A case of gallbladder carcinoma associated with pancreatobiliary reflux in the absence of a pancreaticobiliary maljunction: A hint for early diagnosis of gallbladder carcinoma

Jin Kan Sai, Masafumi Suyama, Yoshihiro Kubokawa

Abstract

A 62-year-old man with progressive thickening of the gallbladder wall visited our outpatient clinic. The biliary amylase level in the common bile duct was 19,900 IU/L and that of the gallbladder was 127,000 IU/L, although endoscopic retrograde cholangiopancreatography revealed no pancreaticobiliary maljunction. Histology demonstrated a moderately differentiated adenocarcinoma of the gallbladder. Pancreatobiliary reflux and associated gallbladder carcinoma were confirmed in the present case, in the absence of a pancreaticobiliary maljunction. Earlier detection of the pancreatobiliary reflux and progressive thickening of the gallbladder wall might have led to an earlier resection of the gallbladder and improved this patient’s poor prognosis.

© 2006 The WJG Press. All rights reserved.

Key words: Amylase; Bile; Gallbladder carcinoma; Pancreatobiliary reflux; Pancreatobiliary maljunction; Diagnosis

Sai JK, Suyama M, Kubokawa Y. A case of gallbladder carcinoma associated with pancreatobiliary reflux in the absence of pancreaticobiliary maljunction: A hint for early diagnosis of gallbladder carcinoma. World J Gastroenterol 2006; 12(28): 4593-4595

http://www.wjgnet.com/1007-9327/12/4593.asp

INTRODUCTION

Regurgitation of pancreatic juice into the biliary tract (pancreatobiliary reflux) usually occurs in patients with pancreaticobiliary maljunction and is closely related to the occurrence of biliary malignancy.\(^1\) Bile mixed with pancreatic juice is known to induce cellular proliferation and stimulate genetic alterations of the biliary tract epithelium, leading to hyperplasia, dysplasia and ultimately, carcinoma of the biliary tract mucosa.\(^2\)

Here we describe a patient with pancreatobiliary reflux in the absence of pancreaticobiliary maljunction, who showed progressive thickening of the gallbladder wall, which developed into an advanced gallbladder carcinoma.
agnosis of the resected specimen was a moderately differentiated adenocarcinoma of the gallbladder’s fundus with invasion of the serosa (Figure 3).

**DISCUSSION**

Pancreatobiliary maljunction is defined as an abnormal union of the pancreatic and biliary ducts that is located outside the duodenal wall, where a sphincter system is not present\(^1\). Thus, two ducts are always communicating, and pancreatic juice freely regurgitates into the biliary tract through this passage. Numerous clinical and experimental studies have supported a relationship between pancreatobiliary reflux and biliary cancer in patients with pancreatobiliary maljunction. Bile mixed with pancreatic juice is known to induce hyperplasia, metaplasia, and ultimately, carcinoma of the biliary tract mucosa in patients with pancreatobiliary maljunction\(^2,3\). In fact, biliary cancer is found in 15% to 67% of adult patients with pancreatobiliary maljunction, and gallbladder carcinoma is found more often in patients with pancreatobiliary maljunction without a congenital choledochal cyst\(^4\).

Pancreatobiliary reflux also occurred in our patient, in the absence of a pancreatobiliary maljunction that was confirmed by elevated amylase levels in the bile sampled at ERCP and cholecystectomy. It was suspected that the extremely high levels of pancreatic enzymes in the bile might have induced carcinoma of the gallbladder as seen in patients with pancreatobiliary maljunction\(^4,5\). It was speculated that pancreatic juice may regurgitate into the biliary system through a common terminal ampulla that is known to exist in 60%–90% of human subjects\(^6\); as pressure generated in the pancreatic duct is usually greater than that observed in the biliary system, it allows for flow from the pancreas to the biliary system\(^7,8\). The precise mechanism of the pancreatobiliary reflux without pancreatobiliary maljunction, and especially its relation to the dysfunction of sphincter of Oddi, should be further clarified.

One of the imaging findings that suggest mucosal changes accompanied by pancreatobiliary reflux is diffuse thickening of the gallbladder wall that might reflect cellular proliferation of the gallbladder epithelium, in patients with pancreatobiliary maljunction\(^2\). In the present case, diffuse thickening of the gallbladder wall was confirmed on ultrasonography and CT, and its relation to pancreatobiliary reflux could be suggested.

In the present case, pancreatobiliary reflux and associated gallbladder carcinoma were confirmed, in the absence of pancreatobiliary maljunction. Earlier detection of the pancreatobiliary reflux and progressive thickening of the gallbladder wall might have led to earlier resection of the gallbladder and improved this patient’s poor prognosis.

**REFERENCES**

1. The Japanese study group on pancreatobiliary maljunction. Diagnostic criteria of pancreatobiliary maljunction. J Hepatobiliary Pancreas Surg 1994; 1: 219-221
2. Hanada K, Itoh M, Fujii K, Tsuchida A, Hirata M, Ishimaru S, Iwao T, Eguchi N, Kajiya G. Pathology and cellular kinetics of gallbladder with an anomalous junction of the pancreaticobiliary duct. Am J Gastroenterol 1996; 91: 1007-1011
3. Tanno S, Obara T, Fujii T, Mizukami Y, Shudo R, Nishino N, Ura H, Klein-Szanto AJ, Kohgo Y. Proliferative potential and K-ras mutation in epithelial hyperplasia of the gallbladder in patients with anomalous pancreaticobiliary duct union. Cancer 1998; 83: 267-275
4. Kimura K, Ohto M, Saisho H, Unozaawa T, Tsuchiya Y, Morita M, Ebara M, Matsutani S, Okuda K. Association of gallbladder carcinoma and anomalous pancreaticobiliary ductal union. Gastroenterology 1985; 89: 1258-1265

---

**Figure 1** A: CT reveals diffuse thickening of the gallbladder wall and dilatation of the common bile duct to 14 mm; B: After 42 mo, CT reveals progressive thickening of the gallbladder wall, suspicious for gallbladder carcinoma.

**Figure 2** A: ERCP shows no pancreatobiliary maljunction, because sphincter of Oddi affected pancreatobiliary junction and connection between pancreatic and biliary ducts was not visible during the contraction phase of sphincter of Oddi; B: ERCP in the relaxation phase of sphincter of Oddi shows the length of the common channel to be 5 mm long.

**Figure 3** Histopathologic examination of the resected specimen demonstrates a moderately differentiated adenocarcinoma of the gallbladder (HE stain, × 40).
5 Yamauchi S, Koga A, Matsumoto S, Tanaka M, Nakayama F. Anomalous junction of pancreaticobiliary duct without congenital choledochal cyst: a possible risk factor for gallbladder cancer. *Am J Gastroenterol* 1987; 82: 20-24

6 Hjorth E. Contributions to the knowledge of pancreatic reflux as a factor in chronic affections of the gallbladder. *Acta Chir Scand* 1947; 96: 12-29

7 Menguy RB, Hallenbeck GA, Bollman JL, Grindlay JH. Intraductal pressures and sphincteric resistance in canine pancreatic and biliary ducts after various stimuli. *Surg Gynecol Obstet* 1958; 106: 306-320

8 Anderson MC, Hagstrom WJ Jr. A comparison of pancreatic and biliary pressures recorded simultaneously in man. *Can J Surg* 1962; 5: 461-470