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【 CASE REPORT 】

A Resected Case of Follicular Cholangitis That Was Positive on ^{18}F-fluorodeoxyglucose-positron Emission Tomography

Takashi Kosone[1], Hitoshi Takagi[1], Satoshi Takakusagi[1], Takashi Hoshino[2], Yozo Yokoyama[1], Kazuko Kizawa[1], Kyoko Marubashi[1], Akira Watanabe[3], Kenichiro Araki[3], Norifumi Harimoto[3], Hayato Ikota[4], Ken Shirabe[3], Kenichi Harada[5], Satoru Kakizaki[6] and Toshio Uraoka[6]

Abstract:
We experienced a case of follicular cholangitis that was positive on fluorodeoxyglucose-positron emission tomography (^{18}F-FDG-PET). A 70-year-old man was admitted for jaundice. Endoscopic retrograde cholangiography showed stenosis of the middle to upper choledocus. ^{18}F-FDG-PET depicted a localized hot spot at the stenotic lesion (maximum standardized uptake value = 8.2). Although no malignant findings were found in the cytology or on a bile duct biopsy, malignancy could not be excluded, so surgical treatment was performed. Follicular cholangitis is a new, rare disease that causes severe biliary stricture. Only 11 cases of follicular cholangitis have been reported, including the present case.

Key words: follicular cholangitis, ^{18}F-FDG-PET, cholangiocarcinoma, biliary stricture

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Introduction

Follicular cholangitis is a new, rare disease that causes severe biliary stricture. Since Aoki et al. first reported it in 2003 (1), only 10 cases of follicular cholangitis have been reported (1-7). The imaging findings include segmental stricture of the bile duct with dilatation of the peripheral bile duct. The disease is often difficult to distinguish from cholangiocarcinoma or autoimmune biliary diseases, such as primary sclerosing cholangitis (PSC) and immunoglobulin (Ig) G4-related sclerosing cholangitis. Although biliary stricture caused by follicular cholangitis is benign, it is usually difficult to diagnose preoperatively (6, 7). ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) is useful and usually used for the differential diagnosis of malignant tumors. However, there is no information concerning the ^{18}F-FDG-PET findings for follicular cholangitis.

We herein report a case of follicular cholangitis with severe biliary stricture reminiscent of choledocus cancer that showed positive findings on ^{18}F-FDG-PET. Several previous reports are mentioned in the discussion.

Case Report

A 70-year-old man was admitted to our hospital for jaundice. He had been receiving medication for diabetes mellitus and hypertension for several years. He had no history of surgery or blood transfusion. His family history was not specific. He had noticed epigastric discomfort and back pain one month earlier.

Laboratory data on admission (Table 1) showed elevated biliary enzymes with a total bilirubin level of 3.5 mg/dL and mild inflammatory reaction. The tumor markers of carcinoembryonic antigen (CEA), CA19-9, SPAN-1, and DUPAN-2 were all in the normal range. IgG and IgG4 were

[1]Department of Gastroenterology and Hepatology, Kusunoki Hospital, Japan, [2]Department of Gastroenterology and Hepatology, Takasaki General Medical Center, Japan, [3]Department of General Surgical Science, Gunma University Graduate School of Medicine, Japan, [4]Department of Human Pathology, Gunma University Graduate School of Medicine, Japan, [5]Department of Human Pathology, Kanazawa University Graduate School of Medicine, Japan and [6]Department of Gastroenterology and Hepatology, Gunma University Graduate School of Medicine, Japan
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Correspondence to Dr. Satoru Kakizaki, kakizaki@gunma-u.ac.jp

Table 1. The Laboratory Data on Admission.

Hematological analyses		Blood chemistry	
WBC	4,940 /μL	TP	7.4 g/dL
RBC	442×10⁴ /μL	Alb	4.1 g/dL
Hb	13.4 g/dL	T.Bil	3.5 mg/dL
Hct	40.5 %	D.Bil	2.1 mg/dL
Platelet count	21.2×10⁴ /μL	AST	198 U/L
		ALT	278 U/L
Tumor marker		LDH	259 U/L
CEA	1.1 ng/mL	ALP	929 U/L
CA19-9	39 U/mL	γ-GTP	285 U/L
DUPAN-2	76 U/mL	AMY	93 U/L
SPAN-1	18.2 U/mL	BUN	19.7 mg/dL
		Cr	0.9 mg/dL
Immunological test		Na	139 mEq/L
IgG	1434 mg/dL	K	4.4 mEq/L
IgG4	48 mg/dL	Cl	102 mEq/L
ANA	negative	LDL-C	58 mg/dL
		TG	121 mg/dL
		CRP	1.22 mg/dL

CEA: carcino embryonic antigen, CA19-9: carbohydrate antigen 19-9, ANA: antinuclear antibody

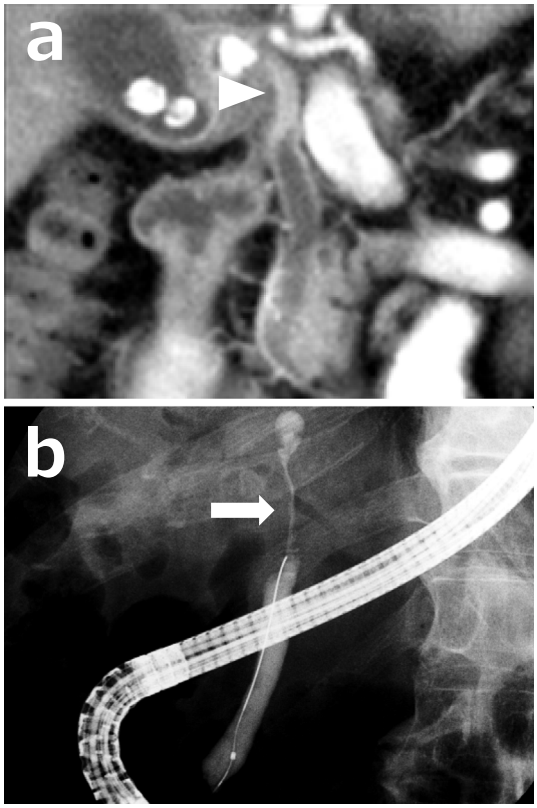

Figure 1. a: Computed tomography demonstrated the stenosis of the upper part of the choledocus. b: Endoscopic retrograde cholangiography showed the stenotic lesion at the upper part of the choledocus.

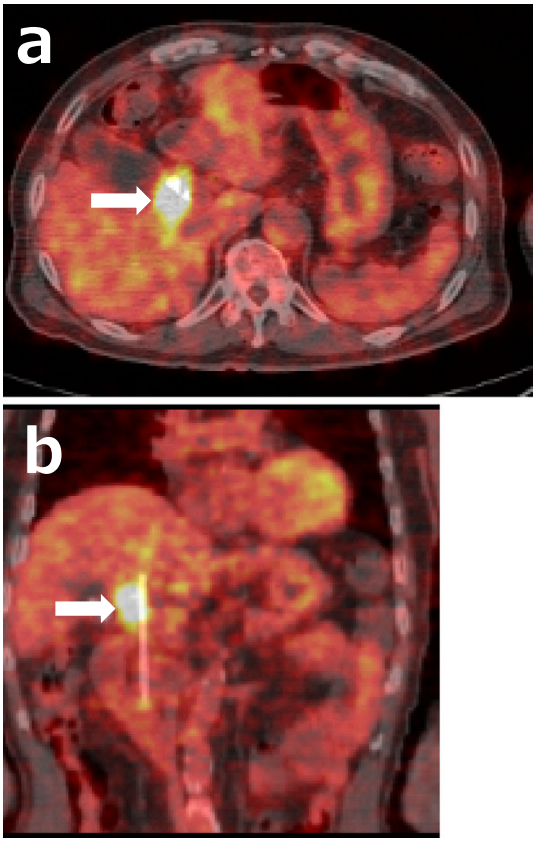

Figure 2. ^{18}F-FDG-PET demonstrated a localized hot spot (SUV_{max}=8.2) at the upper choledocus without any other organ accumulation.

also within normal limits, and the patient's serum was negative for antinuclear antibodies (ANA). Abdominal computed tomography (CT) (Fig. 1a) demonstrated narrowing of the upper bile duct (arrowhead). Endoscopic retrograde cholangiography (ERC) showed stenosis of the middle to upper choledocus (Fig. 1b). A drainage tube was inserted into the bile duct via the papilla of Vater up to the left intrahepatic bile duct. A simultaneous biliary biopsy demonstrated mucoepithelial erosion and regenerative dysplasia with a high degree of inflammatory cell infiltration but no malignant changes (data not shown). Brushing cytology of the stenotic lesion showed no malignant cells. ^{18}F-FDG-PET (Fig. 2) depicted a localized hot spot at the stenotic lesion of the bile duct [maximum standardized uptake value (SUV_{max}) = 8.2] with no other accumulation noted. This accumulation closely resembled malignant accumulation.

Although no malignant findings were found in the cytology or on a bile duct biopsy performed at ERC, malignancy could not be fully excluded. He was therefore transferred to another hospital for surgical treatment. ERC was performed again, and the drainage tube was replaced with an endoscopic nasobiliary drainage (ENBD) tube. A biliary biopsy and brushing cytology of the stenotic lesion were performed again. Cytological analyses of bile juice obtained from the ENBD were performed four times. In total, a biliary biopsy was performed twice, brushing cytology was performed twice, and bile juice cytology was performed four times; all analyses were negative for malignancy. Magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatogra-

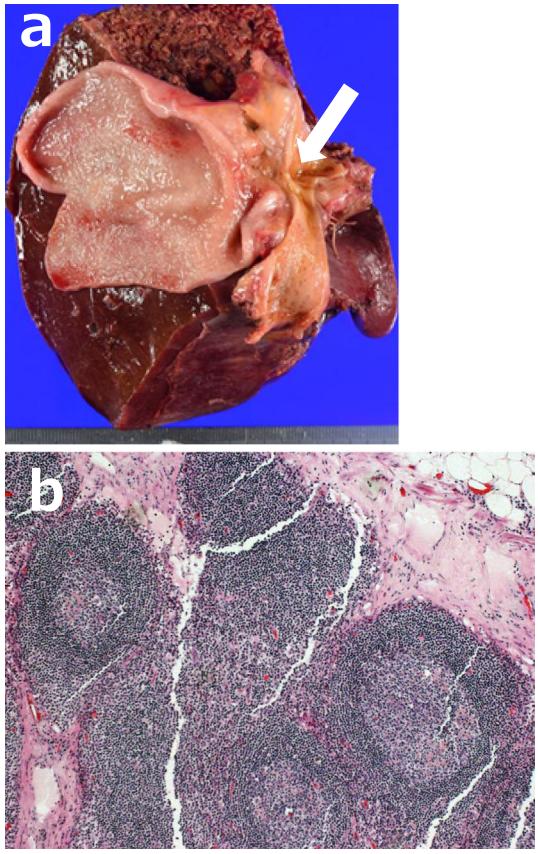

Figure 3. **a: Macroscopic appearance of the resected specimen showed upper bile duct fibrotic stenosis without an obvious solid tumor. b: A microscopic examination revealed follicular cholangitis accompanied by a germinal center (Hematoxylin and Eosin staining).**

phy (MRCP) showed wall thickening and enhancement in the hilar bile duct. Stenosis of the hilar bile duct and dilatation of the upper intrahepatic bile ducts were observed. It was assumed that cholangiocarcinoma had invaded the gallbladder neck, gallbladder duct, and right hepatic duct.

Although cytology and the biopsy revealed no malignant findings, we suspected hilar cholangiocarcinoma based on the imaging findings. On multidetector CT, wall thickening and stenosis were found to have extended to the main left hepatic duct and secondary branch of the right hepatic duct. The preoperative diagnosis was hilar cholangiocarcinoma with Bismuth Type IIIa (8). After percutaneous transhepatic portal vein embolization (PTPE) to increase future remnant liver volume, right hepatic and caudate lobectomy with extrahepatic bile duct resection were performed. The surgical macroscopic findings (Fig. 3a) demonstrated fibrotic stenosis of the upper bile duct with multiple lymphoid follicles (Fig. 3b). Histological features of PSC, such as an onion skin appearance, were not detected in the resected specimen. An immunohistological study showed little staining for IgG4 (Fig. 4, a: IgG1 as control, b: IgG4), suggesting that the disease is an independent entity from IgG4-related sclerosing cholangitis. Immunostaining for CD10 (Fig. 4c) detecting lymphoid cells and MIB-1 (Fig. 4d) was positive. Maspin (Fig. 4e) and p53 (Fig. 4f) as cancer markers were negative. The patient was ultimately diagnosed with follicular cholangitis.

The subsequent course of this case was good without recurrence of biliary stricture or adverse events for two and a half years after the surgery.

Discussion

Benign biliary strictures can be caused by various disorders, including immune-mediated disorders, such as PSC and IgG4-related disease; iatrogenic factors, including surgery and radiation; and choledocolithiasis, sphincter Oddi dysfunction, pancreatitis, Mirizzi syndrome, vascular, infection, and other rare diseases, such as follicular cholangitis (9). Their clinical features often mimic malignancies, despite their benign nature. Even though numerous testing modalities have been developed, the underling etiology of up to 20% of cases remains unclear (10). The preoperative diagnosis of biliary stricture is sometimes difficult. Some resected cases (2.8%) that were preoperatively diagnosed as cholangiocarcinoma have been reported to be benign (11).

Follicular cholangitis is a new entity similar to IgG4-related cholangitis (12). Since the first report by Aoki et al. in 2003 (1), only 11 cases, including the present case, have been reported (1-7). Follicular cholangitis is characterized by severe stricture and dilatation of the peripheral bile duct (1-7). Although the stricture is caused by benign inflammation (6, 7), it mimics cholangiocarcinoma and is sometimes misdiagnosed as cholangiocarcinoma (1-5, 7). The lesions are usually localized at the proximal extrahepatic bile duct and hepatic hilum (1). The histological findings typically show dense fibrosis under the mucosal layer and severe inflammation of the peribiliary glands (7). The inflammatory cells are mostly composed of lymphocytes and plasma cells that form lymphoid follicles containing germinal centers (7). The lymphocytes infiltrating the peribiliary glands are reported to be positive for cell markers, including CD3, CD4, CD8, CD20, and CD79a (3, 4, 6). The germinal centers are negative for Bcl-2, indicating that the follicles are reactive and hyperplastic (7). IgG4-positive cells are few in number or not detected (3, 5, 6); this disease is an independent entity from IgG4-related sclerosing cholangitis (5). It is not complicated with obliterative phlebitis (7). MIB-1 is a representative cell growth marker (13) and was positively stained in the present case. Maspin and p53 staining were negative in our case, and the biliary stricture was thus diagnosed as benign. Maspin and p53 double staining are useful for detecting malignancy, especially cholangiocarcinoma (14).

Only 11 cases of follicular cholangitis (Table 2) have been reported, including the present case (1-7). The disease generally occurs in middle-aged patients with no history of autoimmune disease (1-7). No clear sex predominance has been reported. Patients typically show symptoms such as elevated liver enzymes, abdominal pain, or jaundice. All

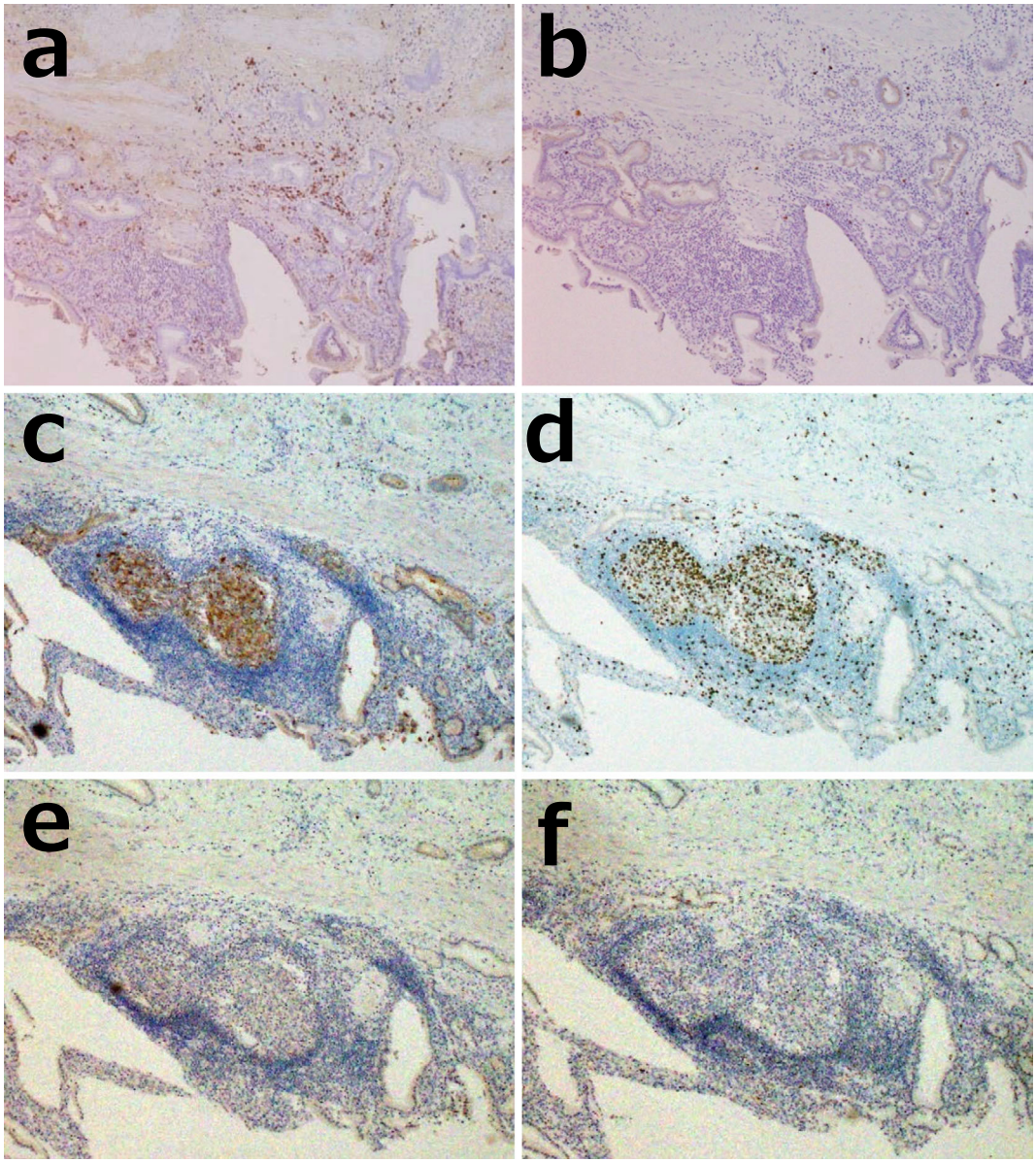

Figure 4. **Immunostaining of the stenotic lesion of the choledocus. a: IgG1 staining as control, b: IgG4 staining, very few IgG4-positive cells were observed. c: CD10 staining showed lymphoid cells, d: MIB-1staining was positive, e: Maspin staining and p53 staining (f) were negative.**

seven cases tested for ANA were negative. Distinguishing follicular cholangitis from cholangiocarcinoma is difficult. All 11 cases were surgically treated because malignancy could not be ruled out based on the findings of the preoperative assessment (1-7, 15, 16). Saito et al. reported a case of follicular cholangitis in which hepatectomy was performed after the eight-year follow-up of biliary stricture (6).

The present case was preoperatively diagnosed as hilar cholangiocarcinoma with Bismuth Type IIIa (8). Thus, right hepatic and caudate lobectomy with extrahepatic bile duct resection were performed. The wall thickening on multidetector CT and tapering changes on cholangiography are useful for diagnosing the progression of the disease. In the present case, we did not perform intraductal ultrasonography (IDUS) or peroral cholangioscopy (POCS). IDUS is useful for the diagnosis of vertical invasion or vascular invasion. Because the present lesion was located distant from the hepatic artery and portal vein, we considered multidetector CT (instead of IDUS) to be sufficient for making a preoperative diagnosis. No malignancy was observed, although biopsy or cytological analyses were performed many times. POCS might have been a useful tool for the preoperative diagnosis. However, high-resolution scopes were not widely used and were not available at time of the diagnosis of this case. POCS with a high-resolution scope will be useful for the preoperative diagnosis of follicular cholangitis in the future.

In particular, because of the strongly positive ^{18}F-FDG-PET findings, we could not exclude cholangiocarcinoma preoperatively. ^{18}F-FDG sometimes accumulates due to inflammation or in benign tumors. In this case, the increased use and uptake of glucose by inflammatory cells, including lymphoid cells, and the increase of blood flow to the lesion

Table 2. Clinical Characteristics of the Reported Patients with Follicular Cholangitis.

No/	References	Reported year	Age (years) / Gender	Symptom at onset	Preoperative diagnosis	ANA	IgG4
1	1)	2003	57/F	Elevation of LEs	CCC	Negative	N/D
2	2)	2005	61/M	Abdominal pain, jaundice, elevation of LEs	CCC	Negative	N/D
3	3)	2010	44/M	Elevation of LEs	CCC	Negative	Negative (IHC)
4		2010	58/F	Elevation of LEs	CCC	Negative	Negative (IHC)
5	4)	2012	73/F	Abdominal pain, jaundice, elevation of LEs	CCC	N/D	24 mg/dL (Serum)
6		2012	70/M	Elevation of LEs	CCC	N/D	N/D
7		2012	42/F	Pruritus and jaundice	PSC	N/D	N/D
8	5)	2014	60/F	Pruritus and jaundice	CCC	Negative	Few (IHC)
9	6)	2016	68/F	Abdominal pain and elevation of LEs	Hepatolithiasis	N/D	Few (IHC)
10	7)	2019	60/M	Elevation of LEs	CCC	Negative	24.2mg/dL (Serum)
11	Present		70/M	Abdominal pain, jaundice, elevation of LEs	CCC	Negative	Few (IHC) 48mg/dL (Serum)

LEs: liver enzymes, CCC: cholangiocarcinoma, PSC: primary sclerosing cholangitis, ANA: antinuclear antibody, IHC: immunohistochemistry, N/D: no data

might have caused the accumulation of ^{18}F-FDG on PET. The findings of ^{18}F-FDG-PET in IgG4-related diseases have been reported (17-19), and this modality has been considered useful for the diagnosis and determination of the therapeutic effect in cases of IgG4-related disease. The average SUV values for involved organs of IgG4-related disease were reported to be 4.14 (range, 0.30-8.78) (17) or 3.2 (range, 1.1-8.3) (19). In contrast, the mean SUV_{max} of biliary malignancy was reported to be 6.4 ± 4.6 (20). The findings of an SUV_{max} of 8.2 and the localized accumulation of ^{18}F-FDG in the present case were thought to hamper the differential diagnosis from biliary malignancy. The ^{18}F-FDG uptake is reported to markedly decrease after corticosteroid treatment for IgG4-related disease (19). ^{18}F-FDG-PET may also be useful for determining the therapeutic effect in follicular cholangitis.

This is the first report of the ^{18}F-FDG-PET findings of follicular cholangitis. Although follicular cholangitis is a relatively rare disease, we should recognize it as a disorder that can cause benign biliary strictures. Further studies or the accumulation of more case reports is needed in order to determine the value of ^{18}F-FDG-PET for diagnosing follicular cholangitis.

The authors state that they have no Conflict of Interest (COI).

References

1. Aoki T, Kubota K, Oka T, Hasegawa K, Hirai I, Makuuchi M. Follicular cholangitis: another cause of benign biliary stricture. Hepatogastroenterology **50**: 639-642, 2003.
2. Lee JY, Lim JH, Lim HK. Follicular cholangitis mimicking hilar cholangiocarcinoma. Abdom Imaging **30**: 744-747, 2005.
3. Fujita T, Kojima M, Kato Y, et al. Clinical and histopathological study of "follicular cholangitis": sclerosing cholangitis with prominent lymphocytic infiltration masquerading as hilar cholangiocarcinoma. Hepatol Res **40**: 1239-1247, 2010.
4. Zen Y, Ishikawa A, Ogiso S, Heaton N, Portmann B. Follicular cholangitis and pancreatitis - clinicopathological features and differential diagnosis of an under-recognized entity. Histopathology **60**: 261-269, 2012.
5. Fujii M, Shiode J, Niguma T, et al. A case of follicular cholangitis mimicking hilar cholangiocarcinoma. Clin J Gastroenterol **7**: 62-67, 2014.
6. Saito R, Fukuda T, Amano H, et al. Follicular cholangitis associated with focal biliary stricture treated with left hepatectomy after 8 years of follow-up: a rare case report. Mol Clin Oncol **4**: 114-118, 2016.
7. Chang LS, Tomimaru Y, Nishida T, et al. Follicular cholangitis mimicking cholangiocarcinoma treated with right hepatectomy: a case report and review of published works. Hepatol Res **49**: 1475-1480, 2019.
8. Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. Ann Surg **215**: 31-38, 1992.
9. Nguyen Canh H, Harada K. Adult bile duct strictures: differentiating benign biliary stenosis from cholangiocarcinoma. Med Mol Morphol **49**: 189-202, 2016.
10. Bowlus Cl, Olson KA, Gershwin ME. Evaluation of indeterminate biliary strictures. Nat Rev Gastroenterol Hepatol **13**: 28-37, 2016.
11. Fujita T, Kojima M, Gotohda N, et al. Incidence, clinical presentation and pathological features of benign sclerosing cholangitis of unknown origin masquerading as biliary carcinoma. J Hepatobiliary Pancreat Sci **17**: 139-146, 2010.
12. Zen Y, Kawakami H, Kim JH. IgG4 related sclerosing cholangitis: all we need to know. J Gastroenterol **51**: 295-312, 2016.
13. Tsokos CG, Krings G, Yilmaz F, et al. Proliferative index facilitates distinction between benign biliary lesions and intrahepatic cholangiocarcinoma. Hum Pathol **57**: 61-67, 2016.
14. Kanzawa M, Sanuki T, Onodera M, et al. Double immunostaining for maspin and p53 on cell blocks increases the diagnostic value of biliary brushing cytology. Pathol Int **67**: 91-98, 2017.
15. Ponchon T, Gagnon P, Berger F, et al. Value of endobiliary brush cytology and biopsies for the diagnosis of malignant bile duct stenosis: results of a prospective study. Gastrointest Endosc **42**: 565-572, 1995.
16. Pugliese V, Conio M, Nicolò G, Saccomanno S, Gatteschi B. Endoscopic retrograde forceps biopsy and brush cytology of biliary

strictures: a prospective study. Gastrointest Endosc **42**: 520-526, 1995.

17. Zhao Z, Wang Y, Guan Z, Jin J, Huang F, Zhu J. Utility of FDG-PET/CT in the diagnosis of IgG4-related diseases. Clin Exp Rheumatol **34**: 119-125, 2014.

18. Lee J, Hyun SH, Kim S, et al. Utility of FDG PET/CT for differential diagnosis of patients clinically suspected of IgG4-related disease. Clin Nucl Med **41**: e237-e243, 2016.

19. Zhang J, Chen H, Ma Y, et al. Characterizing IgG4-related disease with ^{18}F-FDG PET/CT: a prospective cohort study. Eur J Nucl Med Mol Imaging **41**: 1624-1634, 2014.

20. Lee JY, Kim HJ, Yim SH, et al. Primary tumor maximum standardized uptake value measured on ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography is a prognostic value for survival in bile duct and gallbladder cancer. Korean J Gastroenterol **62**: 227-233, 2013.