granulation tissue and presence of bile plugs (E&E, 4×) (**B**).



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References

1 Uchiyama T, Yamamoto T, Mizuta E, Suzuki T: Pancreatic ascites – a collected review of 37 cases in Japan. Hepatogastroenterology 1989;36:244–248.

2 Fernandez-Cruz L, Margarona E, Llovera J, Lopez-Boado MA, Saenz H: Pancreatic ascites. Hepatogastroenterology 1993;40:150–154.

3 Behar J, Corazziari E, Guelrud M, Hogan W, Sherman S, Toouli J: Functional gallbladder and sphincter of Oddi disorders. Gastroenterology 2006;130:1498–1509.

4 Runyon BA: Ascitic fluid bilirubin concentration as a key to choleperitoneum. J Clin Gastroenterol 1987;9:543–545.

5 Niemeier OW: Acute free perforation of the gall-bladder. Ann Surg 1934;99:922–924.

6 Menakuru SR, Kaman L, Behera A, Singh R, Katariya RN: Current management of gall bladder perforations. ANZ J Surg 2004;74:843–846.

7 Dugernier T, Laterre PF, Reynaert MS: Ascites fluid in severe acute pancreatitis: from pathophysiology to therapy. Acta Gastroenterol Belg 2000;63:264–268.

8 Beltran MA, Vracko J, Cumsille MA, Cruces KS, Almonacid J, Danilova T: Occult pancreaticobiliary reflux in gallbladder cancer and benign gallbladder diseases. J Surg Oncol 2007;96:26–31.

9 Kamisawa T, Okamoto A: Biliopancreatic and pancreatobiliary refluxes in cases with and without pancreaticobiliary maljunction: diagnosis and clinical implications. Digestion 2006;73:228–236.

10 Motosugi U, Ichikawa T, Araki T, Kitahara F, Sato T, Itakura J, Fujii H: Secretin-stimulating MRCP in patients with pancreatobiliary maljunction and occult pancreatobiliary reflux: direct demonstration of pancreatobiliary reflux. Eur Radiol 2007;17:2262–2267.

11 Conway JD, Russo MW, Shrestha R: Endoscopic stent insertion into the gallbladder for symptomatic gallbladder disease in patients with end-stage liver disease. Gastrointest Endosc 2005;61:32–36.

12 Jessurun J, Bolio-Solis A, Manivel JC: Diffuse lymphoplasmacytic acalculous cholecystitis: a distinctive form of chronic cholecystitis associated with primary sclerosing cholangitis. Hum Pathol 1998;29:512–517.

13 Liew PL, Lee WJ, Wang W, Lee YC, Chen WY, Fang CL, Huang MT: Fatty liver disease: predictors of nonalcoholic steatohepatitis and gallbladder disease in morbid obesity. Obes Surg 2008;18:847–853.