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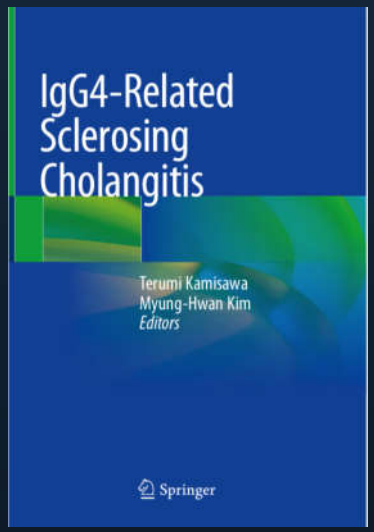
# IgG4-related sclerosing cholangitis (IgG4-SC)

Short Review



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# Characteristic Features

- Elevated serum IgG4 level (10% of IgG4-SC cases show lower serum IgG4 level than cutoff value)
- Pancreas is the most common organ involved other than the bile duct
- IgG4-related disease (IgG4-RD) including IgG4-SC was originally suspected to be an autoimmune disorder based on its frequent association with ANA positivity and steroid responsiveness.
- Patients with IgG4-RD are older (median age, 67 years) and 80% are male

**Table 7.1** Diagnostic criteria with histologic and imaging findings, serum tests, organ manifestation pattern, and response to immunosuppressive therapy (HISORt criteria) for IgG4-related sclerosing cholangitis (cited from [7])

| Feature | Characteristics |
|---|---|
| Histology of bile duct | Lymphoplasmacytic sclerosing cholangitis on resection specimens (lymphoplasmacytic infiltrate with >10 IgG4-positive cells/HPF within and around bile ducts with associated obliterative phlebitis and storiform fibrosis)[a] |
| Imaging of bile duct | One or more strictures involving intrahepatic, proximal extrahepatic, or intrapancreatic bile ducts fleeting/migrating biliary strictures |
| Serology | Increased levels of serum IgG4 |
| Other organ involvement[b,c] | Pancreas, classic features of autoimmune pancreatitis on imaging or histology[d]; suggestive pancreatic imaging findings, focal pancreatic mass/enlargement without pancreatic duct dilatation, multiple pancreatic masses, focal pancreatic duct stricture without upstream dilatation, pancreatic atrophy<br>Retroperitoneal fibrosis<br>Renal lesions: single or multiple parenchymal low-attenuation lesions (round, wedge-shaped, or diffuse patchy)<br>Salivary/lacrimal gland enlargement |
| Response to steroid therapy | Normalization of liver enzyme levels or resolution of stricture[e] |

[a]Bile duct biopsy specimens often do not provide sufficient tissue for a definitive diagnosis. In such specimens, IgG4 immunostaining showing >10 IgG4-positive cells/HPF is suggestive of IgG4-related sclerosing cholangitis (IgG4-SC); however, the specificity of this finding is not known

[b]IgG4 immunostaining of involved organs shows >10 IgG4-positive cells/HPF

[c]The presence of inflammatory bowel disease (IBD) suggests primary sclerosing cholangitis rather than IgG4-SC; however, the absence of IBD does not help diagnose IgG4-SC in an individual patient

[d]Diffusely enlarged pancreas with delayed enhancement and capsule-like rim. Diffusely irregular, attenuated main pancreatic duct multiple strictures or long stricture without upstream dilatation

[e]Complete resolution of stricture may not be seen in all patients, especially those early in the course of treatment (<6 weeks) or with predominantly fibrotic strictures

Gastroenterology. 2008;134:706–15

**Table 7.2** Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012 (cited from [12])

| |
|---|
| A. Diagnostic criteria |
| 1. Biliary tract imaging reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with the thickening of bile duct wall |
| 2. Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dl) |
| 3. Coexistence of autoimmune pancreatitis, IgG4-related dacryoadenitis/sialadenitis, or IgG4-related retroperitoneal fibrosis |
| 4. Histopathological examination shows:<br>(1) Marked lymphocytic and plasmacyte infiltration and fibrosis<br>(2) Infiltration of IgG4-positive plasma cells, >10 IgG4-positive plasma cells/HPF<br>(3) Storiform fibrosis<br>(4) Obliterative phlebitis |
| Option: effectiveness of steroid therapy<br>A specialized facility, in which detailed examinations such as endoscopic biliary biopsy and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) can be administrated, may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or biliary cancers have been ruled out. |
| B. Diagnosis |
| Definite diagnosis: 1 + 3, 1 + 2 + 4 (1) (2), 4 (1) (2) (3), 4 (1) (2) (4)<br>Probable diagnosis: 1 + 2 + option<br>Possible diagnosis: 1 + 2 |

Note: It is necessary to exclude primary sclerosing cholangitis, malignant diseases such as pancreatic or biliary cancers, and secondary sclerosing cholangitis caused by the diseases with obvious pathogenesis. If IgG4-related sclerosing cholangitis cannot be clinically ruled out, a patient must not be treated with facile steroid therapy but should be referred to a specialized medical facility

J Hepatobiliary Pancreat Sci. 2012;19:536–42.

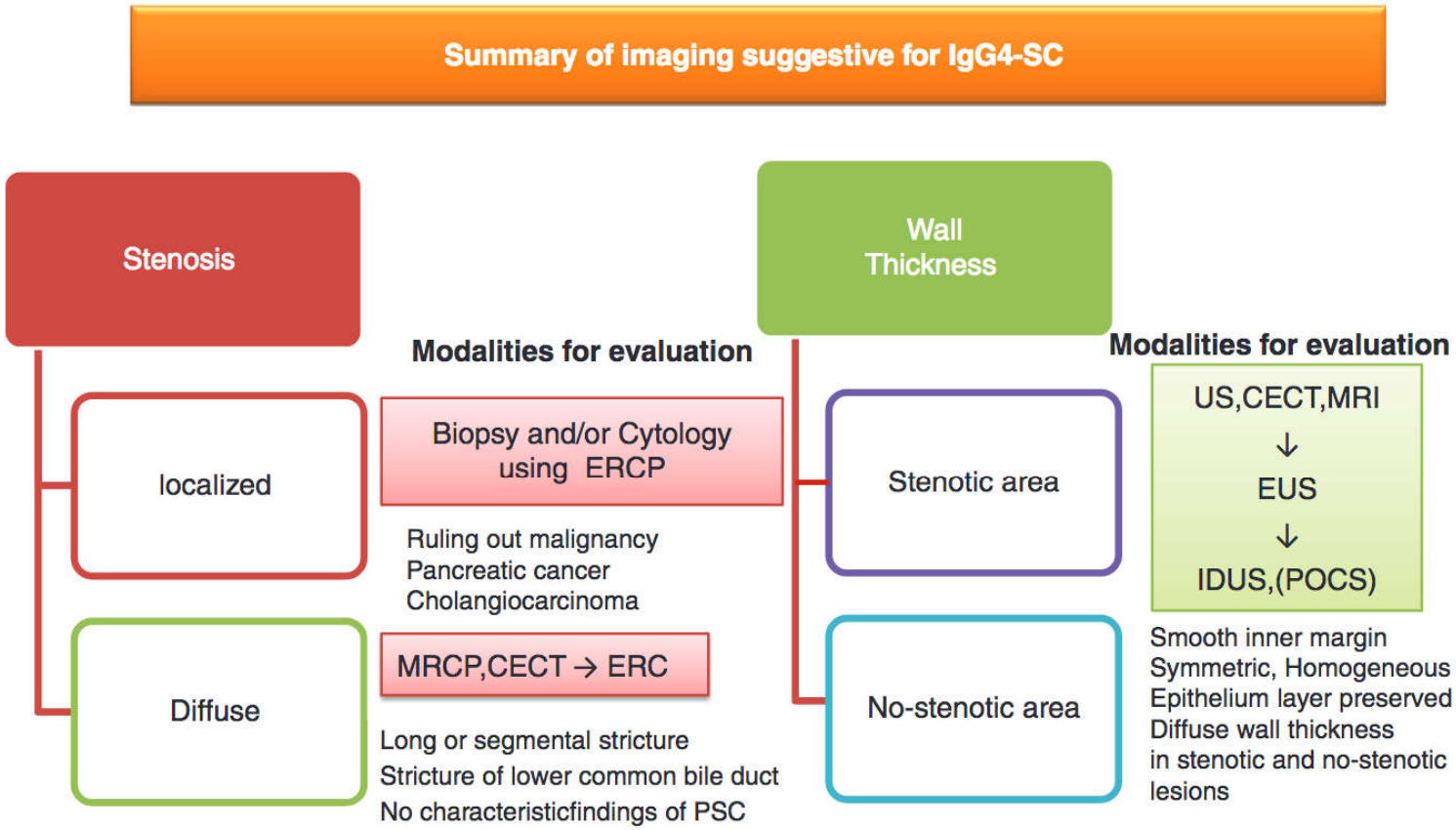
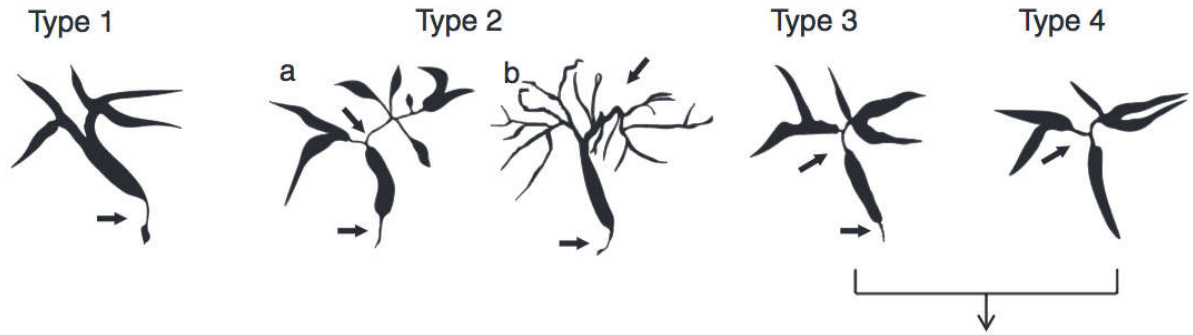



**Fig. 1.2** Images suggestive for IgG4-SC. If stenosis is localized, bile duct biopsy is necessary in order to rule out cholangiocarcinoma. If stenosis is diffusely distributed, cholangiography can discriminate IgG4-SC from PSC. Diffuse bile duct wall thickness without injury of epithelium is characteristic for IgG4-SC




| | | | |
|---|---|---|---|
| Differential diagnosis | Pancreatic cancer<br>Bile duct cancer<br>Chronic pancreatitis | Primary sclerosing cholangitis | Bile duct cancer<br>Gallbladder cancer |
| Useful modalities | IDUS* (bile duct)<br>EUS-FNA** (pancreas)<br>Biopsy (bile duct) | Liver biopsy<br>Colonoscopy<br>(R/O coexistence of IBD ***) | EUS (bile duct, pancreas)<br>IDUS (bile duct)<br>Biopsy (bile duct) |

**Type 1** Stenosis is located only in the lower part of the common bile duct

**Type 2** Stenosis is diffusely distributed in the intra and extrahepatic bile ducts

Type 2a. Extended narrowing of the intrahepatic bile ducts with prestenotic dilation is widely distributed.

Type 2b Narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches is widely distributed.

**Type 3** Stenosis is detected in both the hilar hepatic lesions and the lower part of the common bile ducts.

**Type 4** strictures of the bile duct are detected only in the hilar hepatic lesions.

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# Treatment

» The treatment strategy is basically similar to that for type 1 AIP. Steroid (prednisone at a dose of 0.6 mg/Kg/day) and titrating down the dose as the laboratory results including serum IgG4 improve.

» Although disease relapse is relatively common, IgG4-SC is considered a “benign” disease with a low risk of liver failure and biliary malignancy

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# Treatment

» Maintenance Therapy ???

» Immunomodulatory Agents second-line therapies for refractory cases (AZA, 6-MP, and MMF)

» Rituximab (RTX)

**Table 19.1** Treatment response and relapse rate of patients with IgG4-SC

| Reference | IgG4-SC/ IgG4-RD[a] (%) | Treatment[a] | | Response to treatment[a] (%) | Relapse[a] (%) | Follow-up[b] (range) |
|---|---|---|---|---|---|---|
| Kamisawa et al. [7] | 314/563 (56) | Steroid therapy | 459 | 451/459 (98) | 110/451 (24) | N.A. |
| | | Surgical resection or observation | 104 | 77/104 (74) | 32/77 (42) | |
| Ghazale et al. [8] | 53/53 (100) | Steroid therapy | 30 | 29/30 (97) | 16/30 (53) | 29.5 |
| | | Surgical resection | 18 | 18/18 (100) | 8/18 (44) | 58 |
| | | Conservative | 5 | N.A. | 0 (0) | 35 |
| Sandanayake et al. [9] | 23/28 (82) | Steroid therapy | 28 | 28/28 (100) | 8/23 (35) | 29 (6–53) |
| Huggett et al. [10] | 68/115 (59) | Steroid therapy | 98 | 95/97 (97) | 58/115 (50) | 32.5 (0.8–107) |
| | | Surgical resection or observation | 17 | N.A. | | |
| Hart et al. [11] | 458/724 (63) | Steroid therapy | 684 | 681 (99) | 245/681 (36) | N.A. |
| | | Surgical resection | 150 | 147 (98) | 46/139 (33) | |
| | | Conservative | 67 | 37 (55) | 11/57 (19) | |

*IgG4-SC* IgG4-related sclerosing cholangitis, *IgG4-RD* IgG4-related disease, *N.A.* not available
[a]The number of patients is shown
[b]Median months of follow-up are shown

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# IgG4-related hepatic inflammatory pseudotumor

» Hepatic inflammatory pseudotumors are **benign**

» chronic inflammatory cell infiltration and proliferating fibrous tissue

» 2 type
  – **fibrohistiocytic**
  – **lymphoplasmacytic**

**Table 1** Comparison of histological features between hepatic inflammatory pseudotumors of fibrohistiocytic and lymphoplasmacytic types

| | *Fibrohistiocytic type* (n = *10*) | *Lymphoplasmacytic type* (n = *6*) | P-*value* |
|---|---|---|---|
| Xanthogranulomatous inflammation | 10 (100%) | 0 | <0.001 |
| Multinucleated giant cells | 5 (50%) | 0 | 0.043 |
| Epithelioid granuloma | 1 (10%) | 0 | 0.439 |
| Nodular eosinophilic deposition | 3 (30%) | 0 | 0.150 |
| Neutrophil infiltration (>10 per hpf) | 6 (60%) | 0 | 0.020 |
| Eosinophil infiltration (>5 per hpf) | 1 (10%) | 4 (67%) | 0.022 |
| Plasma cell infiltration (>20 per hpf) | 10 (100%) | 6 (100%) | Identical |
| Russell bodies | 7 (70%) | 6 (100%) | 0.150 |
| Involvement of bile ducts within nodule | 6 (60%) | 6 (100%) | 0.083 |
| *Venous changes* | | | |
| Obliterative phlebitis | 6 (60%) | 6 (100%) | 0.083 |
| Venous occlusion | 4 (40%) | 0 | 0.083 |
| *Cholangitis* | | | |
| Inflammatory cholangitis | 6 (60%) | 0 | 0.020 |
| Sclerosing cholangitis | 0 | 6 (100%) | <0.001 |

hpf, high-power fields; n, number of cases.

Modern Pathology (2007) 20, 884–894

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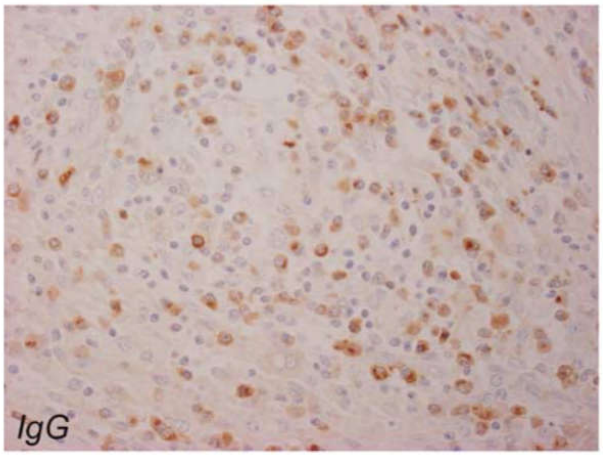
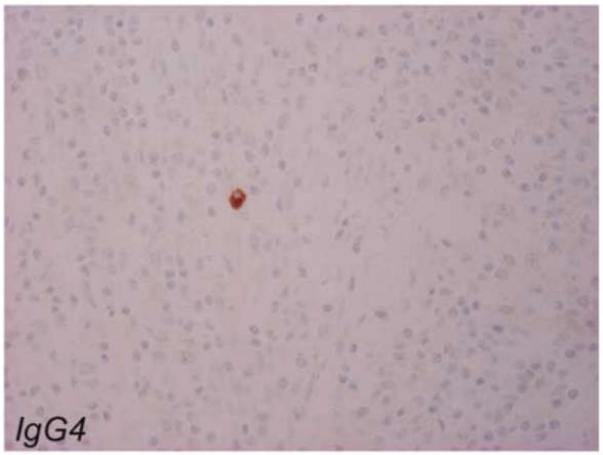
# Immunostaining of IgG4 in Hepatic Inflammatory Pseudotumor

» IgG4-positive plasma cells were significantly more numerous in the **lymphoplasmacytic** than fibrohistiocytic type

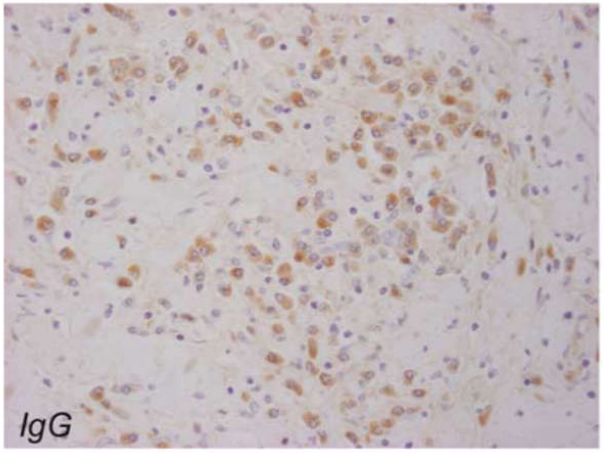
» lymphoplasmacytic inflammatory pseudotumor seems to be a unique disease and to correspond to IgG4-related disease

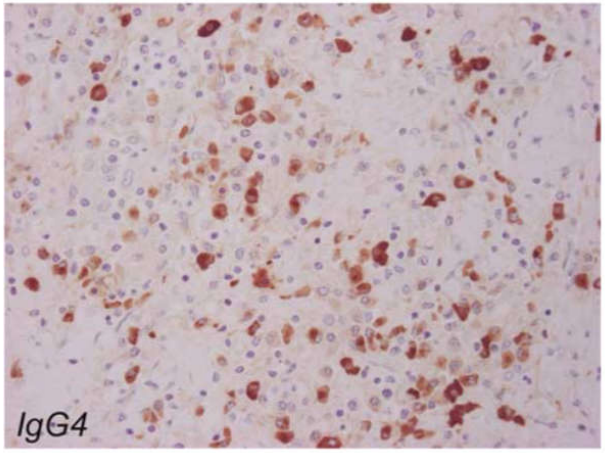
Fibohistiocytic type




Lymphoplasmacytic type




Modern Pathology (2007) 20, 884–894

Case report

# IgG4-related hepatic inflammatory pseudotumor with sclerosing cholangitis: a case report and review of the literature

Itaru Naitoh[1], Takahiro Nakazawa[1]*, Hirotaka Ohara[1], Tomoaki Ando[1], Kazuki Hayashi[1], Hajime Tanaka[1], Fumihiro Okumura[1], Hitoshi Sano[2] and Takashi Joh[1]

Addresses: [1]Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku Nagoya 467-8601, Japan and [2]Department of Gastroenterology, Gifu Prefectural Tajimi Hospital, 5-161 Maehata-cho, Tajimi, 507-8522, Japan

**Table 1.** Summary of reported eight and our IgG4-related hepatic IPT cases

| case | Age (Y) | sex | Clinical Diagnosis | Solitary/multiple | Pancretic IPT | SC | Treatment |
|---|---|---|---|---|---|---|---|
| 1 | 59 | M | Liver cancer | solitary | – | + | Segmentectomy of the liver |
| 2 | 79 | M | ICC | solitary | head | + | Segmentectomy of the liver |
| 3 | 56 | M | ICC | solitary | – | + | Lobectomy of the liver |
| 4 | 64 | M | ICC | solitary | – | + | Lobectomy of the liver |
| 5 | 67 | M | Hepatic hilar cholangiocarcinoma | solitary | – | + | Lobectomy of the liver |
| 6 | 59 | M | Hepatic IPT+AIP | multiple | head | IHBD CBD (MRCP) | PSL |
| 7 | 48 | M | ICC+AIP | multiple | head | lowerCBD (ERCP) | Lobectomy of the liver+PSL |
| 8 | 54 | M | Hepatic IPT+AIP | solitary | head | lowerCBD (ERCP) | No treatment |
| our case | 77 | M | ICC | solitary | – | + | Lobectomy of the liver |

ICC, Intrahepatic cholangiocarcinoma; AIP, Autoimmune pancrealitis; IPT, Inflammatory pseudotumor; PSL, Prednizolone.
case1-5 cited from reference 7, case6 from reference 1, case7 from reference 2, case8 from reference 3.

**Table 1.** Demographic, clinical, laboratory and radiologic characteristics of the 12 patients with localized intrahepatic IgG4-related sclerosing cholangitis.

| Case | Year/country | Sex | Age | Clinical presentation | Serum IgG4 (mg/dL) | Radiologic findings | | Other IgG4-related disease | Treatment | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Location | Imaging feature | | | |
| 1 [16] | 2007/ Japan | M | 54 | Jaundice | 213 | Left lobe | Mass forming-type + Stricture-type | Autoimmune pancreatitis | EBD and biopsy of the hepatic mass; EBD was removed after 7 d | Pancreatic and hepatic masses disappeared naturally after 3 months and 12 months, respectively |
| 2 [17] | 2009/ Japan | M | 77 | Epigastric pain | NA | Left lateral lobe | Mass forming-type | NA | Surgical left lobectomy | NA |
| 3 [20] | 2009/ USA | M | 68 | Obstructive jaundice | 4160 | NA | Mass forming-type | Salivary gland and retroperitoneum | Steroid treatment | Complete biochemical response of liver function tests on steroids |
| 4 [24] | 2010/ Korea | M | 51 | NA | 392 | NA | Stricture-type | NA | Liver biopsy, liver resection and steroid treatment | No relapse |
| 5 [24] | 2010/ Korea | M | 76 | NA | 53 | NA | Stricture-type | NA | Liver biopsy, liver resection and steroid treatment | No relapse |
| 6 [25] | 2011/ Germany | M | 75 | Cholestasis | 0.84 | Left lobe | Mass forming-type | Intrahepatic cholangiocarcinoma | Left hemihepatectomy | More than 2 years after hemihepatectomy, the patient is well, CT scan of thorax and abdomen show no relapse |
| 7 [18] | 2012/ Japan | F | 71 | Routine examination | 241 | Right anterior biliary branches | Periductal infiltrating-type | Autoimmune pancreatitis | Anterior sectionectomy of the liver | NA |
| 8 [19] | 2013/ Japan | M | 78 | Epigastric pain | NA | Left lobe | Stricture-type | No | Lobectomy of the liver | No relapse when 8 months after the operation |
| 9 [21] | 2013/ USA | NA | NA | NA | NA | Right segmental intrahepatic bile duct | Stricture-type | NA | NA | NA |
| 10 [22] | 2014/ USA | NA | 76 | Painless jaundice | 102 | Left hepatic duct | Stricture-type | NA | Radical resection | No relapse of IgG4-RD in any organ |
| 11 [23] | 2017/ USA | NA | NA | NA | NA | Intrahepatic | Mass forming-type | NA | NA | NA |
| 12* | 2017/ China | M | 46 | Routine examination | 1070 | Left lobe | Mass forming-type | Enlargement of axillary lymph node | Left lobectomy of the liver and biopsy for the axillary lymph node | No relapse |

*Present report.
EBD: endoscopic biliary drainage; NA: no information was available

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# Thank You