

[CASE REPORT]

Multiple Malignant Lymphomas of the Bile Duct Developing after Spontaneous Regression of an Autoimmune Pancreatitis-like Mass

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Abstract:

We herein report a 67-year-old woman with malignant lymphomas of the bile duct that developed after regression of a pancreatic head mass. Computed tomography suggested the mass was pancreatic head cancer. Endoscopic ultrasonography showed a low-echoic mass with hyperechoic strands resembling autoimmune pancreatitis. Her serum IgG4 concentration was elevated to 674 mg/dL. After the pancreatic head mass spontaneously diminished, three masses were detected in the common bile duct. A biopsy of the major papilla revealed high-grade B-cell lymphoma with *MYC*, *BCL2* and/or *BCL6* rearrangement. Systemic chemotherapy with rituximab plus etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin resulted in complete remission.

Key words: non-Hodgkin lymphoma, high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements, bile duct, autoimmune pancreatitis, IgG4-related disease

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Introduction

Non-Hodgkin lymphoma (NHL) arising from the extrahepatic bile duct is rare, with only about 30 cases reported to date in the English-language literatures (1-3). The most frequent histological type of NHL arising from the extrahepatic bile duct has been reported to be B cell lymphoma, particularly diffuse large B-cell lymphoma (DLBCL).

Autoimmune pancreatitis (AIP) is a relatively rare type of pancreatitis with a hypothesized autoimmune mechanism (4-6). Type 1 AIP is a pancreatic manifestation of systemic immunoglobulin G4-related disease (IgG4-RD) and is often associated with increased immunoglobulin G4 (IgG4) concentrations (4, 7, 8). IgG4-RD has been reported to lead

to the development of various malignancies, including lymphoma (9-16).

We herein report a rare case of multiple malignant lymphomas of the bile duct that developed after the spontaneous regression of an AIP-like mass. The tumors were found to be high-grade B-cell lymphoma with *MYC*, *BCL2* and/or *BCL6* rearrangement (17), as shown by fluorescent *in situ* hybridization (FISH).

Case Report

A 67-year-old woman visited a local hospital complaining of dark urine. Contrast-enhanced abdominal computed tomography (CT) showed a pancreatic head mass, suggesting pancreatic head cancer, accompanied by obstructive jaun-

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dice. She was subsequently treated by endoscopic placement of a biliary plastic stent and was referred to our hospital for a closer examination and treatment.

She had a history of uterine myoma, and her family history included an elder brother with lung cancer. She was a non-smoker and social drinker. Her pancreatic enzymes were elevated, including amylase 389 IU/L (reference range: 40-113 IU/L), lipase 1,112 IU/L (reference range: 11-53 IU/L) and elastase I 5,444 ng/dL (reference range: <300 ng/dL). Serum concentrations of the tumor markers carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9) and DUPAN 2 were normal. Serum IgG4 was elevated to 674 mg/dL (reference range: <135 mg/dL). Contrast-enhanced abdominal CT demonstrated a 20-mm hypovascular mass in the pancreatic head (Fig. 1). Diffusion-weighted magnetic resonance imaging (MRI) revealed diffusion restriction of the mass (Fig. 2a). The main pancreatic duct (MPD) and lower common bile duct (CBD) were obstructed by the mass, causing upstream dilatation on magnetic resonance cholangiopancreatography (MRCP) (Fig. 2b). Endoscopic ultrasonography (EUS) showed a low-echoic mass



Figure 1. Contrast-enhanced abdominal computed tomography showing a 20-mm hypovascular mass in the pancreatic head (arrows).

with hyperechoic strands in the pancreatic head (Fig. 3a). Endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) of the mass in the pancreatic head was performed using a 22-gauge needle (Fig. 3b), but there was no evidence of either malignancy or AIP due to insufficient material. One month later, the pancreatic head mass diminished spontaneously. The elevation of serum IgG4, characteristics of EUS imaging, spontaneous regression of the pancreatic head mass and lack of evidence of malignancy on EUS-FNA suggested a diagnosis of mass-forming pancreatitis, particularly focal type 1 AIP.

Three months later, however, this patient developed obstructive jaundice due to dysfunction of the plastic stent. CT showed three masses, one each in the perihilar bile duct and the middle and lower portions of the CBD (Fig. 4a-c), along with the invasion of the major papilla from the mass into the lower portion of the CBD (Fig. 4d). Endoscopic retrograde cholangiography (ERC) showed filling defects at the three sites (Fig. 5a), and endoscopic nasobiliary drainage (ENBD) was subsequently performed. Although the finding of the major papilla was normal on ERC at the onset (Fig. 5b), it was invaded by the mass in the lower portion of the CBD (Fig. 5c). The proliferation of oval cells with a high nucleus/cytoplasm ratio was observed on a biopsy of the major papilla (Fig. 6a). Immunohistochemistry showed that the masses were positive for the B cell marker CD20 but negative for the T cell markers CD3 and CD5 (Fig. 6b, c). The Ki-67 index was almost 100%. A biopsy of the major papilla and the mass in the middle portion of the CBD resulted in a diagnosis of DLBCL. ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning revealed the strong accumulation of radioactivity, corresponding to the three masses revealed by CT as well the right peri-renal lesion. Her serum concentration of soluble interleukin-2 receptor (sIL-2R) was elevated to 852 U/mL (reference range: 127-582 U/mL).

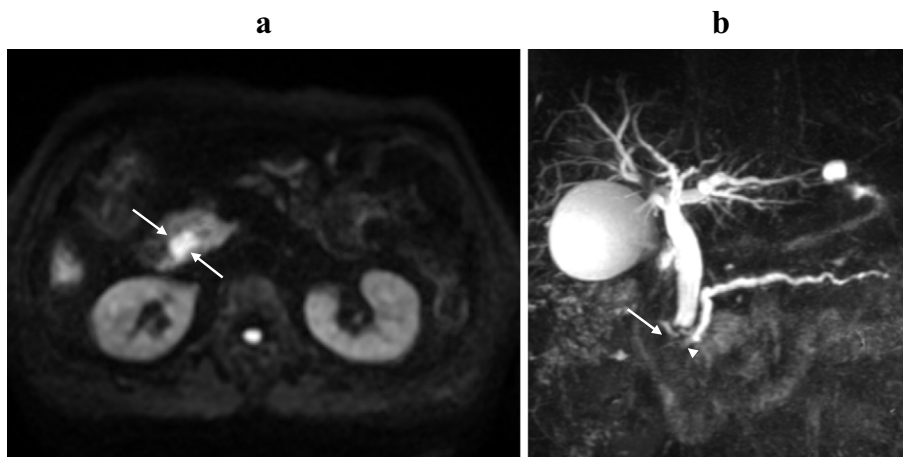


Figure 2. a: Diffusion-weighted magnetic resonance imaging showing diffusion restriction of the mass (arrows). b: Magnetic resonance cholangiopancreatography showing defects of the main pancreatic duct (MPD) (arrowhead) in the pancreatic head and of the lower common bile duct (CBD) (arrow), accompanied by upstream dilatation of the MPD and CBD.

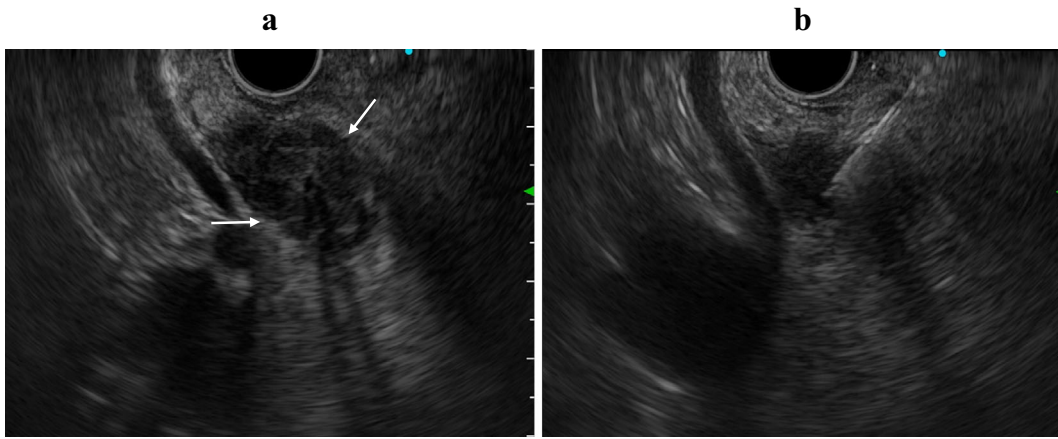


Figure 3. a: Endoscopic ultrasonography showing a low-echoic mass with hyperechoic strands in the pancreatic head (arrows). b: Endoscopic ultrasonography-guided fine needle aspiration of the pancreatic head mass, performed using 22-gauge needle, showing no evidence of malignancy or AIP.

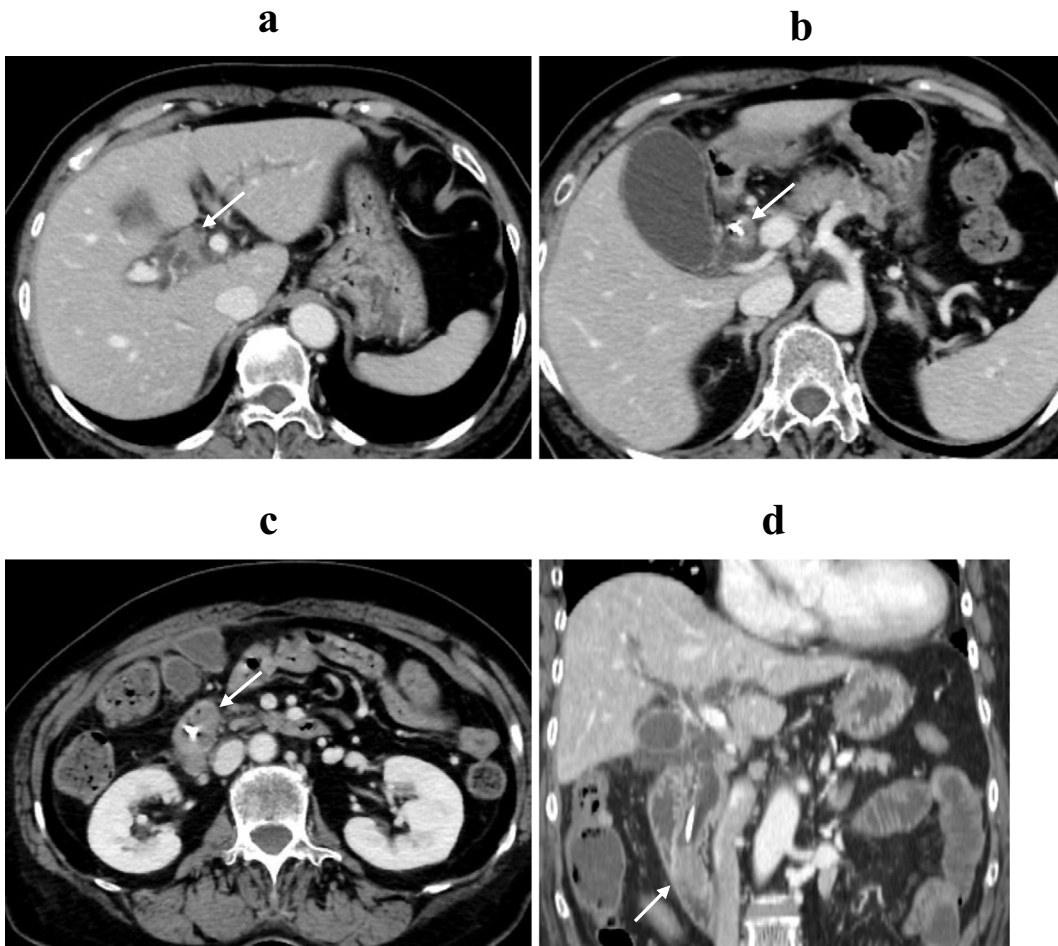


Figure 4. Contrast-enhanced abdominal computed tomography showing one mass each in the perihilar bile duct (a) and middle (b) and lower (c) portions of the common bile duct (arrows). The mass in the lower portion of common bile duct (d) suggested invasion of the major papilla (arrow).

Based on a diagnosis of DLBCL, she was treated with systemic chemotherapy, consisting of rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). FISH, however, showed rearrangement of *MYC* and *BCL2* (Fig. 6d, e), and she was re-diagnosed with high-grade

B-cell lymphoma (HGBL), with *MYC*, *BCL2* and/or *BCL6* rearrangement (17). Her systemic chemotherapy regimen was switched to rituximab plus etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin (DA-EPOCH-R) (18). After one cycle of DA-EPOCH-R, the three masses

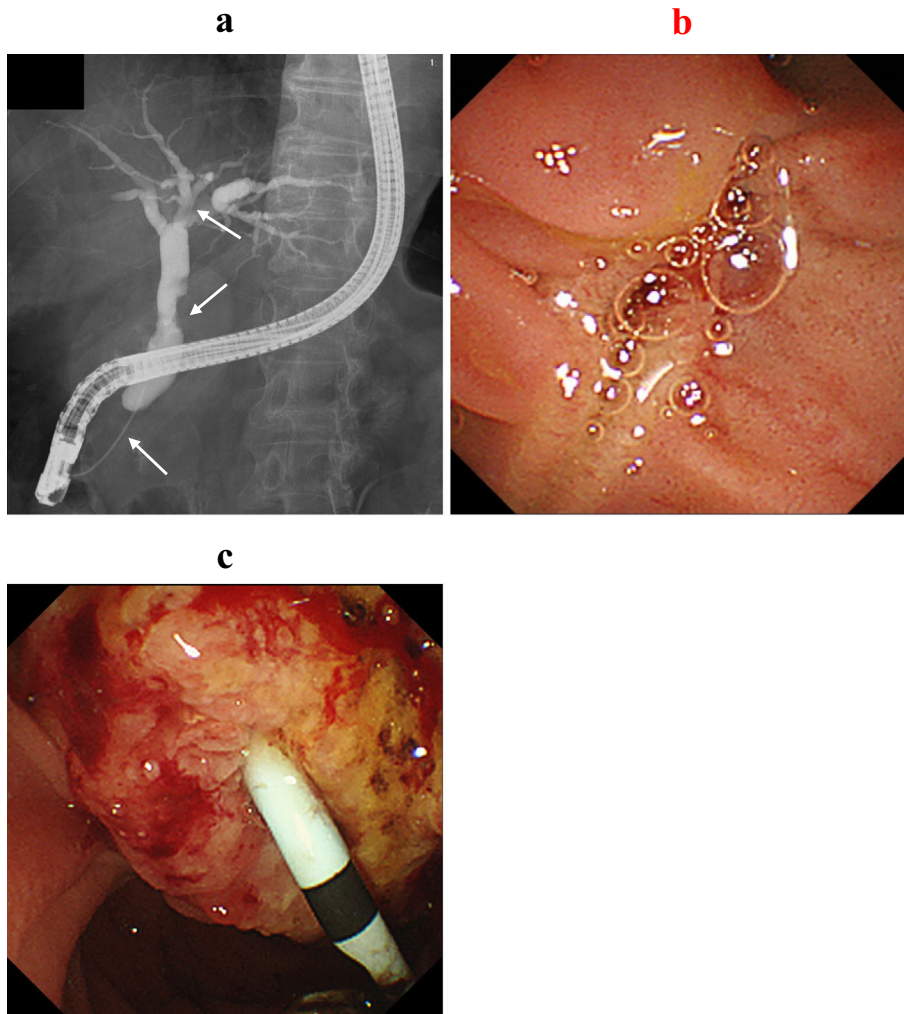


Figure 5. a: Endoscopic retrograde cholangiography showing filling defects in the perihilar bile duct and the middle and lower portions of the common bile duct (arrows). b: Normal findings of the major papilla on endoscopic retrograde cholangiography at the onset. c: Invasion of the major papilla by the mass in the lower portion of the common bile duct, followed by a biopsy of the major papilla.

in her bile duct were dramatically reduced in size. She was treated with eight cycles of DA-EPOCH-R. Complete remission has been maintained for 18 months since the tumor onset.

Discussion

NHL accounts for 1-2% of all cases of malignant biliary obstruction (19). NHL arising from the extrahepatic bile duct is very rare, with only about 30 cases reported to date in the English-language literature (1-3). The most frequent histological type of NHL arising from the extrahepatic bile duct has been reported to be B cell lymphoma, particularly DLBCL. These tumors can be treated with surgery alone or surgery followed by chemotherapy and/or radiotherapy. To our knowledge, this is the first case report of a high-grade B-cell lymphoma with *MYC*, *BCL2* and/or *BCL6* rearrangement (17) in the bile duct. In addition, although most reported NHLs arising from the extrahepatic bile duct con-

sisted of only one lesion and were not diagnosed preoperatively (1-3), the NHL in the present patient consisted of three masses that developed simultaneously in the bile duct and were diagnosed as NHL by an endoscopic biopsy.

This patient was not evaluated by endoscopic retrograde pancreatography (ERP), and the EUS-FNA biopsy of the pancreatic head mass showed no evidence of AIP. Over 60% of patients with AIP were reportedly unable to be histologically diagnosed by EUS-FNA alone (4). Therefore, based on the 2018 Japanese diagnostic criteria for AIP (20), the pancreatic head mass in this patient could not be diagnosed as type 1 AIP. Typical EUS findings of AIP have been reported to be a relatively diffuse homogeneous hypoechoic pattern and linear or reticular (tortoiseshell pattern) hyperechoic inclusions (21). In addition, the characteristic findings of EUS in patients with AIP have been reported to be hyperechoic foci in 32 (100%) patients, hyperechoic strands in 26 (81.3%), lobularity in 17 (53.1%) and lobular outer margins in 19 (62.5%) (22). In contrast, the ultrasonographic image

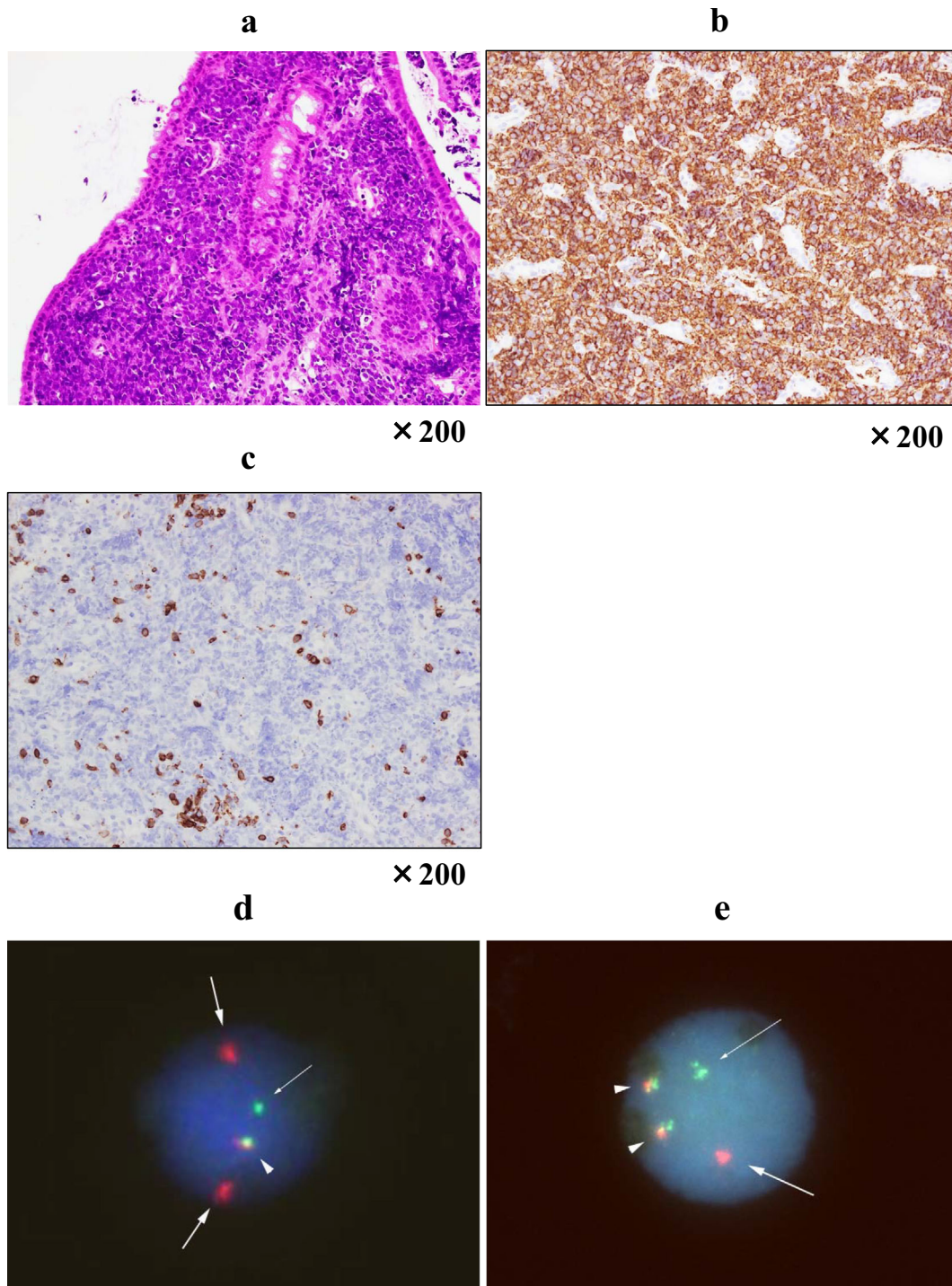


Figure 6. Morphologic suspicion of a diffuse large B cell lymphoma based on a biopsy of the major papilla, followed by a subsequent diagnosis by FISH of high-grade B-cell lymphoma, with *MYC* and *BCL2* rearrangement. a: Hematoxylin and Eosin staining. b: Immunohistochemistry for CD20 was positive. c: Immunohistochemistry for CD3 was negative. d: Red (thick arrows), green (thin arrow) and yellow (arrowhead) signals indicate 5' *MYC*, 3' *MYC* and 5'/3' *MYC* probes, respectively. e: Red (thick arrow), green (thin arrow) and yellow (arrowheads) signals indicate *BCL2* (18q21), *IGH* (14q32) and *IGH/BCL2* probes, respectively. *MYC* break apart probe (d) and *IGH/BCL2* fusion probe (e) showing *MYC* and *IGH/BCL2* rearrangement.

of primary pancreatic lymphoma has been reported to be heterogeneous or hypoechoic (23, 24). The EUS findings of the pancreatic head mass in this patient were consistent with the typical EUS findings of AIP but not pancreatic lym-

phoma. These findings, along with the elevated serum IgG4 levels, spontaneous regression of the pancreatic head mass and lack of evidence of malignancy by EUS-FNA, suggested a diagnosis of focal type 1 AIP, although the possibility of

primary pancreatic lymphoma was not completely excluded.

Various types of malignancy, including lung cancer, colon cancer and lymphoma, have been observed in 11 (10.4%) of 106 patients with IgG4-RD (9). In addition, 18 cancers were detected in 15 (13.9%) of 108 patients with AIP during a median follow-up period of 3.3 years (10), suggesting that AIP may develop into a paraneoplastic syndrome in some patients. The frequency of prior malignancy has been reported to be over three-fold higher in IgG4-RD patients than in matched controls (11), suggesting that cancer may trigger the expression of autoantigens, leading to IgG4-RD. Malignancies were found in 12 (10.1%) of 118 patients with IgG4-RD, with lymphoma being the most frequent (12). However, other studies have found that the incidence of malignancies in patients with AIP and IgG4-RD was similar to that observed in the general population (25-27). Whether or not the incidence of malignancies is higher in patients with IgG4-RD than in the general population is thus unclear.

A study of eight patients with lymphoma combined with IgG4-RD found that two had mucosa-associated lymphoid tissue (MALT) lymphomas, four had DLBCL, one had lymphoplasmacytic lymphoma, and one had low-grade follicular lymphoma (13), whereas a reported describing three patients with B-cell lymphomas combined with IgG4-RD found that two had been diagnosed with AIP (14). In East Asia, however, MALT lymphoma is the dominant histopathological type of lymphoma observed in patients with IgG4-RD (15, 16). The likelihood of developing lymphoma may be higher in individuals with IgG4-RD than in those without it, and there may even be an etiologic link between these two conditions (9, 13, 14, 28). In addition, chronic antigenic stimulation in patients with IgG4-RD may increase the risk of malignancies (9, 13, 15, 28). Two mechanisms of carcinogenesis, i.e. chronic inflammation-induced carcinogenesis and paraneoplastic syndrome, are speculated to be involved in the relationship between autoimmune diseases and malignancies (10, 29). Chronic inflammation has been reported to induce carcinogenesis in the affected organs, such as with gastric cancer induced by *Helicobacter pylori* and hepatocellular carcinoma induced by hepatitis C viral infection. Lymphoma of the lower portion of the CBD in our patient developed near the pancreatic head mass and diminished spontaneously. The mechanism by which lymphoma developed in our case is still unclear. The time interval between the onset of AIP and lymphoma (three months) seems too short for inflammation-induced carcinogenesis. Thus, it is possible that paraneoplastic theory or other unknown mechanisms might be involved in our case. The underlying mechanisms between IgG4-RD and malignant lymphoma with a large case series should be explored in a future study to improve the management of patients with IgG4-RD.

HGBL with *MYC*, *BCL2* and/or *BCL6* rearrangements has been described as a high-risk variant of aggressive NHL with a poor prognosis (30, 31). Although the three-year relapse-free survival (RFS) and overall survival (OS) rates did not differ significantly in patients who did and did not

undergo autologous stem-cell transplantation (autoSCT), the three-year RFS rates were lower in patients who received R-CHOP than intensive therapy, including DA-EPOCH-R (18). Although the present patient was initially treated with R-CHOP, based on a diagnosis of DLBCL, she was switched to DA-EPOCH-R following the diagnosis of HGBL with FISH-determined *MYC*, *BCL2* and/or *BCL6* rearrangement (18), resulting in complete remission.

In conclusion, we herein report a rare case of multiple malignant lymphomas of the bile duct that developed after spontaneous regression of an AIP-like mass. The patient was diagnosed with HGBL with FISH-detected *MYC*, *BCL2* and/or *BCL6* rearrangement.

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

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