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Young female with pancreaticobiliary maljunction presenting with acute pancreatitis : a case report and review of the literature

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Abstract

We report a case of pancreaticobiliary maljunction which presented with acute pancreatitis. Pancreaticobiliary maljunction and its complications are mostly observed in the Asian population. There are only few western publications concerning this subject. We reviewed the literature for current knowledge and opinions concerning the pathophysiology and optimal treatment, with special emphasis on the oncologic aspect of this condition. Those patients without a choledochal cyst should at least receive a prophylactic cholecystectomy. Firstly, to prevent further pancreatitis due to biliopancreatic reflux more or less promoted by gallbladder contraction, and secondly, more important, to prevent the occurrence of gallbladder cancer. Patients with choledochal cyst should receive a prophylactic cholecystectomy, and an excision of the extrahepatic bile duct, followed by hepaticojejunostomy. (Acta gastroenterol. belg., **2007**, 70, **363-366**).

Key words : ????

Introduction

We report a case of pancreaticobiliary maljunction, presenting in a young female adult as a first episode of mild pancreatitis. The diagnosis was made during Endoscopic Retrograde Cholangiopancreaticography (ERCP). We reviewed the literature for current knowledge and opinions concerning the pathophysiology and optimal treatment with special emphasis on the oncologic aspect of this condition.

Case report

A 20 year old female patient was admitted in our hospital for severe epigastric, stabbing and colic pain. The pain started two hours after a small breakfast. Intensity increased during the day and the patient consulted the outpatient clinic eight hours later. There was no irradiation of pain to the back or flanks. She had no knowledge of previous similar pain episodes, nor did she or her family mention any medical history. The only medication she took was an oral contraceptive once daily (cyproteronacetate 2 mg/ ethinylestradiol 0,035 mg). She drank one unit of alcohol every week, beer or wine. She smoked 15 cigarettes a day, bud did not use any other drugs. She was a student in laboratory science.

At presentation, the patient was given pethidine 50 mg intravenously to ease the pain.

Physical examination showed a girl with slim figure, normal haemodynamics and no fever. Epigastric palpation was tender with active muscle contraction. Murphy sign was negative.

Laboratory studies disclosed the following values : Amylase 3682 U/L (normal value : 28-100 U/L), Lipase 7790 U/L (normal value : 13-60 U/L), aspartate aminotransferase 94 U/L (normal value : $\leq$ 32 U/L), alanine aminotransferase 89 U/L (normal value : $\leq$ 31 U/L), γ-glutaminyl transferase 116 U/L (normal value : $\leq$ 35 U/L), alkaline phosphatase 486 U/L (normal value : $\leq$ 240 U/L), total bilirubin : 1.6 mg/dl (normal value : $\leq$ 1.00 mg/dL). Normal serum calcium, normal lipid profile, and absence of antinuclear autoantibodies or anti-neutrophil cytoplasmic autoantibodies.

A plain film of the abdomen revealed no pathology. Computed tomography (CT) showed an acute pancreatitis, CT severity index 6 (28), with enlargement of the pancreas, diffuse infiltration of the mesenterial and omental fatty tissue, and a moderate quantity of free intraperitoneal fluid. CT scan also detected dilation of the extrahepatic (9.5 mm) and intrahepatic bile ducts, but no dilation of the pancreatic ducts, choledocholithiasis or cholecystolithiasis.

Endoscopic retrograde cholangiopancreatography (ERCP) revealed a long common channel (22 mm) (Fig. 1), a dilated extrahepatic bile duct (95 mm) without a true choledochal cyst, and normal pancreatic ducts. Visualisation of the pancreatic ducts was performed when the diagnostic catheter was introduced with the tip under the biliary bifurcation and spontaneous contrast 'overflow' was seen to the pancreatic ducts. There was no evidence of choledocholithiasis. We also detected a small radicle arising from the common channel (Fig. 1). Protein plugs evacuated spontaneously during the investigation from the biliary tract through the major papilla. We established the diagnosis of pancreaticobiliary maljunction without choledochal cyst. Because of the dilated extra- and intrahepatic bile ducts and because of the protein plug evacuation we performed a sphincterotomy. After this procedure there was a fast normalisation of the biochemical abnormalities and clinical image.

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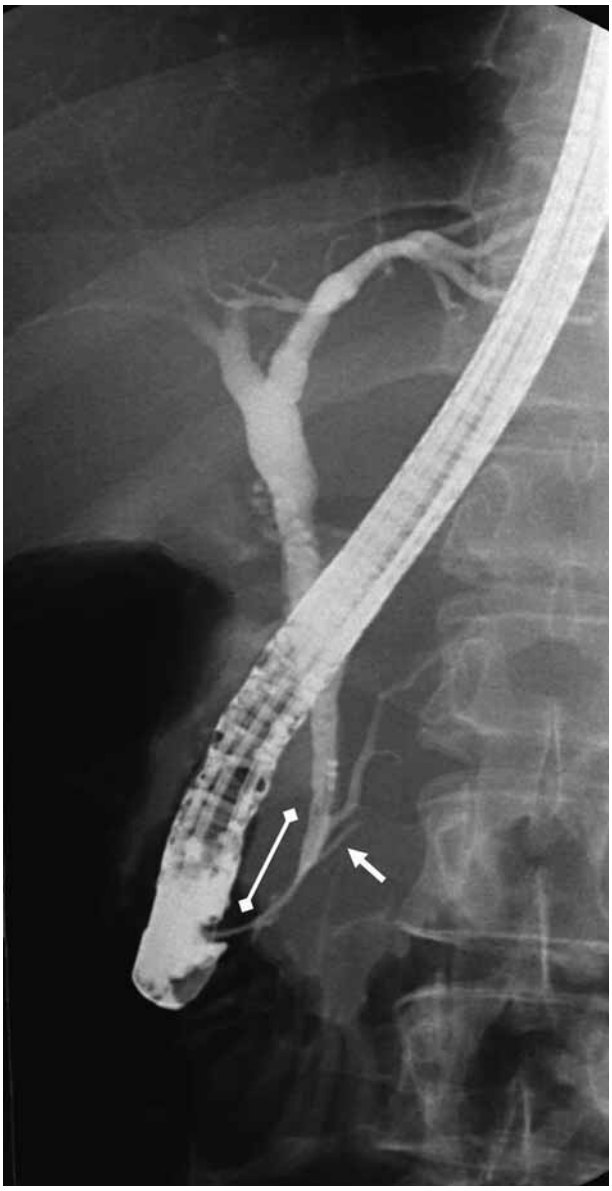

Fig. 1. — ERCP image with long common channel of 22 mm (line) and radicle (arraw).

The patient was referred to the abdominal surgeons for cholecystectomy which was performed uneventful. The patient is now six months without complaints.

Discussion

There are three ways in which the pancreatic and bile duct can open into the duodenum : separate, together or with a common channel. Pancreaticobiliary maljunction (PBM) has been defined by the Japanese Study Group on Pancreaticobiliary Maljunction (1) as a congenital anomaly in which a junction of the pancreatic and biliary duct is detected radiologically and/or anatomically outside the duodenal wall. Hence, there will be no sphincter muscle surrounding this junction (1,2), promoting free communication of pancreatic fluid and bile respectively to the biliary en pancreatic duct. PBM was first described by Babbitt in 1969 (3). It is a congenital disorder frequently associated with a choledochal cyst. Most cases have been reported in Asian countries, especially in Japan.

The embryogenic aetiology of PBM is still under discussion. Some authors believe that PBM develops because of an arrest in migration of the choledochopancreatic junction into the duodenal wall before the eight week of gestation, and that, as a result, a long common channel is formed (4,5). In contrast, Matsumoto *et al.* (5,6) proposed that PBM is caused by a disturbance in the embryonic connections (disarrangement) of the choledochopancreatic duct system in the extremely early embryo, in which the choledochal duct joins prematurely with a secondary pancreatic duct of the ventral pancreas. Therefore, they believe that in patients with PBM the “common channel” is actually the main pancreatic duct, and a true “common channel” is not formed. They also showed the presence of small pancreatic radicles arising from the “common channel” in 18% of patients with PBM (36 out of 202 patients) (6).

The distance between the junction of the ducts and the orifice of the papilla of Vater varies, ranging from 0.5 to 5 cm on direct cholangiograms (6). In 2003, a nationwide and retrospective survey in Japan was performed at which 1627 patients with PBM were detected over ten years, and 76% had developed a choledochal cyst (7). The average age was 24 years with a ratio of males to females of 1:3.2 in those patients with a choledochal cyst. Those patients without a choledochal cyst had an average age of 47 years and a ratio of males to females of 1:2.7. Yamouchi et al reported an incidence of 1.5% of PBM in patients undergoing ERCP (8).

In Western countries the disorder has also been recognized. Samavedy *et al.* (9) reported in his ERCP population an incidence of 0.25% patients with PBM. There were 13 women and 5 men ranging in age from 6 to 76 years (mean age 36 years). Of these patients 40% had developed a choledochal cyst (9).

The clinical features of PBM without a choledochal cyst include relapsing acute pancreatitis, intermittent abdominal pain, slight jaundice, and elevated risk of gallbladder cancer. When associated with a choledochal cyst, the clinical features are primary bile duct stones, acute cholangitis, including acute obstructive suppurative cholangitis, biliary stone pancreatitis ; and elevated risk of bile duct and gallbladder carcinoma (5).

In normal circumstances, pancreatic fluid is under higher hydropressure than bile fluid (10,11). Therefore, pancreatic fluid refluxes more common into the bile duct then vice versa. It can be shown by dynamic magnetic resonance cholangiopancreaticography after pancreas stimulation with secretin (12).

Opacification of the pancreatic duct during cholangiography, as seen in our patient, is an artificial situation in which dye is being injected under high pressure. However, in spite of the high pancreatic hydropressure,

biliopancreatic reflux is certainly possible in natural circumstances. This is shown by the occasionally detection of gallbladder cancer cells in the main pancreatic duct (13). Also, drip infusion cholangiography multidetector computed tomography (DIC MDCT) showed in vivo biliopancreatic reflux after yolk-induced gallbladder contraction in a patient with a long common channel (11 mm) and choledochal cyst (14). In our patient, contraction of the gallbladder with biliopancreatic reflux could have resulted in acute pancreatitis.

PBM is associated with mucosal proliferation, mucosal dysplasia and carcinogenesis of gallbladder and biliary tract (15-18). It is not known if mucosal proliferation exists from birth, or is acquired during life. Satoshi *et al.* (17) proposed that in PBM chronic irritation and damage of the gallbladder mucosa by regurgitation of pancreatic juice containing various pancreatic enzymes would result in repetitive exfoliation and regeneration, i.e., increased cell proliferation of the gallbladder mucosa. Under these conditions, certain agents, such as mutagen(s), tumour promoters, and growth factors, would trigger the conversion of the hyperplastic-growth mucosa into carcinoma in the gallbladder.

K-ras mutations in the biliary and gallbladder epithelium have been reported to be one of the important genetic alterations involved in gallbladder carcinogenesis in patients with PBM (17-20).

The nationwide and retrospective survey in Japan reported the following data concerning carcinogenesis in PBM (7) : Those developing a choledochal cyst had an 11% incidence of biliary cancer of which 65% gallbladder cancer and 34% extrahepatic bile duct cancer. Those without a choledochal cyst had a 38% risk to develop biliary cancer, almost all gallbladder cancer (93%).

Samavedy *et al.*, showed in a Western population only a 40% incidence of choledochal cyst in PBM (9). In their small series, 14% of those with choledochal cyst had gallbladder cancer, and 9% of those without a cyst (9). In two French reports three female patients were diagnosed with PBM without choledochal cyst ; all of them had gallbladder carcinoma at time of diagnosis (21,22). Inversely, 11% to 17% of patients with primary gallbladder carcinoma had PBM in two series (23,24).

In our patient the pancreaticobiliary maljunction (PBM) was nicely shown on ERCP, as was a small radicle originating from the common channel. Concordant with literature, our patient is a woman, presenting with mild pancreatitis, however not recurrent. The age of presentation is rather young, especially when the absence of a choledochal cyst is taken into account. The length of the common channel was approximately 22 mm, and during ERCP there was spontaneous evacuation of protein plugs. At presentation, we performed a sphincterotomy. We believed it would prevent bile stasis in the common duct and would promote evacuation of protein plugs. This opinion is being shared by others (9,25). Stasis of protein plugs in the long common channel are thought to be risk factor for developing pancreatitis (26,27). We also hoped to decrease biliopancreatic and pancreaticobiliary reflux by enhancing fluid evacuation this way.

In conclusion, we believe it is important to be aware of pancreaticobiliary maljunction in a young patient presenting with acute pancreatitis. Those patients without a choledochal cyst should at least receive a prophylactic cholecystectomy. Firstly, to prevent further pancreatitis due to biliopancreatic reflux more or less promoted by gallbladder contraction, and secondly to prevent the occurrence of gallbladder cancer. Patients with choledochal cyst should receive a prophylactic cholecystectomy, *and* an excision of the extrahepatic bile duct, followed by hepaticojejunostomy. It is unclear if patients without a choledochal cyst need excision of the extrahepatic bile duct. If only cholecystectomy has been performed, we believe follow up is needed. Interval, duration, and method of this follow up still needs to be cleared out.

References

1. THE JAPANESE STUDY GROUP ON PANCREATICOBILIARY MALJUNCTION. Diagnostic criteria of pancreaticobiliary maljunction. *J. Hepatobiliary Pancreat. Surg.*, 1994, **1** : 219-221.
2. SUDA K., MIYANO T., KONUMA I., MATSUMOTO M. An abnormal pancreatico-choledocho-ductal junction in cases of biliary tract carcinoma. *Cancer*, 1983, **52** : 2086-2088.
3. BABBITT D.P. Congenital choledochal cyst : new etiological concept based on anomalous relationships of common bile duct and pancreatic bulb. *Ann. Radiol.*, 1969, **12** : 231-241.
4. WONG K.C., LISTER J. Human fetal development of the hepatopancreatic duct junction. A possible explanation of congenital dilatation of the biliary tract. *J. Pediatr. Surg.*, 1981, **16** : 139-145.
5. MATSUMOTO Y., FUJII H., ITAKURA J., *et al.* Recent advances in pancreaticobiliary maljunction. *J. Hepatobiliary Pancreat. Surg.*, 2002, **9** : 45-54.
6. MATSUMOTO Y., FUJII H., ITAKURA J., MOGAKI M., MATSUDA M., MOROZUMI A., FUJINO A.M., SUDA K. Pancreaticobiliary maljunction : etiologic concepts based on radiologic aspects. *Gastrointest. Endosc.*, 2001, **53** : 614-619.
7. TASHIRO S., IMAIZUMI T., OHKAWA H., OKADA A., KATOH T., KAWAHARADA Y. *et al.* Pancreaticobiliary maljunction : retrospective and nationwide survey in Japan. *J. Hepatobiliary Pancreat. Surg.*, 2003, **10** : 345-351.
8. YAMAUCHI S., KOGA A., MATSUMOTO S., TANAKA M., NAKAYAMA F. Anomalous junction of pancreaticobiliary duct without congenital cyst, a possible risk factor for gallbladder cancer. *Am. J. Gastroenterol.*, 1987, **82** : 20-4.
9. SAMAVEDY R., SHERMAN S., LEHMAN G.A. Endoscopic therapy in anomalous pancreatobiliary duct Junction. *Gastrointest. Endosc.*, 1999, **50** : 623-7.
10. TANAKA M., IKEDA S., KAWAKAMI K., NAKAYAMA F. The presence of a positive pressure gradient from pancreatic duct to choledochal cyst demonstrated by duodenoscopic microtransducer manometry : clue to pancreaticobiliary reflux. *Endoscopy*, 1982, **14** : 45-7.
11. CARR-LOCKE D., GREGG J.A. Endoscopic manometry of pancreatic and biliary sphincter zones in man. Basal results in healthy volunteers. *Dig. Dis. Sci.*, 1981, **26** : 7-15.
12. HOSOKI T., HASUIKE Y., TAKEDA Y., MICHITA T., WATANABE Y., SAKAMORI R. *et al.* Visualization of pancreaticobiliary reflux in anomalous pancreaticobiliary junction by secretinstimulated dynamic magnetic resonance cholangiopancreatography. *Acta Radiol.*, 2004, **45** : 375-382.
13. SUDA K., MIYANO T. Bile pancreatitis. *Arch. Pathol. Lab. Med.*, 1985, **109** : 433-436.
14. SUGIYAMA M ., HARADOME H., TAKAHARA T., IZUMISATO Y., ABE N., MASAKI T., MORI T., HACHIYA J., ATOMI Y. Biliopancreatic reflux via anomalous pancreaticobiliary junction. *Surgery*, 2004, **135** : 457-9.

15. YAMAMOTO M., NAKAJO S., TAHARA E., ITO M., TANIYAMA K., SHIMAMOTO F. *et al.* Mucosal changes of the gallbladder in anomalous union with the pancreatico-biliary duct system. *Pathol. Res. Pract.*, 1991, **187** : 241-246.
16. HANADA K., ITOH M., FUJII K., TSUCHIDA A., HIRATA M., ISHIMARU S. *et al.* Pathology and cellular kinetics of gallbladder with an anomalous junction of the pancreaticobiliary duct. *Am. J. Gastroenterol.*, 1996, **91** : 1007-1011.
17. TANNO S., OBARA T., FUJII T., MIZUKAMI Y., SHUDO R., NISHINO N. *et al.* Proliferative potential and K-ras mutation in epithelial hyperplasia of the gallbladder in patients with anomalous pancreaticobiliary ductal union. *Cancer*, 1998, **83** : 267-275.
18. TSUCHIDA A., ITOI T., ENDO M., KITAMURA K., MUKAIDE M., ITOKAWA F. *et al.* Pathological features and surgical outcome of pancreaticobiliary maljunction without dilatation of the extrahepatic bile duct. *Oncol. Rep.*, 2004, **11** : 269-276.
19. OHASHI K., TSTSUMI M., NAKAJIMA Y., NAKANO H., KONISHI Y. Ki-ras point mutations and proliferation activity in biliary tract carcinomas. *Br. J. Cancer*, 1996, **74** (6) : 930-5.
20. MATSUBARA T., SAKURAI Y., SASAYAMA Y., HORI H., OCHIAI M., FUNABIKI T. *et al.* K-ras point mutations in cancerous and noncancerous biliary epithelium in patients with pancreaticobiliary maljunction. *Cancer*, 1996, **77** : 1752-1757.
21. ADHAM M., VALETTE P.J., PARTENSKY CH. Pancreaticobiliary maljunction without choledochal dilatation associated with gallbladder cancer : report of 2 European cases. *Surgery*, 2005 Nov, **138** (5) : 961.
22. TUECH J.J., PESSAUX P., AUBE C., REGENET N., CERVI C., BERGAMASCHI R., ARNAUD J.P. Cancer of the gallbladder associated with pancreaticobiliary maljunction without bile duct dilatation in a european patient. *J. Hepatobiliary Pancreat. Surg.*, 2000, **7** (3) : 336-8.
23. KIMURA K., OHTO M., SAISHO H. *et al.* Association of gallbladder carcinoma and anomalous pancreaticobiliary ductal union. *Gastroenterology*, 1985, **89** : 1258-65.
24. CHIJIIWA I.F., TANAKA M., NAKAYAMA F. Adenocarcinoma of the gallbladder associated with anomalous pancreaticobiliary ductal junction. *Am. Surg.*, 1993, **59** : 430-4.
25. NG W.D., LIU K., WONG M.K. *et al.* Endoscopic sphincterotomy in young patients with choledochal dilatation and a long common channel : a preliminary report. *Br. J. Surg.*, 1992, **79** (6) : 550-2.
26. KANEKO A., ANDO H., ITO T., WATANABE Y., SEO T., HARADA T. *et al.* Protein plugs cause symptoms in patients with choledochal cysts. *Am. J. Gastroenterol.*, 1997, **92** : 1018-1021.
27. OCHIAI K., KANEKO K., KITAGAWA M., ANDO H., HAYAKAWA T. Activated pancreatic enzyme and pancreatic stone protein (PSP/reg) in bile of patients with pancreaticobiliary maljunction/ choledochal cysts. *Dig. Dis. Sci.*, 2004, **49** (11-12) : 1953-6.
28. MORTEL KJ., WIESNER W., INTRIERE L. A Modified CT Severity Index for Evaluating Acute Pancreatitis : Improved Correlation with patient outcome. *Am. J. Roentgenol.*, 2004, **183** : 1261-1265.