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Case Report

Intraductal Papillary Neoplasm of the Bile Duct With Invasive Adenocarcinoma Complicating IgG4-related Sclerosing Cholangitis: Report of a Case

Ryo Ashida[1], Teiichi Sugiura[1], Yukiyasu Okamura[1], Takaaki Ito[1], Keiko Sasaki[2], Yasuni Nakanuma[2], and Katsuhiko Uesaka[1]

[1]*Division of Hepato-Biliary-Pancreatic Surgery, and* [2]*Division of Pathology, Shizuoka Cancer Center, Shizuoka, Japan*

Although there have been many previous studies of IgG4-related SC focusing on the differential diagnosis from cholangiocarcinoma, only a few patients with cholangiocarcinoma against a background of IgG4-related SC have been reported. We herein present a case of intraductal papillary neoplasm of the bile duct (IPNB) associated with invasive carcinoma complicating IgG4-related sclerosing cholangitis. A 71-year-old female with icterus was admitted to a local hospital, where stricture of the extrahepatic bile duct were detected, and subsequently referred to our hospital for possible surgery. Abdominal multidetector-row computed tomography demonstrated marked wall thickening along the entire extrahepatic bile duct. The left lateral superior bile duct (B2) and left lateral inferior duct (B3) were individually obstructed, and percutaneous transhepatic biliary drainage catheters were placed in B2 and B3 separately. The patient was diagnosed to have diffusely spread cholangiocarcinoma and underwent right hepatic trisectionectomy with caudate lobectomy and pancreatoduodenectomy. A histological examination revealed intraductal papillary tumors composed of fibrovascular stalks covered by neoplastic epithelium. Carcinomatous invasion of the papillary tumors was observed in the fibromuscular layer, and there was abundant infiltration of inflammatory cells with fibrosis outside of the cancerous tissue. The inflammatory cells were primarily composed of plasma cells, a majority of which were positive for IgG4 (>30 cells/high-power field); the postoperative serum IgG4 level was 890 mg/dL. Therefore, a diagnosis of

Reprint requests: Katsuhiko Uesaka, MD, Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center, Shizuoka, Japan, 1007, Shimo-Nagakubo, Sunto-Nagaizumi, Shizuoka, Japan, 411-8777.
Tel.: +81 55 989 5222; Fax: +81 55 989 5551; E-mail: k.uesaka@scchr.jp

coexisting IPNB associated with invasive carcinoma and IgG4-related sclerosing cholangitis was made. To the best of our knowledge, this is the first report of IPNB complicating IgG4-related sclerosing cholangitis.

Key words: Intraductal papillary neoplasm of the bile duct – IgG4-related sclerosing cholangitis – Cholangiocarcinoma

Immunoglobulin G4 (IgG4)–related sclerosing cholangitis (SC) is a rare benign disease, characterized by the presence of localized or diffuse biliary stricture and a high serum IgG4 concentration.[1] Pathological studies show abundant infiltration of IgG4-positive plasma cells in the bile duct wall, as seen in the pancreas in patients with autoimmune pancreatitis (AIP).[2] Recently, IgG4-related SC has been recognized to be a biliary manifestation of IgG4-related systemic disease and often accompanies AIP.[2]

There have been many previous studies of IgG4-related SC focusing on the differential diagnosis from cholangiocarcinoma,[3–7] as these 2 separate entities present with similar imaging findings and clinical symptoms. Although some cases of pancreatic cancer[8] or intraductal papillary mucinous neoplasm (IPMN) of the pancreas[9–11] associated with AIP have been described, only a few patients with cholangiocarcinoma against a background of IgG4-related SC have been reported.[12–14] We herein describe the first case of a diffusely spread intraductal papillary neoplasm of the bile duct (IPNB) and IgG4-related SC without accompanying AIP that was treated with radical hepatopancreatoduodenectomy.

Case Report

A 71-year-old female with icterus was admitted to a local hospital, where obstructive jaundice and stricture of the extrahepatic bile duct were detected, and she was subsequently referred to our hospital for possible surgery. The serum carbohydrate antigen 19-9 level was elevated at 1102 U/mL, although the serum carcinoembryonic antigen level was within the standard range (1.7 ng/mL). Abdominal multidetector-row computed tomography demonstrated marked wall thickening of the entire extrahepatic bile duct as well as perihilar duct. The intrahepatic segmental and sectional bile ducts—including the left lateral superior (B2), left lateral inferior (B3), left medial, right anterior superior ventral, right anterior superior dorsal, and right posterior ducts—were individually obstructed with proximal dilatation (Fig. 1); percutaneous transhepatic biliary drainage (PTBD) catheters were separately placed in B2 and B3. Cholangiography showed biliary stricture over a wide area between the distal and perihilar ducts. Biliary cytology obtained via the PTBD catheters confirmed the presence of adenocarcinoma cells. Under a preoperative diagnosis of diffusely spread cholangiocarcinoma, right hepatic trisectionectomy with caudate lobectomy and pancreatoduodenectomy was carried out following portal vein embolization of the right trisection.

Grossly, diffuse thickening of the extrahepatic bile duct wall and prominent intraluminal coalescent papillary protrusions measuring 55 mm in length were found to be distributed from the distal bile duct to the perihilar duct in the resected specimen (Fig. 2).

Microscopically, papillary protrusions were densely arranged papillae, measuring 7 to 9 mm in height, composed of fibrovascular stalks covered by cuboidal or columnar neoplastic epithelium (Fig. 3a). The epithelium constituted a well-differentiated carcinoma of the pancreatobiliary phenotype arranged in a single layer (Fig. 3b), with multilayering and nuclear atypia observed in some parts (Fig. 3b). Carcinomatous invasion from papillary neoplasia was focally observed in the fibromuscular layer of the extrahepatic bile duct (Fig. 3c), although it did not reach the pancreatic parenchyma or periductal connective tissue. These features were compatible with a diagnosis of intraductal papillary neoplasm of the bile duct (IPNB) associated with invasive carcinoma.[15] Extensive superficial spread of noninvasive cancer cells from the papillary tumors to the perihilar regions (Fig. 3d), proximally and near the papilla of Vater distally, were detected. The fibrovascular stalks with variable lymphoplasmacytic infiltration observed in the neoplastic papillae were relatively fine on the apical side, while, in the deeper areas, the stalks became wider due to the infiltration of dense inflammatory cells (Fig. 3a).

There was also moderate to marked infiltration of inflammatory cells with fibrosis and lymphoid

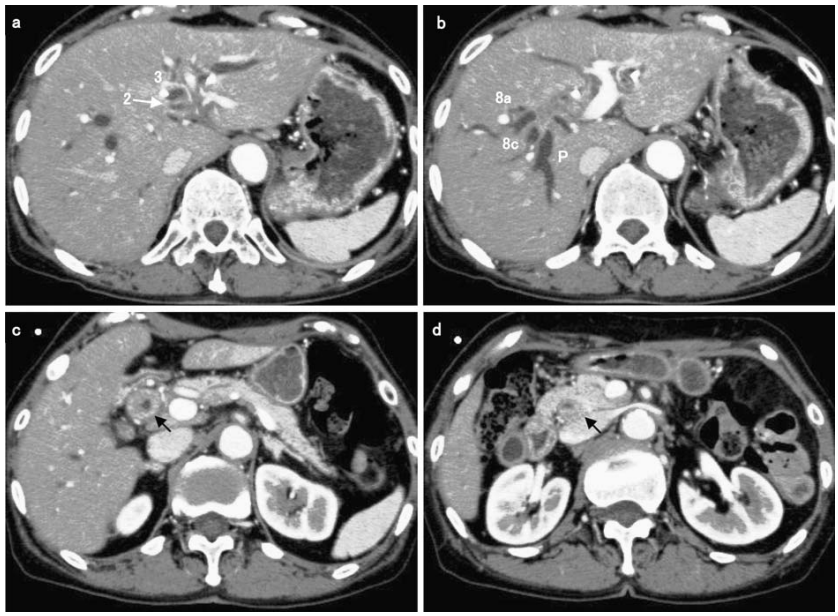

Fig. 1 Abdominal multidetector-row computed tomography. (a) The left lateral superior (B2) and left lateral inferior (B3) bile ducts are individually obstructed with proximal dilatation. (b) The right anterior superior ventral (8a), right anterior superior dorsal (8c), and right posterior bile ducts (P) are individually obstructed with proximal dilatation. (c) Marked wall thickening of the extrahepatic bile duct (arrow). (d) Marked wall thickening of the intrapancreatic bile duct (arrow).

follicle formation outside the cancerous tissue (Fig. 3c), continuous with inflammatory changes in the tumor. In addition, fibroinflammatory lesions extended from the papilla of Vater to the intrahepatic large bile ducts. The inflammatory cells were primarily composed of plasma cells and lymphocytes with occasional eosinophils (Fig. 3e), the majority of which were positive for IgG4 [>30 cells/high-power field (HPF)], with an IgG4/IgG ratio of more than 40% in both the tumor and fibroinflammatory lesions outside of the tumor (Fig. 3f). Storiform fibrosis and obliterative phlebitis were also noted (Fig. 3g). The fibroinflammatory lesions in the bile ducts were compatible with IgG4-related SC.[1] Lymphoplasmacytic infiltration with predominant IgG4 plasma cells extended into the pancreas, primarily around the pancreatic branch ducts with focal parenchymal involvement (Fig. 4), as well as in the liver, mainly around the intrahepatic large bile ducts and peribiliary glands at the hepatic hilus (Fig. 3d). Based on these findings, the patient was diagnosed to have IPNB associated with invasive carcinoma, pT1N0M0, stage IA, according to the UICC classification, and coexistent with IgG4-related SC. The resected margins in B2 and B3 were free from cancer cells.

The serum IgG4 concentration (normal range, 4.8–105 mg/dL) was measured postoperatively, with the following results: 890 mg/dL at 2 months, 256 mg/dL at 11 months, 310 mg/dL at 14 months, 289 mg/dL at 17 months and 291 mg/dL at 26 months. Positron emission tomography using fluorodeoxyglucose performed 2 months after surgery disclosed no sites of abnormal accumulation. The patient did not receive either adjuvant chemotherapy or steroids postoperatively and is currently doing well without any signs of relapse of IPNB

Fig. 2 Gross findings of the bile duct lesions in the resected specimen. Intraluminal coalescent papillary protrusions from the distal duct to the perihilar duct are grossly identifiable. The resected stumps of the left lateral superior (B2) and left lateral inferior (B3) bile ducts are free from the papillary tumor (broken lines).

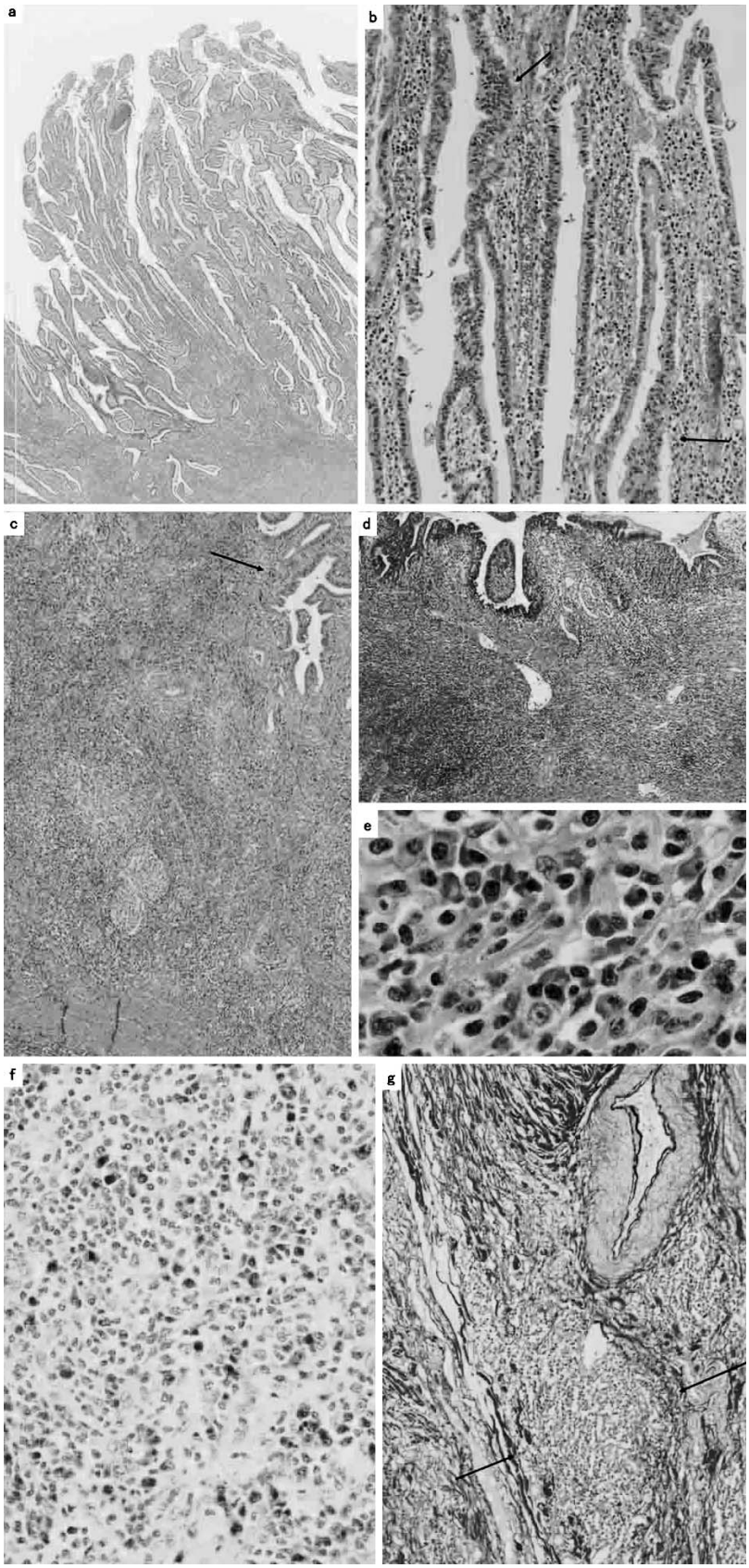

Fig. 3 Microscopic findings of the bile duct. (a) The papillary neoplasm is composed of fibrovascular stalks covered by a single layer of neoplastic epithelium. The stalks on the apical side are fine, while those in deeper areas are thick due to the presence of lymphoplasmacytic infiltration [hematoxylin and eosin (H&E); original magnification, ×50]. (b) The neoplastic epithelium in the majority of the papillae is cuboidal or low columnar and arranged in a single layer, with multilayered areas in some parts (H&E; original magnification, ×100). (c) There is dense lymphoplasmacytic infiltration with lymph follicle formation and fibrosis around the papillary tumor of the extrahepatic bile duct. The arrow denotes the infiltration of cancer cells (H&E; original magnification, ×50). (d) Superficial spread of noninvasive cancer cells from the papillary neoplasm is noted in the intrahepatic large bile duct. Dense lymphoplasmacytic infiltration and fibrosis are observed in the deeper layer of the bile duct (H&E; original magnification, ×120). (e) Many plasma cells and lymphocytes with occasional eosinophils are found in the bile duct wall around the papillary lesions (H&E; original magnification, ×400). (f) Immunohistochemical study showing positive immunoreactivity for IgG4 in the plasma cells. Many of the plasma cells are IgG4-positive (original magnification, ×250). (g) Obliterative phlebitis (arrows) in the vicinity of an artery is observed on Elastica van Gieson staining (original magnification, ×300).

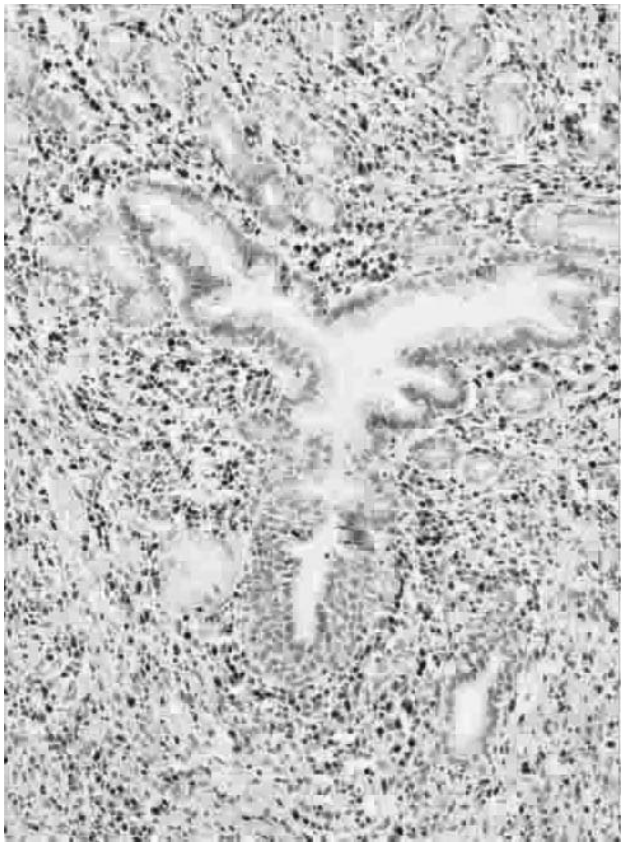

Fig. 4 Microscopic findings of the pancreas. Marked lymphoplasmacytic infiltration is observed around the branch pancreatic duct. A majority of these cells were positive for IgG4 (original magnification, ×300).

associated with invasive carcinoma or IgG4-related disease 26 months after the operation.

Discussion

Immunoglobulin G4–related sclerosing cholangitis, first described by Zen *et al*[2] in 2004, belongs to the same disease entity as AIP, and is considered to be a biliary manifestation of IgG4-related systemic disease. Ohara *et al*[1] proposed clinical diagnostic criteria for IgG4-related SC in 2012. These criteria consist of 4 diagnostic items: images of the biliary tract, an elevated serum IgG4 concentration (>135 mg/dL), the coexistence of other IgG4-related diseases (such as AIP), and histopathological findings. The characteristic microscopic findings include: (1) marked lymphocytic and plasmacytic infiltration and fibrosis; (2) IgG4-positive plasma cell infiltration (>10 cells/HPF); (3) storiform fibrosis; and (4) obliterative phlebitis. The fulfillment of (1) + (2) + (3) or (1) + (2) + (4) is sufficient pathologically for a definitive diagnosis of IgG4-related SC. In the present case, the pathological examination showed all four characteristic findings in the bile duct wall, and the present case thus satisfied the diagnostic criteria for IgG4-related SC. Although IgG4-positive cells were also found in the pancreas, the present patient did not satisfy the diagnostic criteria for AIP.[16]

Several studies have described various degrees of IgG4-positive plasma cell infiltration in cases of cholangiocarcinoma. For example, Kimura *et al*[17] and Harada *et al*[18] reported that 37–43% of cholangiocarcinoma cases involve >10 IgG4-positive cells/HPF in and around cancerous nests. Kimura *et al*[17] also reported that IgG4-positive plasma cells are prominent in the invasive area facing the noncancerous bile duct wall and in the surrounding fibroadipose tissue; and that the perineural infiltration of IgG4-positive cells was common, whereas obliterative phlebitis and storiform fibrosis are rarely seen in patients with cholangiocarcinoma. Meanwhile, Harada *et al*[18] emphasized the close association between IgG4 reactions in cases of cholangiocarcinoma and the interleukin (IL)-10–predominant regulatory cytokine milieu induced by cancer cells themselves both directly and indirectly. The authors also described that the IgG4 reactions observed in patients with cholangiocarcinoma may reflect evasion from immunosurveillance, as IL-10 plays a primary role in suppressing immune responses. Interestingly, Kimura *et al*[17] reported a poorer prognosis among cholangiocarcinoma patients with >20 IgG4-positive cells/HPF than those with <20 cells, which may confirm the legitimacy of the above description provided by Harada *et al*.[18]

We considered that the prominent infiltration of IgG4-positive plasma cells detected in the present case was primarily caused by IgG4-related SC rather than IgG4 reactions in the setting of IPNB because the patient satisfied the diagnostic criteria for IgG4-related SC proposed by Ohara *et al*.[1] The present case involved both obliterative phlebitis and storiform fibrosis microscopically, which are rarely seen in cases of cholangiocarcinoma, and lacked the perineural infiltration of IgG4-positive cells, which is commonly detected in cholangiocarcinoma patients. In addition, the persistently high serum IgG4 concentration of >200 mg/dL observed even after the complete removal of the IPNB lesion associated with invasive carcinoma strongly suggested the presence of IgG4-related systemic disease, although

any such disease has remained clinically dormant since surgery.

Chronic biliary inflammation and cholestasis are known risk factors for cholangiocarcinoma.[19] In particular, the development of intrahepatic cholangiocarcinoma in patients with primary sclerosing cholangitis is well documented.[20] In contrast, only 3 cases of cholangiocarcinoma accompanying IgG4-related SC have been previously reported in the English literature. Among them, 2 patients with extrahepatic cholangiocarcinoma[12,13] had AIP, while 1 patient with intrahepatic cholangiocarcinoma[14] did not. Recently, several cases of IPMN of the pancreas, which shares common histologic and phenotypic features with IPNB,[21,22] have been reported to be associated with AIP.[9–11] However, the relationship between IPMN and AIP in these cases was considered to be coincidental.[9–11] Another recent study demonstrated significant and frequent K-*ras* mutations in the pancreas, bile duct, and gallbladder in patients with AIP, which suggests that AIP may be a risk factor for pancreatobiliary cancer.[23] However, it remains unknown whether the same mechanism works in the bile duct in patients with IgG4-related SC, and this issue should be investigated in the future.

In conclusion, to the best of our knowledge, this is the first report of IPNB associated with invasive carcinoma complicating IgG4-related SC without AIP. It is necessary to accumulate more cases in order to investigate the cause-and-effect relationship between IgG4-related SC and cholangiocarcinoma or IPNB as well as assess the dissimilarities between IgG4-related SC and IgG4 reactions in patients with bile duct malignancies.

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References

1. Ohara H, Okazaki K, Tsubouchi H, Inui K, Kawa S, Kamisawa T *et al*. Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. *J Hepatobiliary Pancreat Sci* 2012;**19**(5):536–542
2. Zen Y, Harada K, Sasaki M, Sato Y, Tsuneyama K, Haratake J *et al*. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis. *Am J Surg Pathol* 2004; **28**(9):1193–1203
3. Chung DT, Tang CN, Lai EC, Yang GP, Li MK. Immunoglobulin G4-associated sclerosing cholangitis mimicking cholangiocarcinoma. *Hong Kong Med J* 2010;**16**(2):149–152
4. Maeda M, Shimada K. A case of IgG4-related sclerosing cholangitis mimicking an intrahepatic cholangiocellular carcinoma. *Jpn J Clin Oncol* 2012;**42**(2):153
5. Erdogan D, Kloek JJ, ten Kate FJ, Rauws EA, Busch OR, Gouma DJ *et al*. Immunoglobulin G4-related sclerosing cholangitis in patients resected for presumed malignant bile duct strictures. *Br J Surg* 2008;**95**(6):727–734
6. Kim JH, Byun JH, Lee SJ, Park SH, Kim HJ, Lee SS *et al*. Differential diagnosis of sclerosing cholangitis with autoimmune pancreatitis and periductal infiltrating cancer in the common bile duct at dynamic CT, endoscopic retrograde cholangiography and MR cholangiography. *Eur Radiol* 2012; **22**(11):2502–2513
7. Tabata T, Kamisawa T, Hara S, Kuruma S, Chiba K, Kuwata G *et al*. Differentiating immunoglobulin g4-related sclerosing cholangitis from hilar cholangiocarcinoma. *Gut Liver* 2013;**7**(2): 234–238
8. Loos M, Esposito I, Hedderich DM, Ludwig L, Fingerle A, Friess H *et al*. Autoimmune pancreatitis complicated by carcinoma of the pancreatobiliary system. *Pancreas* 2011; **40**(1):151–154
9. Tabata T, Kamisawa T, Hara S, Kuruma S, Chiba K, Kuwata G *et al*. Intraductal papillary mucinous neoplasm of the pancreas and IgG4-related disease. *Pancreatology* 2013;**13**(4):379–383
10. Bateman AC, Culver EL, Sommerlad M, Chetty R. Intraductal papillary mucinous neoplasm of the pancreas: a tumor linked with IgG4-related disease? *J Clin Pathol* 2013;**66**(8):671–675
11. Vaquero EC, Salcedo MT, Cuatrecasas M, De León H, Merino X, Navarro S *et al*. Autoimmune pancreatitis type-1 associated with intraductal papillary mucinous neoplasm: report of two cases. *Pancreatology* 2014;**14**(4):316–318
12. Oh H-C, Kim J G, Kim J W, Lee KS, Kim MK, Chi KC *et al*. Early bile duct cancer in a background of sclerosing cholangitis and autoimmune pancreatitis. *Inter Med* 2008; **47**(23):2025–2028
13. Douhara A, Mitoro A, Otani E, Furukawa M, Kaji K, Uejima M *et al*. Cholangiocarcinoma developed in a patient with IgG4-related disease. *World J Gastrointest Oncol* 2013;**5**(8):181–185
14. Straub BK, Esposito I, Gotthardt D, Radeleff B, Antolovic D, Flechtenmacher C *et al*. IgG4-associated cholangitis with cholangiocarcinoma. *Virchows Arch* 2011;**458**(6):761–765
15. Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. *WHO Classification of Tumors of the Digestive System*. 4th ed. Lyon, France: IRC Press, 2010
16. Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M *et al*. International consensus diagnostic

criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas*. 2011; **40**(3):352–358

17. Kimura Y, Harada K. Nakanuma Y. Pathologic significance of immunoglobulin G4-positive plasma cells in extrahepatic cholangiocarcinoma. *Human Pathology* 2012;**43**(12):2149–2156
18. Harada K, Shimoda S, Kimura Y, Sato Y, Ikeda H, Igarashi S *et al*. Significance of immunoglobulin G4 (IgG4)-positive cells in extrahepatic cholangiocarcinoma: molecular mechanism of IgG4 reaction in cancer tissue. *Hepatology* 2012;**56**(1):157–164
19. Lazaridis KN, Gores GJ. Cholangiocarcinoma. *Gastroenterology* 2005;**128**(6):1655–1667
20. Bergquist A, Ekbom A, Olsson R, Kornfeldt D, Lööf L, Danielsson A *et al*. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. *J Hepatol* 2002;**36**(3):321–327
21. Nakanuma Y. A novel approach to biliary tract pathology based on similarities to pancreatic counterparts: is the biliary tract an incomplete pancreas? *Payhol Int* 2010;**60**(6):419–429
22. Rocha FG, Lee H, Katabi N, DeMatteo RP, Fong Y, D'Angelica MI *et al*. Intraductal papillary neoplasm of the bile duct: a biliary equivalent to intraductal papillary mucinous neoplasm of the pancreas? *Hepatology* 2012;**56**(4):1352–1360
23. Kamisawa T, Tsuruta K, Okamoto A, Horiguchi S, Hayashi Y, Yun X *et al*. Frequent and significant K-ras mutation in the pancreas, the bile duct, and the gallbladder in autoimmune pancreatitis. *Pancreas* 2009;**38**(8):890–895