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【 CASE REPORT 】

Primary Bile Duct Diffuse Large B-cell Lymphoma Diagnosed by Repeated Endoscopic Ultrasound-guided Fine-needle Aspiration and Endoscopic Retrograde Cholangiopancreatography

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Abstract:

A 54-year-old man was admitted with obstructive jaundice. Computed tomography showed common bile duct stricture and a tumor around the celiac artery. Repeated endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endoscopic retrograde cholangiopancreatography (ERCP) as well as a laparotomic biopsy around the celiac artery were diagnostically unsuccessful. Since the bile duct stricture progressed, EUS-FNA and ERCP were performed a third time, finally leading to the diagnosis of diffuse large B-cell lymphoma. The treatment plan and prognosis of obstructive jaundice differ greatly depending on the disease. It is important to conduct careful follow-up and repeated histological examinations with appropriate modifications until a diagnosis is made.

Key words: diffuse large B-cell lymphoma, bile duct, obstructive jaundice, EUS-FNA, ERCP

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Introduction

Approximately 40% of cases of diffuse large B-cell lymphoma (DLBCL) occur at extranodal sites, with lesions in the gastrointestinal tract being the most common (1). Among sites, the biliary system has little lymphatic tissue, and primary bile duct DLBCL is rare.

We herein report a case of DLBCL that developed as obstructive jaundice, resulting in difficulty distinguishing it from cholangiocarcinoma and IgG4 related diseases before a diagnosis was finally achieved by performing endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endoscopic retrograde cholangiopancreatography (ERCP) multiple times.

Case Report

Our patient was a 54-year-old man. Due to a history of epilepsy, he had been taking 1,000 mg of sodium valproate. Regarding his family history, his father had a history of cerebral infarction, while his mother had a history of uterine cancer. The patient had a history of smoking 20 cigarettes a day from 20 to 30 years old, along with a history of drinking 350-700 mL of beer twice a week. On becoming aware of brown urine and jaundiced skin, he visited his primary care doctor. Blood tests confirmed that enzymes in his hepatobiliary system had increased, so he was referred to our hospital for further examination and treatment in July, 20 XX.

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Table 1. Laboratory Findings on First Visit.

Biochemistry		Hematology	
Total protein	7.9 g/dL	White blood cell	4,890 /μL
Albumin	4.4 g/dL	Hemoglobin	15.9 /μL
LDH	335 U/L	Platelet	28.8 ×10⁴/μL
AST	535 U/L	PT-INR	0.87
ALT	1,011 U/L	APTT	30.7 s
ALP	1,734 U/L	Serology	
γ-GTP	1,333 U/L	CRP	0.24 mg/dL
Total bilirubin	3.74 mg/dL	HBs Ag	(-)
Direct bilirubin	2.58 mg/dL	HCV Ab	(-)
BUN	12 mg/dL	sIL-2R	428 U/mL
Creatinine	0.8 mg/dL	AFP	4.4 ng/mL
Sodium	140 mEq/dL	PIVKA-II	47 mAu/mL
Potassium	4.6 mEq/dL	CEA	0.9 ng/mL
		CA19-9	35.2 U/mL
		IgG4	69.3 mg/dL

LDH: lactate dehydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, BUN: blood urea nitrogen, PT-INR: prothrombin time international normalized ratio, APTT: acti-vated partial thromboplastin time, CRP: C-reactive protein, HBs: hepatitis B surface, Ag: antigenemia, HCV: hepatitis C virus, Ab: antibody, sIL-2R: soluble interleukin-2 receptor, AFP: alpha Fetoprotein, PIVKA-II: protein induced by vitamin K absence-II, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9

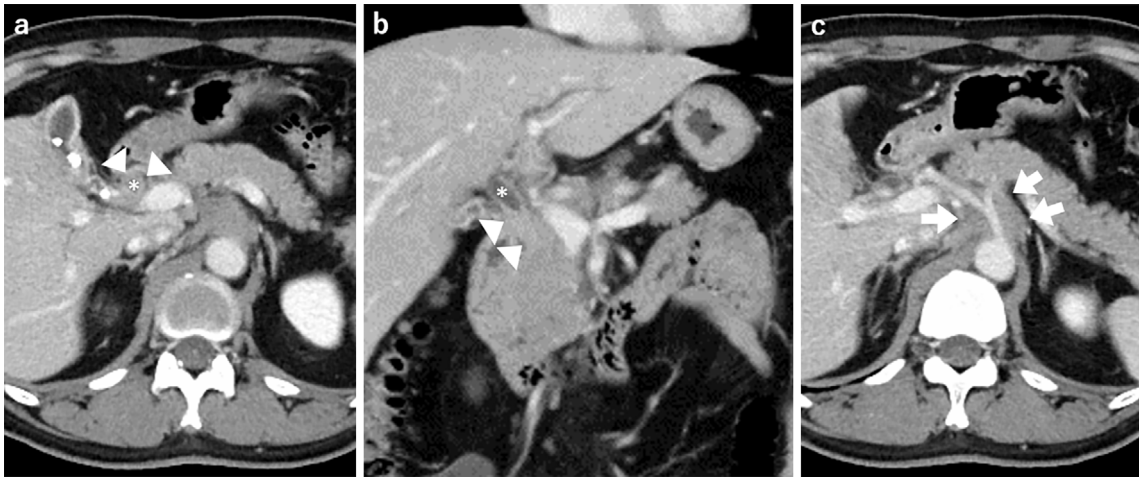

Figure 1. Contrast-enhanced CT (CE-CT) of the abdomen (July, 20XX). (a) Axial, (b) coronal; CE-CT confirmed circumferential wall thickening and stenosis in the common bile duct (*) with a contrast effect. (c) Axial CE-CT confirmed a soft tissue mass around the celiac artery (arrow).

He was 176 cm tall, weighed 68 kg and was found to have conjunctival icterus. No spontaneous pain or tenderness was observed in his abdomen. Blood tests confirmed that enzymes in his hepatobiliary system had increased, although tumor markers were not increased (Table 1). Contrast-enhanced computed tomography (CE-CT) of his abdomen confirmed circumferential wall thickening and stenosis in the common bile duct with a contrast effect and a soft tissue mass around the celiac artery and the superior mesenteric artery (Fig. 1). As a result, cholangiocarcinoma with nerve plexus invasion was suspected. EUS confirmed wall thickening localized in the common bile duct (Fig. 2a, b).

Since a soft tissue mass mixed with hypoechoic and hyperechoic areas was observed around the celiac artery, EUS-FNA was performed using a conventional needle (EZ Shot 3; Olympus, Tokyo, Japan; 25G, twice with 20-mL syringe suction) (Fig. 2c, d). However, it was difficult to evaluate with few specimens, and no malignant findings were confirmed. ERCP confirmed stenosis of the common bile duct, so endoscopic biliary stenting (EBS) was performed. Although four fluoroscopy-guided biopsies (2.0 mm; Radial Jaw; Boston Scientific, Natick, USA) were performed from the stenosis of the common bile duct, the specimen volume was small, and only inflammatory cells were detected, with

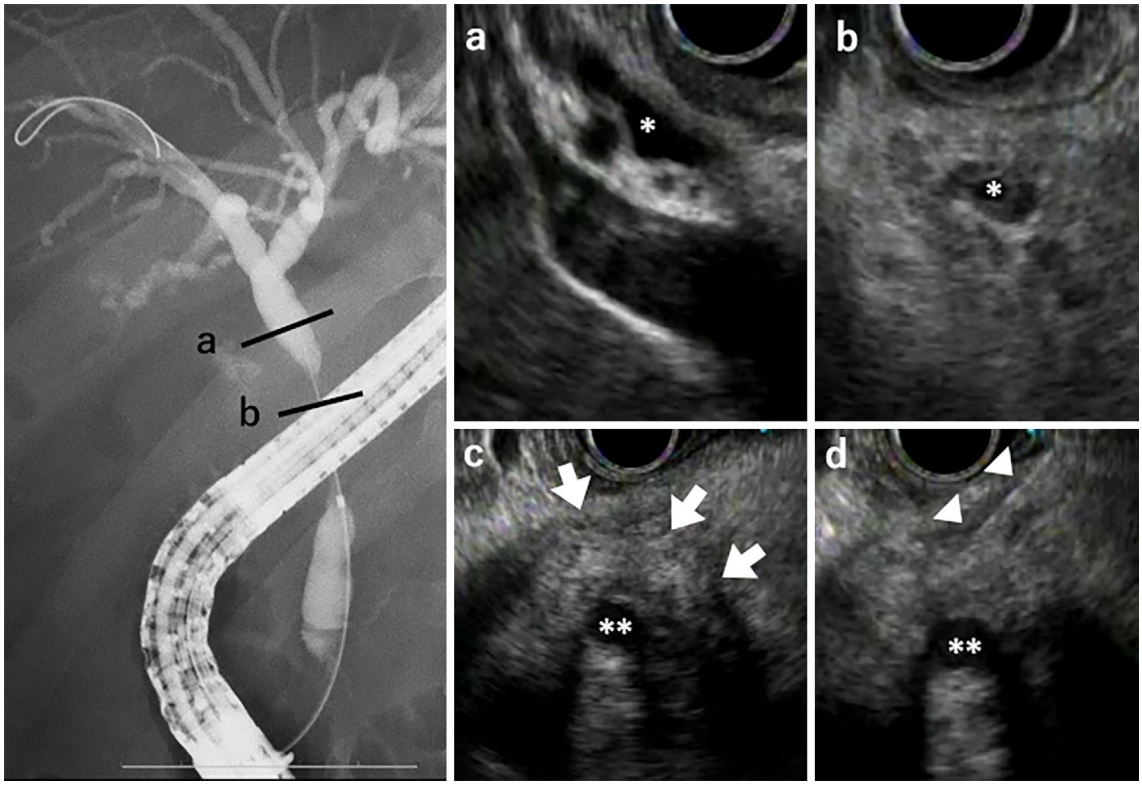

Figure 2. **ERCP and EUS images (July, 20XX). (a, b) EUS confirmed wall thickening localized in the common bile duct (*bile duct lumen). (c, d) A soft tissue mass (arrow) with a mixture of low and high echoes was observed around the celiac artery (**), so EUS-FNA was performed (arrowhead).**

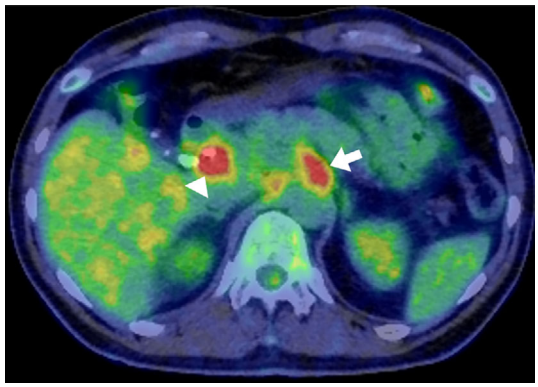

Figure 3. **PET-CT (July, 20XX). Accumulation with an SUVmax of 5.0→6.6 confined to the common bile duct (arrowhead) was observed, along with accumulation with an SUVmax of 4.1→4.9 (arrowhead) against the soft tissue mass surrounding the celiac artery.**

no malignant findings. Positron emission tomography (PET)-CT confirmed accumulation with a maximum standardized uptake value (SUVmax) of 5.0→6.6 localized in the common bile duct and SUVmax 4.1→4.9 in the soft tissue mass around the celiac artery (Fig. 3).

Although there was no evidence of elevated IgG4 or soluble interleukin-2 receptor (sIL-2R) values, imaging findings suggested the possibility of IgG4-related disease or malignant lymphoma. When EUS was performed again in August, 20XX, stenosis of the common bile duct was visualized as hypoechoic interstitial thickening (Fig. 4a', b'). EUS-FNA was performed again at the site of thickening of the common bile duct using a Franseen needle (Acquire; Boston Scientific; 25G, once with 20-mL syringe suction) and a fork-tip needle (SharkCore; Medtronic, Minneapolis, USA; 22G, twice with 20-mL syringe suction) as well as at the soft tissue mass around the celiac artery using a conventional needle (EZ Shot 3 Plus; Olympus; 22G, twice with 20-mL syringe suction). Immunostaining showed an undeniable finding of malignant lymphoma, but strong fibrosis prevented a proper assessment of the lymphocyte morphology.

At that time, ERCP was performed to observe the inside of the bile duct using a cholangioscope. The common bile duct gradually rose up to form completely circumferential narrowing, a finding that prompted us to suspect submucosal invasion (Fig. 4a-c). Epithelial changes could not be ruled out, so four cholangioscopy-guided biopsies (2.0 mm, Radial Jaw; Boston Scientific) were performed at the narrowing site. However, no malignant findings were observed.

There was a possibility that insufficient specimens had been collected, so a biopsy of the abdomen was performed via laparotomy in September, 20XX. No disseminated lesions were found in the abdominal cavity, although uniform hardness was observed in the hepatoduodenal ligament, including the common bile duct from the celiac artery. A biopsy of the hard tissue around the celiac artery was performed, but no malignant findings were found, with few IgG 4-positive cells detected. Despite not being able to make a

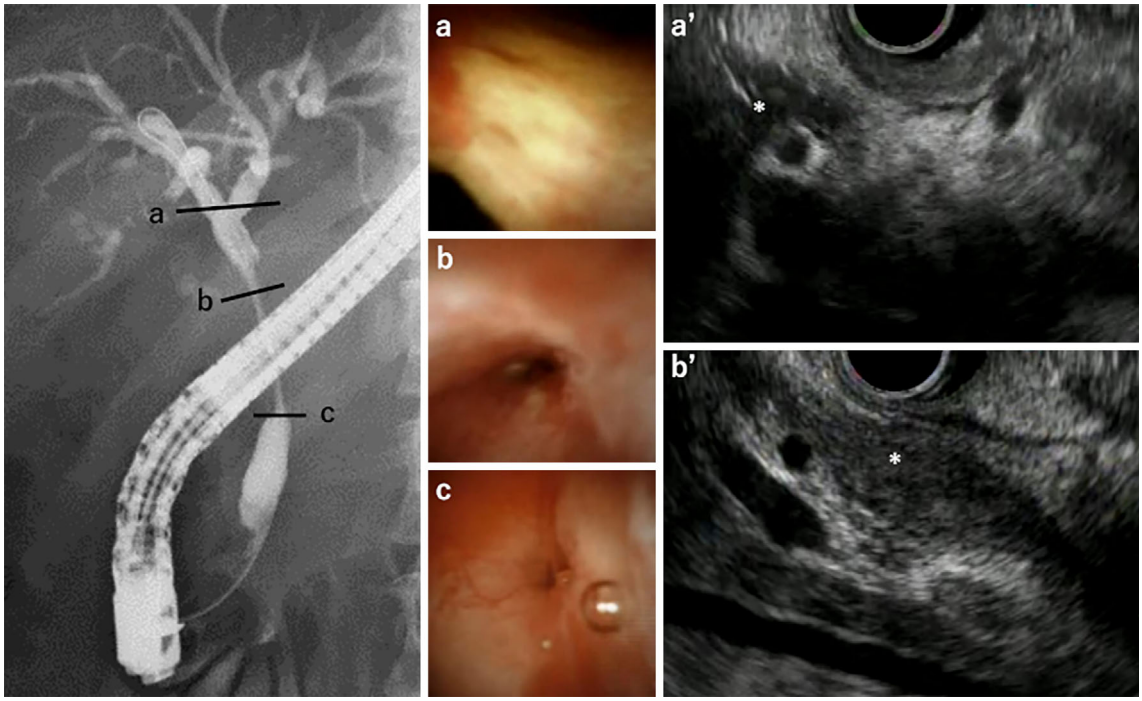

Figure 4. **ERCP, cholangioscopy, and EUS images (August, 20XX). (a, b, c) Cholangioscopy showed that the common bile duct gradually rose up to form a completely circumferential narrowing, a finding that prompted us to suspect submucosal invasion. (a', b') On EUS, stenosis of the common bile duct was depicted as a hypoechoic stroma (*bile duct lumen).**

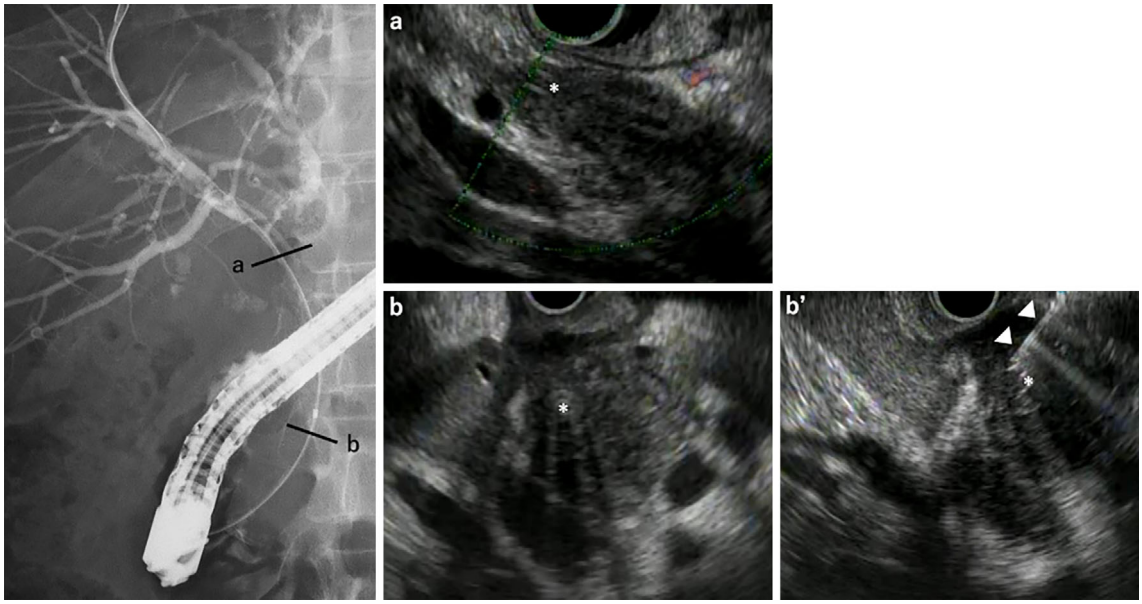

Figure 5. **ERCP and EUS images (January, 20XX+1). a, b The wall thickening of the common bile duct was exacerbated, with the stenosis extending to the intrahepatic bile duct (a: long axis b: short axis) (*bile duct lumen). (b') EUS-FNA (arrowhead) was performed for the thickened wall of the common bile duct that was exacerbated along the short axis (*bile duct lumen).**

pathological diagnosis, we could not rule out the possibility of IgG4-related disease, so the administration of PSL 40 mg/day was initiated as a steroid trial in November, 20XX.

However, despite two weeks of continuous administration, there was no decrease in the wall thickening of the common bile duct or the soft tissue mass around the celiac artery. Therefore, steroids were gradually reduced and discontinued. Wall thickening of the common bile duct was exacerbated, and newly enlarged lymph nodes were observed when CE-CT and EUS were performed again in January, 20XX+1 (Fig. 5, 6). EUS-FNA was performed again at the site of thickening of the common bile duct using a conventional

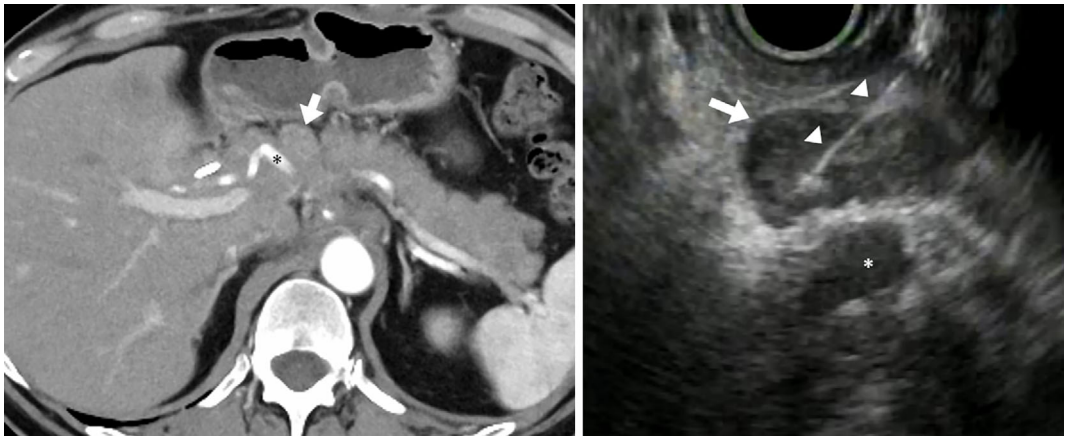

Figure 6. **CE-CT and EUS images (January, 20XX+1). EUS-FNA (arrowhead) was performed for the #8a lymph nodes (arrow) (*common hepatic artery).**

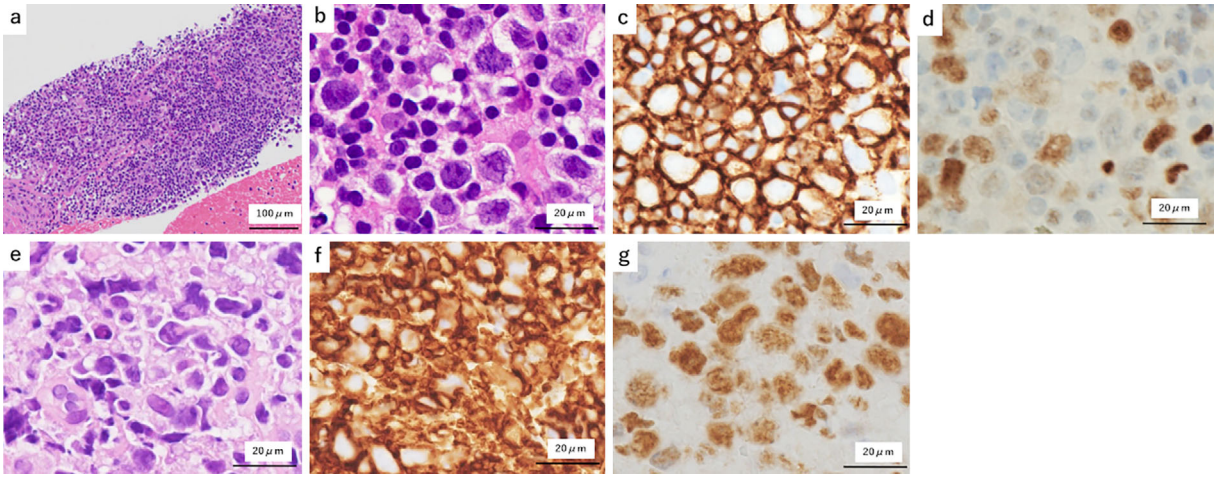

Figure 7. **Pathological findings of EUS-FNA and ERCP specimens (a-d: #8a lymph nodes, EUS-FNA; e-g: wall thickening of the common bile duct, ERCP). (a) Hematoxylin and Eosin (H&E) staining (low-power field); (b, e) H&E staining (high-power field); (c, f) Immunostaining (CD20); (d, g) Immunostaining (Bcl-6). Regarding the pathology of the lymph nodes (#8a) and bile duct, atypical lymphocyte cells exhibiting nuclei with markedly irregular shapes were observed by H&E staining, while immunostaining showed CD20 and Bcl-6 to be positive.**

needle (EZ Shot 3 Plus; Olympus; 22G, twice with 20-mL syringe suction) (Fig. 5b') and at the #8a lymph nodes using a Franseen needle (SonoTip TopGain; Mediglobe, Achenmühle, Germany; 22G, twice with 20-mL syringe suction) (Fig. 6). On ERCP, the wall thickening of the common bile duct extended to the intrahepatic bile duct, so six fluoroscopy-guided biopsies (2.0 mm, Radial Jaw; Boston Scientific) were performed from the stenosis.

Regarding the pathology of both specimens, atypical lymphocyte cells exhibiting nuclei with markedly irregular shapes were observed by hematoxylin-eosin staining, while immunostaining revealed that CD20 and Bcl-6 were positive, and CD3, CD10, CD21, and Bcl-2 were negative, leading to a diagnosis of DLBCL (Fig. 7).

The sIL-2R value increased to 1,344 U/mL (Fig. 8). PET-CT confirmed strong accumulation in the perihilar bile duct, lesser curvature of the stomach, abdominal aorta, and superior mesenteric artery. No bone marrow infiltration of the tumor cells was observed by bone marrow aspiration. Based on these findings, the patient was diagnosed with stage II E DLBCL with a low-risk International Prognostic Index (IPI) score of 1.

In February, 20XX+1, two courses of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP; 700 mg of rituximab, 1,350 mg of cyclophosphamide, 90 mg of doxorubicin, 2 mg of vincristine, and 110 mg of prednisolone) were administered, which improved the bile duct stenosis. In April, 20XX+1, the EBS was removed due to improvement in the bile duct stenosis (Fig. 9). In December, 20XX+1, the soft tissue mass around the celiac artery had improved (Fig. 9).

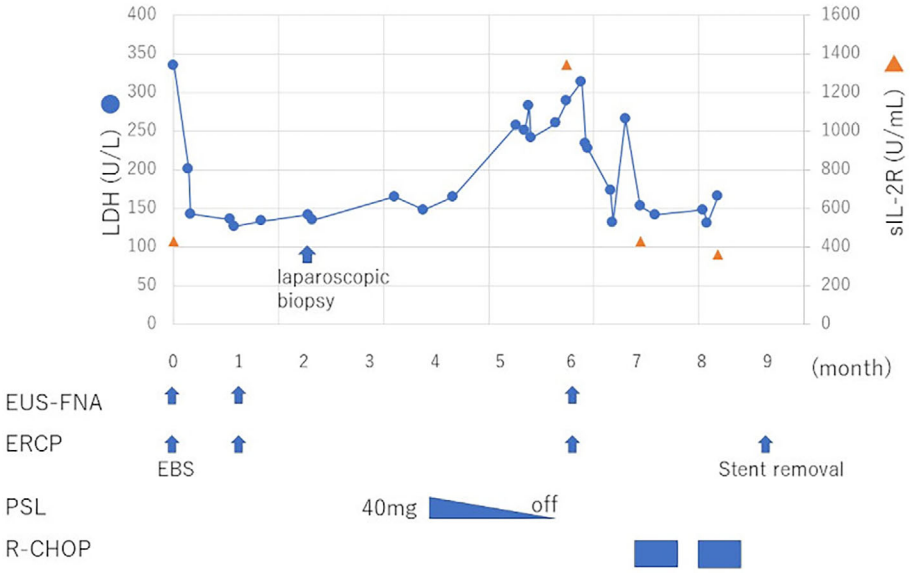

Figure 8. **Clinical course.**

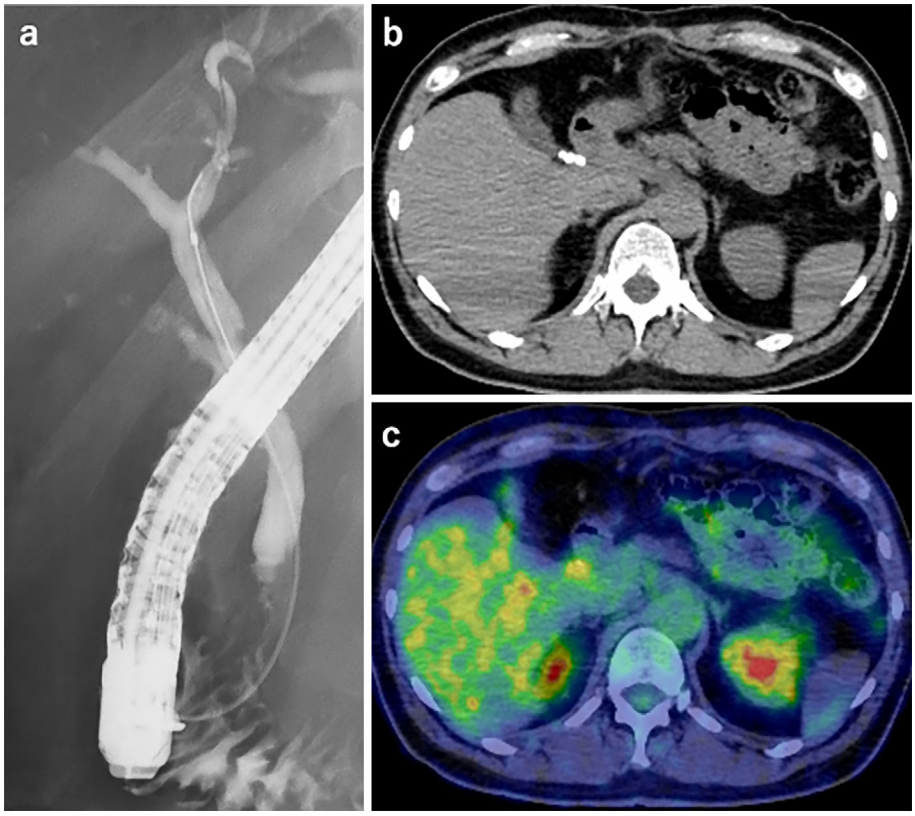

Figure 9. **ERCP (April, 20XX+1) and PET-CT (December, 20XX+1) findings. Stenosis of the common bile duct and the soft tissue mass around the celiac artery had improved (a. ERCP, b. plain CT, c. PET-CT).**

Discussion

DLBCL has the highest incidence among non-Hodgkin's lymphoma (NHL), accounting for 30% to 40% of cases (2). As the first symptom of DLBCL, obstructive jaundice is observed in approximately 1% of cases (3, 4). The cause is mostly secondary to compression of the extrahepatic bile duct due to lymphadenopathy (5), with primary bile duct NHL being a rare disease.

In the present case, wall thickening of the bile duct and a soft tissue mass around the celiac artery were observed. Since lymphadenopathy that compresses the bile duct was not confirmed by CE-CT at the first visit, this case was be-

Table 2. Summary of Literature of Primary Bile Duct DLBCL.

Case	Age (y)/ sex	Diagnostic modality	Treatment modality	Outcome	References
1	39/F	Surgery	Surgery+chemotherapy (CHOP)+RT	Alive after 13 mo	(22)
2	41/M	Surgery	Surgery	Unknown	(23)
3	36/M	Surgery	Surgery+chemotherapy (CHOP)	Alive after 68 mo	(24)
4	51/M	US-guided needle biopsy	Chemotherapy (R-CHOP)	Alive after 18 mo	(24)
5	21/F	Surgery	Surgery+chemotherapy (CHOP)+RT	Alive after 17 mo	(25)
6	63/M	Surgery	Surgery+chemotherapy (R-CHOP)	Alive after 8 mo	(26)
7	60/M	Surgery	Surgery+chemotherapy	Unknown	(27)
8	40/F	Surgery	Surgery+chemotherapy	Alive after 10 mo	(28)
9	77/M	ERCP, surgery	Surgery+chemotherapy (R-CHOP)	Died after 6 mo	(29)
10	57/M	ERCP, surgery	Surgery+chemotherapy (R-CVP)	Alive after 60 mo	(30)
11	32/M	ERCP, surgery	Surgery+chemotherapy (R-CHOP)	Unknown	(31)
12	66/M	Surgery	Surgery	Unknown	(32)
13	59/F	Surgery	Surgery	Died after 2 mo	(33)
14	61/F	EUS-FNA, bone marrow biopsy, diagnostic laparoscopy	Chemotherapy (R-CHOP)	Alive after 8 mo	(20)
15	54/M	ERCP, EUS-FNA, diagnostic laparoscopy	Chemotherapy (R-CHOP)	Alive	This case

US: ultrasound, ERCP: endoscopic retrograde cholangiopancreatography, EUS-FNA: endoscopic ultrasound-fine needle aspiration, RT: radiotherapy, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, R-CVP: rituximab, cyclophosphamide, vincristine, and prednisone

lieved to be primary bile duct NHL. There are no clear criteria for knowing whether or not the bile duct is the primary site, and whether the lesion in this case originated from the bile duct or the soft tissue mass around the celiac artery is unclear. Nevertheless, localized stenosis of the bile duct was observed without any significant lymphadenopathy, findings that are in line with those of previous reports. Primary extrahepatic bile duct NHL has been reported in 44 cases since Nguyen et al. (6) first reported it in 1,982 (7, 8). In particular, 15 cases of DLBCL of the primary bile duct have been reported, including our case (Table 2). The patients (5 females and 10 males) ranged in age from 21 to 77 (average: 50.5) years old. Surgery was performed for diagnostic purposes in 12 cases. Patients who were able to start chemotherapy appropriately after the diagnosis obtained a relatively long survival.

It is difficult to distinguish bile duct stenosis due to NHL from cholangiocarcinoma and IgG4-associated sclerosing cholangitis by imaging alone, as there are no findings specific to NHL; however, Yoon (9) reported that if smooth and mild bile duct stenosis without mucosal irregularities is observed despite confirming diffuse thickening of the bile duct wall via CT/magnetic resonance imaging, primary NHL of the bile duct should be considered. Of note, cholangiocarcinomas are often accompanied by severe stenosis due to invasive growth, causing fibrosis (10). Although IgG4-associated sclerosing cholangitis is relatively easy to diagnose in cases with high IgG4 levels or other IgG4-related complications, the bile duct images may vary, so it is important to distinguish it from cholangiocarcinoma. Many primary bile duct NHLs may be diagnosed as cholangiocarcinoma prior to surgery and subject the patient to unnecessary surgery. An accurate diagnosis is therefore important, as the treatment method and prognosis differ greatly depending on whether the lesion is primary bile duct NHL or another disease causing obstructive jaundice.

In the present case, a soft tissue mass around the celiac artery was observed in addition to bile duct stenosis. NHL that occurs in the retroperitoneum has a strong tendency to form soft tissue masses, making it difficult to distinguish it from retroperitoneal fibrosis, which is an IgG4-related disease, by imaging examinations alone (11). In NHL, while other forms of lymphadenopathy are said to be significantly more common than retroperitoneal fibrosis (11), in the present case, lymphadenopathy could not be determined at the first visit.

In malignant lymphomas, histological transformation often occurs, wherein indolent lymphomas, such as follicular lymphomas, are converted to an aggressive subtype, such as DLBCL. Histological transformation into aggressive lymphoma, which is expected to occur at a rate of 2% to 3% each year, is associated with rapid progression, treatment resistance, and a poor prognosis (12). The possibility of transformation should thus be considered in the presence of any of the following conditions: increased lactate dehydrogenase (LDH) levels, B-symptoms, rapidly growing adenopathy, development of new extranodal sites, or hypercalcemia (13). In the present case, there were no B-symptoms or hypercalcemia, and there was no evidence of prior follicular lymphoma on pathology, but at the time of the diagnosis, LDH levels were increased, and lymphadenopathy was newly detected, suggesting that transformation may have occurred. Of note, it has been reported that idiopathic retroperitoneal fibrosis and related diseases (multifocal fibroscle-

roses, including sclerosing cholangitis and Riedel's thyroiditis) can develop into high-grade lymphomas such as DLBCL during follow-up (14). Accordingly, it might be possible that histological transformation from fibrosis into lymphoma occurred in this case.

With recent advances in EUS-FNA technology, the procedure's usefulness has been reported increasingly frequently. For primary bile duct NHL, surgical procedures have been performed in most cases thus far (15). However, the diagnostic ability of EUS-FNA for malignant bile duct stenosis has been reported (16), so it may be possible to avoid surgery if a case is properly diagnosed. In the present case, the type of puncture needle was changed to a fine-needle biopsy (FNB) needle (Franseen and fork-tip needles), as the diagnosis had not been reached with an FNA needle like a conventional needle. FNB needles are considered capable of collecting more tissue than FNA needles (17). The use of large-bore needles has been considered effective in improving the rate of histologic material acquisition. However, large-bore needles compromise maneuverability owing to their increased rigidity and stiffness. If the diagnostic yields of different-sized needles are equal and the puncture target is located near a large blood vessel or if a blood vessel is located in the puncture route, a thinner needle is preferable. Given that there is reportedly no significant difference in diagnostic rates between 22- and 25-G needles (18), a 25-G needle was used first in this case, and when the diagnosis was unsuccessful, the needle was changed to a larger 22-G needle.

Several cases in which a diagnosis was made based on ERCP findings have also been reported (19). ERCP can relieve obstructive jaundice while simultaneously performing a tissue biopsy with the procedure. Since EUS-FNA and ERCP can be performed with minimal invasiveness, these procedures should be actively performed.

Immune tissue staining is essential for making a diagnosis of NHL, so it is difficult to make a precise diagnosis if sufficient samples cannot be collected (20). In the present case, to collect a sufficient amount of specimen, the needle type and gauge were changed for EUS-FNA, and the number of biopsies was increased for ERCP.

Regarding treatment, chemotherapy is the first choice if a diagnosis of DLBCL is made. The R-CHOP regimen is a common therapy (21). Rituximab can increase the survival rate of DLBCL (21).

It is difficult to distinguish primary bile duct NHL from cholangiocarcinoma and IgG4-related diseases by imaging findings alone. However, the treatment policy and prognosis differ depending on whether a lesion is NHL or some other disease. Although NHL is rarely the cause of obstructive jaundice, histopathological examinations with EUS-FNA and/or ERCP should be actively performed, keeping the possibility of NHL in mind. In addition, it is important to conduct a careful follow-up on the progress of the disease. Even if a clear diagnosis cannot be made, it is also necessary to not only repeat examinations but also select an appropriate tissue sampling method and evaluate the specimen according to the suspected disease (Fig. 7).

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

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