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CASE REPORT

A case of follicular cholangitis mimicking hilar cholangiocarcinoma

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Abstract Follicular cholangitis is a sclerosing cholangitis with hilar biliary stricture that must be differentiated from both immunoglobulin G4-related sclerosing cholangitis and primary sclerosing cholangitis. This disorder is extremely rare and difficult to distinguish from hilar biliary cholangiocarcinoma. We report here a case of a Japanese female patient in her 60s with this disease. The patient visited a family doctor for itching and general fatigue. Blood examination showed elevated hepatobiliary enzyme levels. Various imaging studies showed dilation of the bilateral intrahepatic bile duct and wide stenosis from the proximal bile duct to the right and left hepatic duct. They also showed the enlargement of multiple lymph nodes in the hepatoduodenal ligament, periaorta, and mesocolon. Based on endoscopic retrograde cholangiopancreatography-directed brush cytology, we diagnosed this patient with hilar cholangiocarcinoma and performed left trisegmentectomy of the liver. The pathology results showed that the wall from the bilateral hepatic duct to the proximal bile duct had thickened irregularly with dense fibrosis and a marked formation of lymph follicles. The mucosal epithelia did not have malignant findings. The diagnosis was follicular cholangitis. This case indicates that follicular cholangitis should be considered as a differential diagnosis of hilar biliary stricture.

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Introduction

In the diagnosis of diseases causing hilar biliary strictures, determining whether the stenosis is malignant or benign is extremely important [1]; however, distinguishing between malignant and benign biliary strictures remains a challenge [2]. There have been many reports of the difficulty in distinguishing between hilar biliary cholangiocarcinoma and sclerosing cholangitis. It has also been reported that the stenosis in approximately 10 % of patients preoperatively diagnosed with hilar cholangiocarcinoma is benign [3]. The diagnosis of diseases that cause hilar biliary strictures is difficult. Representative disorders of sclerosing cholangitis are primary sclerosing cholangitis (PSC) [4] and immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) [5]. Distinguishing between the two is extremely important because the prognosis and treatment plans are totally different [6]. In addition, there have been few reports of follicular cholangitis in sclerosing cholangitis causing hilar biliary strictures [7–10]. The characteristics of this disease are different from those of IgG4-SC and PSC. We report this case because of the difficulty we faced in distinguishing follicular cholangitis from hilar cholangiocarcinoma.

Case report

A woman in her 60s visited a family doctor for itching and general fatigue. She had no relevant family medical

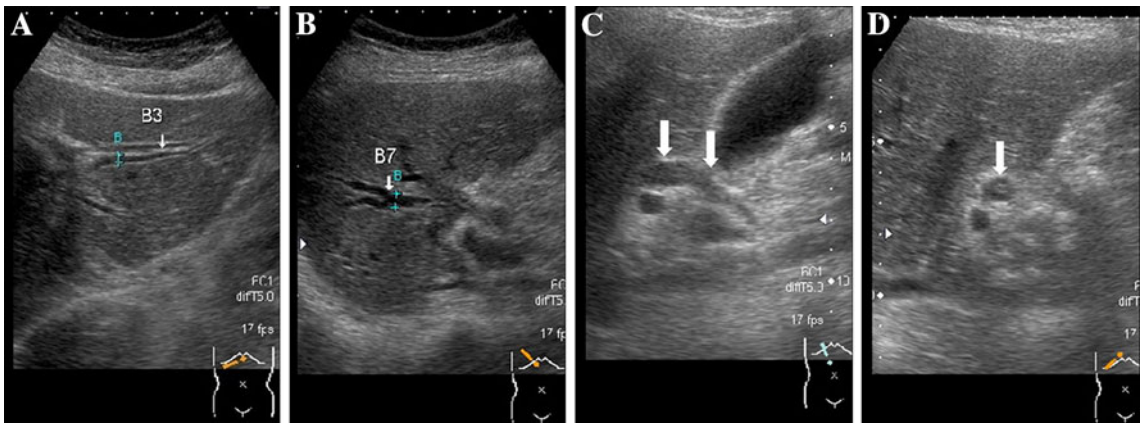

Fig. 1 Abdominal ultrasonography showed dilation of the bilateral intrahepatic bile duct (**a**, **b**) and wall thickness of the bile duct (*arrow*) from the proximal bile duct to the left and right hepatic duct (**c**, **d**)

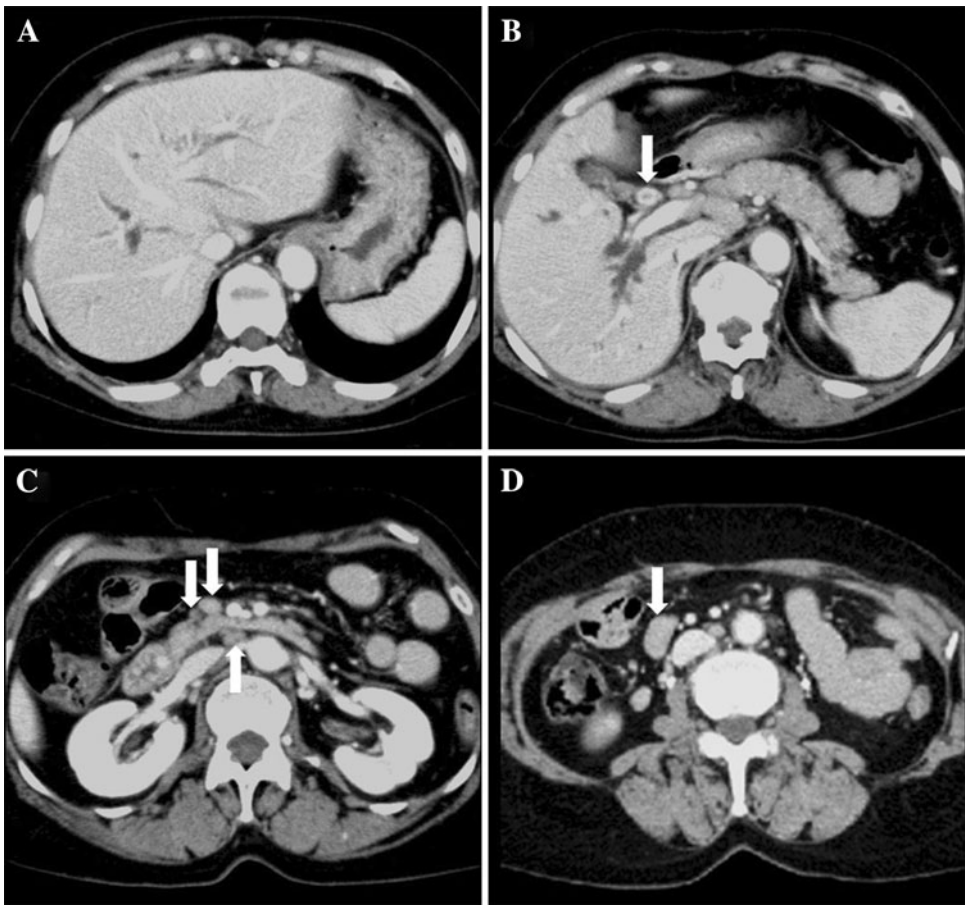

Fig. 2 Abdominal contrast CT showed increased wall thickness of the bile duct (*arrow*) in the wide area from the proximal bile duct to the left hepatic duct B4 branch, right anterior branch B5, and the B8 intrahepatic duct (**a**, **b**). CT showed multiple swellings of lymph nodes (*arrow*) in the hepatoduodenal ligament, periaorta (**c**), and mesocolon (**d**)

history. Her drinking history was opportunity drinking. A blood test showed liver function disorder, and she was referred to our hospital. She was 153 cm tall and weighed 57 kg. Her blood pressure was 143/75 mmHg, and her pulse was 76/min. She was afebrile. She did not have anemia, but had jaundice. She did not have abdominal pain. Blood examination showed elevated hepatobiliary enzyme levels. Aspartate aminotransferase was 104 IU/L (normal 10–35 IU/L), alanine aminotransferase 172 IU/L (normal 7–42 IU/L), γ-glutamyl transpeptidase 519 IU/L (normal 5–40 IU/L), total bilirubin 3.7 mg/dL (normal 0.2–1.2 IU/L), and direct bilirubin 2.5 mg/dL (normal 0.0–0.2 IU/L). Autoimmune antibodies, including antinuclear antibody, anti-smooth muscle antibody and antimitochondrial antibody, were all negative. Serum IgG, IgG4, carcinoembryonic antigen, and carbohydrate antigen 19–9 levels

remained within normal limits. Abdominal ultrasonography showed dilation of the bilateral intrahepatic bile duct and wall thickness of the bile duct from the proximal bile duct to the left and right hepatic duct (Fig. 1). Abdominal contrast computed tomography (CT) showed increased wall thickness of the bile duct in the wide area from the proximal bile duct to the left hepatic duct B4 branch, right anterior branch B5, and the B8 intrahepatic duct. CT also showed multiple swellings of lymph nodes in the hepatoduodenal ligament, periaorta, and mesocolon (Fig. 2). Magnetic resonance cholangiopancreatography (MRCP) showed constriction of the hilar bile duct. A biliary stricture extended from the hepatic confluence to near the end of the first branch of the right and left main bile ducts (Fig. 3). Endoscopic retrograde cholangiopancreatography (ERCP) showed stenosis from the proximal bile duct to the near B4 bile duct branch. In the stenosis, intraductal ultrasonography (IDUS) showed an iso-echoic or a slightly low echoic mass, and the outer hyperechoic layer was comparatively normal (Fig. 4). Bile duct brush cytology of the narrow segment showed cellular atypia, which was strongly suggestive of adenocarcinoma (Fig. 5). We diagnosed this patient with hilar biliary cholangiocarcinoma. As preoperative treatments, we inserted endoscopic nasobiliary drainage into the posterior segment area. In

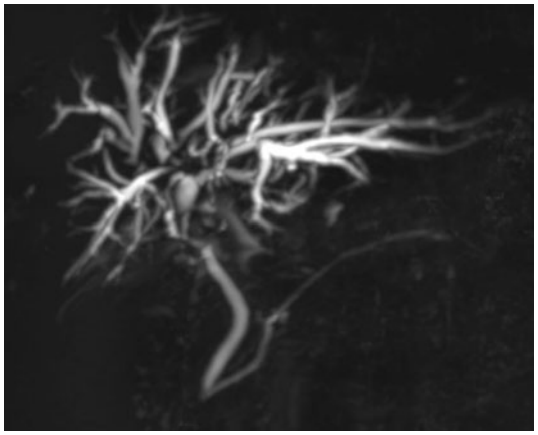

Fig. 3 Magnetic resonance cholangiopancreatography (MRCP) showed constriction of the hilar bile duct. A biliary stricture had extended from the hepatic confluence to near the end of the first branch of the right and left main bile ducts

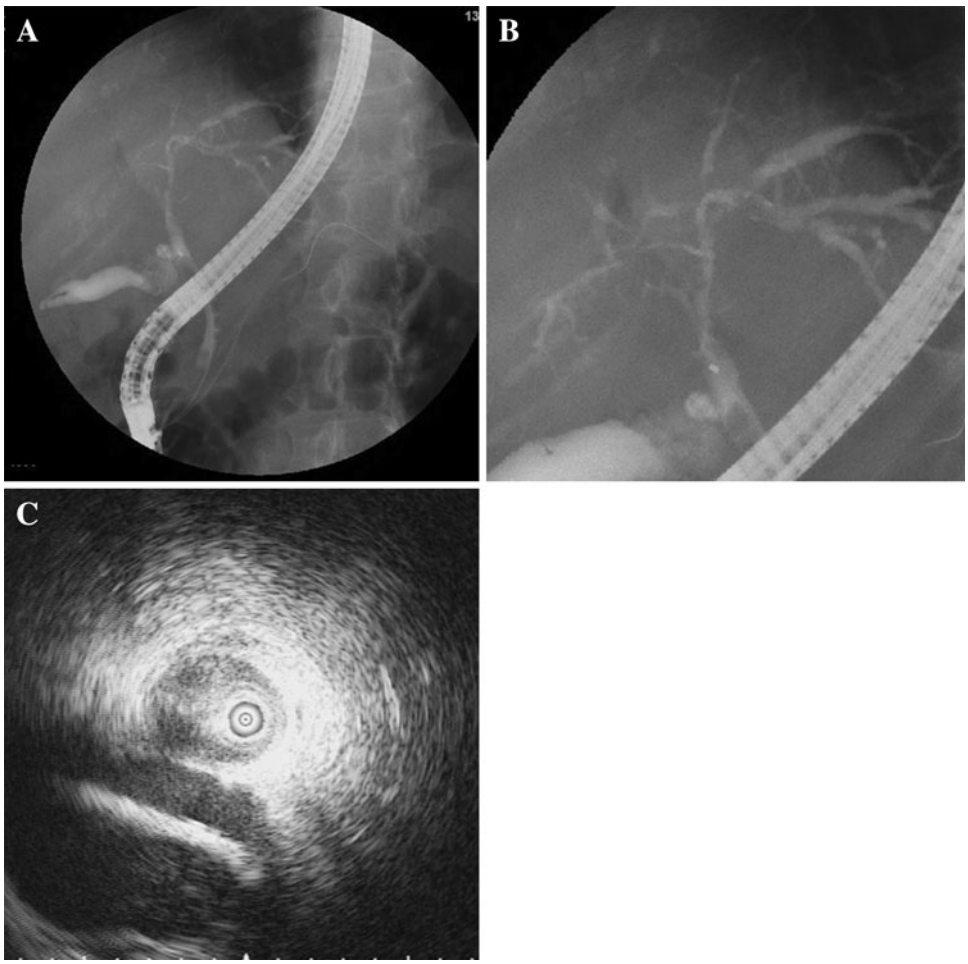

Fig. 4 ERCP showed stenosis from the proximal bile duct to the near B4 bile duct branch (**a**, **b**). In the stenosis, intraductal ultrasonography (IDUS) showed an iso-echoic or a slightly low echoic mass, and the outer hyperechoic layer was comparatively normal (**c**)

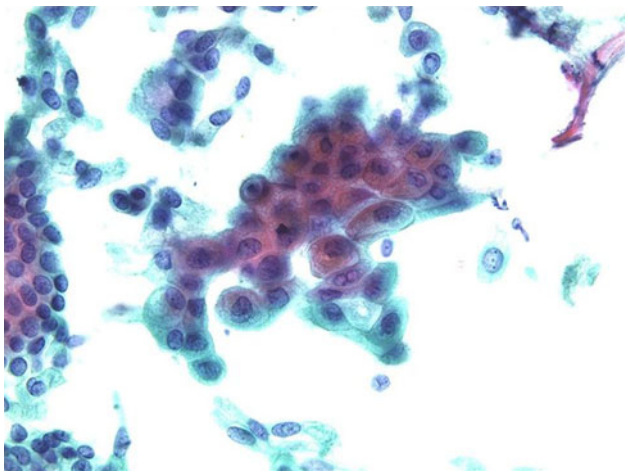

Fig. 5 Bile duct brush cytology of the narrow segment showed cellular atypia, which was strongly suggestive of adenocarcinoma (Papanicolaou staining, ×20)

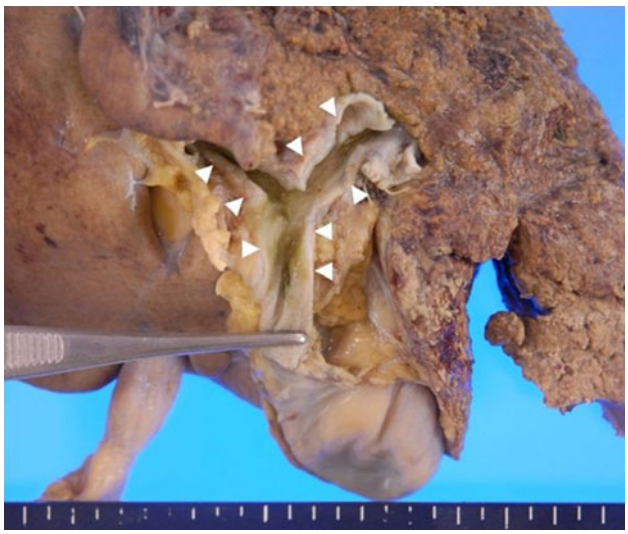

Fig. 6 Left trisegmentectomy of the liver after embolization on the 21st day. The hepatic hilum in this specimen showed no apparent tumors, but showed marked wall thickening

addition, we performed transcatheter portal embolization of the left and anterior branch portal vein via the internal iliac vein. Asialo liver scintigraphy showed an improvement of liver function on the 17th day of embolization. In accordance with the assumption of liver function after left trisegmentectomy of the liver, the indocyanine green retention value at 15 min decreased from 24.9 to 18.6 %. We performed left trisegmentectomy of the liver after embolization on the 21st day. The hepatic hilum in this specimen showed no apparent tumors, but showed marked wall thickening (Fig. 6). Pathology results showed that the wall from the bilateral hepatic duct to the proximal bile duct was irregularly thickened with dense fibrosis and a marked formation of lymph follicles. The mucosal epithelia showed no findings of malignancy and instead showed inflammation or reproduction. A large number of plasma cells coexisted with small lymphocytes among a marked formation of lymph follicles. This case showed sclerosing cholangitis with a marked formation of lymph follicles. This case did not have the pattern of fibrosis and bile duct elimination images that is characteristic of PSC. The immunostaining of bcl-2 was negative. There were few IgG4-positive cells (Fig. 7). We diagnosed this patient with follicular cholangitis. The postoperative course was good, and there have been no postoperative recurrences in the 24-month follow-up period, during which time the patient has been followed in the outpatient department. Furthermore, the enlargement of multiple lymph nodes has improved one year after surgery (Fig. 8).

Discussion

Follicular cholangitis was first described by Aoki et al. [7]. After the first report of follicular cholangitis, another report of this entity was described by Lee [8]. In 2010, Fujita et al. also [9] reported two cases. In 2012, Zen et al. [10] reported three cases of follicular cholangitis and two cases of follicular pancreatitis. Follicular cholangitis is a sclerosing cholangitis causing hilar biliary stricture. The characteristics of this disorder are different from those of IgG4-SC and PSC. This disease has therefore been thought to be an independent disorder, based on the four reported articles. Of the 176 reported operations for hilar biliary stricture, it has been reported that 2 (1.1 %) have been due to follicular cholangitis [7]. The clinical features of this disorder are as follows. Patients are generally middle-aged, and both sexes can be affected. There is no medical history of autoimmune disease. Patients present with gradual progression of the disease with liver dysfunction. The disorder is localized to hilar biliary strictures. Antinuclear antibody is negative. It has been reported that the prognosis of follicular cholangitis also seemed to be distinctive. All patients have undergone surgical treatment. One patient showed progressive recurrent cholangitis 2 years after surgery, and died of liver failure. Another patient also showed recurrent cholangitis 10 months after surgery, and has since undergone careful follow-up. This patient was treated with corticosteroids and moderate improvement was observed. Therefore, treatment with corticosteroids may improve the disease [9]. On the other hand, Zen et al. [10] reported the postoperative course of their patients was uneventful, without evidence of recurrence (follow-up period 17–65 months). The pathological features are as follows. The wall of the bile duct is thickened, and marked formation of lymph follicles is recognized in the subserosal layer of the granularly elevated part of the hepatic duct.

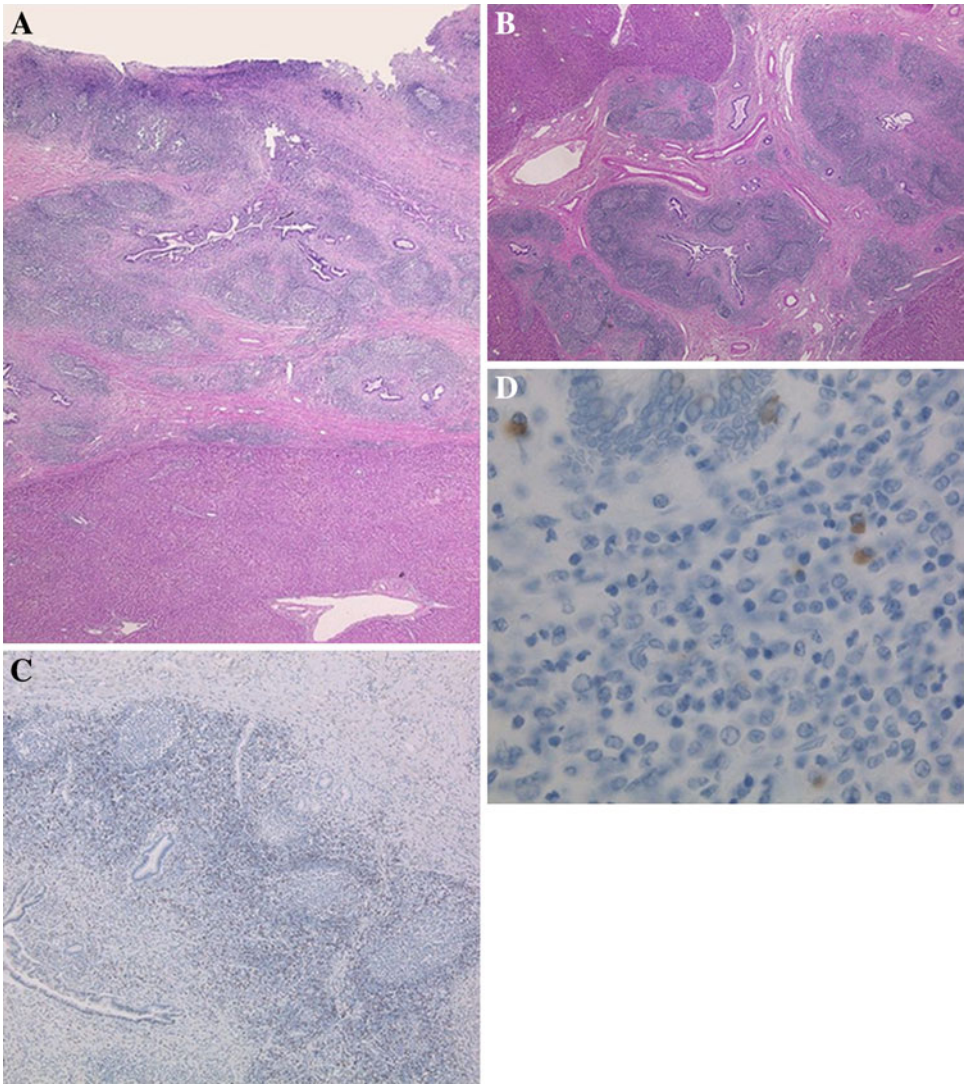

Fig. 7 Pathology results showed that the wall from the bilateral hepatic duct to the proximal bile duct was irregularly thickened with dense fibrosis and a marked formation of lymph follicles. The mucosal epithelia showed no findings of malignancy. This case showed sclerosing cholangitis with a marked formation of lymph follicles. This case also did not have the pattern of fibrosis and bile duct elimination images that is characteristic of PSC (H&E staining, ×1.25) (**a**), (H&E staining, ×4) (**b**). Immunostaining of bcl-2 was negative (×10) (**c**). There were few IgG4-positive cells (×40) (**d**)

Germinal centers are richly formed in the lymph follicles, but they show no tumors and are considered to be reactive hyperplastic follicles [7]. The lesion is localized at the proximal extrahepatic bile duct and the hepatic hilum; however, the peripheral intrahepatic bile ducts are almost intact. Immunostainings of CD3, CD4, CD8, CD20, CD79a are positive; IgG4 is negative.

It is extremely difficult to differentiate this disease from hilar cholangiocarcinoma using imaging studies. Most of the reported cases were diagnosed as hilar cholangiocarcinoma preoperatively, and surgical resections were performed. For accurate diagnosis, this disease should be taken into consideration as a differential diagnosis of the diseases which cause hilar biliary strictures. There have been only five reports of follicular cholangitis including this report, and useful typical findings for a diagnosis are not clear. However, the enlargement of multiple lymph nodes described here may be an important characteristic of the disease, because they improved postoperatively.

The diagnosis of a disorder causing hilar biliary strictures is extremely important, because of the massive surgical invasion. It may therefore be useful to perform cholangioscopy and biopsy of the lymph gland by endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) for the diagnosis of this disease. Recent studies have evaluated the efficacy of peroral cholangioscopy

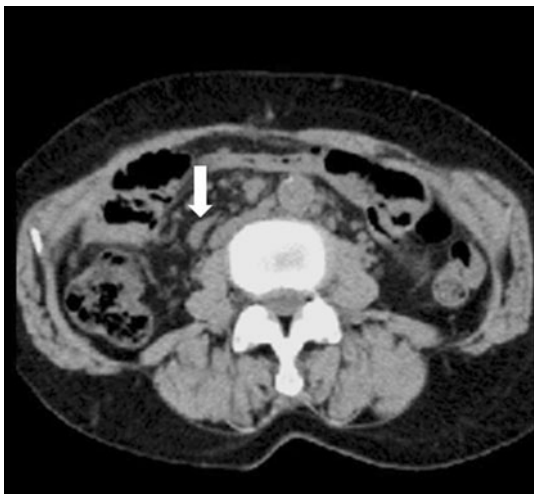

Fig. 8 Enlargement of multiple lymph nodes has improved (*arrow*)

(POCS) for diagnosis of biliary diseases [11–15]. POCS may reveal characteristic finding of this disorder. In addition, there are some reports about the usefulness of the qualitative diagnosis of EUS-FNA for intra-abdominal lymphadenopathy [4, 16, 17]. If the pathologic features of intra-abdominal lymphadenopathy are revealed in the future, EUS-FNA for lymphadenopathy may help the diagnosis of this disease.

Because the concept of this disease has not yet been established, neither the optimal treatment method nor the prognosis are clear. Further investigations and accumulation of data for this disease are needed.

In conclusion, we treated a case of follicular cholangitis that was difficult to distinguish from hilar biliary cholangiocarcinoma. We should recognize this disease (so-called follicular cholangitis) as one of the disorders causing hilar biliary stricture.

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Disclosures

Conflict of Interest: Masakuni Fujii, Junji Shiode, Takefumi Niguma, Mamoru Ito, Shuhei Ishiyama, Akiko Fujiwara, Soichiro Nose, Masao Yoshioka, and Tetsushige Mimura declare that they have no conflict of interest.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008(5).

Informed Consent: Informed consent was obtained from all patients for inclusion in the study.

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