Gallbladder wall thickening in patients with IgG4-related diseases, with special emphasis on IgG4-related cholecystitis

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Abstract

Objectives. Gallbladder (GB) wall thickening sometimes occurs in patients with autoimmune pancreatitis (AIP), a condition for which the name, IgG4-related cholecystitis, was proposed. We examined the radiological findings of the GB in patients with IgG4-related diseases and clinical features of patients with GB wall thickening and presented a hypothesis of its pathogenesis.

Materials and methods. GB wall thickening was defined by thickness ≥ 4 mm. GB wall thickness was examined in 258 patients with IgG4-related disease. Clinical and imaging findings of 200 patients with AIP with and without GB wall thickening were then compared.

Results. GB wall thickening was detected in 58 patients (29%) with AIP and two patients with isolated IgG4-related sclerosing cholangitis. In the 60 GBs examined, wall thickening was diffuse, with the walls possessing a smooth inner surface. No GB wall thickening was detected among the 56 patients with IgG4-related disease without AIP or IgG4-related sclerosing cholangitis. Bile duct stenosis was detected in 56 patients (97%) with AIP with GB wall thickening. Intraductal ultrasonography indicated cystic duct wall thickening connected to bile duct wall thickening in 11 of 14 (79%) patients with AIP or IgG4-related sclerosing cholangitis with GB wall thickening. Forty-eight patients

in whom IgG4-related cholecystitis was diagnosed experienced resolution of the GB wall thickening after receiving steroid therapy.

Conclusions. Most cases of GB wall thickening in IgG4-related diseases are closely associated with IgG4-related sclerosing cholangitis and may be a manifestation of IgG4-related disease throughout the biliary tract, including the bile duct, cystic duct, and GB.

Keywords: IgG4-related cholecystitis, autoimmune pancreatitis, gallbladder wall thickening, cystic duct

Introduction

Autoimmune pancreatitis (AIP), first proposed in 1995, presumably has an autoimmune etiology [1]. It is characterized by elevated serum IgG4 levels, dense infiltration of IgG4-positive plasma cells and lymphocytes along with storiform fibrosis in the pancreas, and steroid responsiveness. It is currently recognized as a pancreatic manifestation of IgG4-related disease [2]. Stenosis of the bile duct is the most common finding in AIP, and the bile duct wall is usually thickened extensively. Histopathological findings of bile duct lesions in AIP are quite similar to those observed in the pancreas, and the lesions are often described as representing IgG4-related sclerosing cholangitis (IgG4-SC), which is also considered a biliary manifestation of IgG4-related disease [3]. IgG4-related disease can occur in a variety of organs throughout the body synchronously or metachronously.

In 2003, Abraham et al. reported histological evidence of transmural chronic cholecystitis in seven of 20 patients with AIP [4]. Our preliminary report, published in 2006, described gallbladder (GB) wall thickening on imaging studies in ten of 19 patients with AIP [5]. Transmural GB wall thickening stemming from dense fibrosis and abundant infiltration of IgG4-positive plasma cells was detected histopathologically in four of eight patients with AIP. Based on these findings, we proposed sclerosing

cholecystitis associated with AIP as a novel disease entity [5]. In 2012, the name, IgG4-related cholecystitis, was proposed for IgG4-related GB lesions [6]. Several clinical case reports describing IgG4-related cholecystitis [7-14] and one histopathological study analyzing the GB of 22 patients with AIP [15] have thus far been published. The present study examined the radiological findings of the GB in patients with IgG4-related diseases and clinical features of patients with the GB wall thickening and offered a hypothesis of its pathogenesis.

Materials and methods

Patient characteristics

The present study included 258 patients who received the diagnosis of IgG4-related disease between 1992 and 2020 at Tokyo Metropolitan Komagome Hospital or Toho University Omori Medical Center. The cohort included 200 patients with AIP and 58 patients with other IgG4-related diseases (e.g., IgG4-related sialadenitis and/or dacryoadenitis (n=49), IgG4-related retroperitoneal fibrosis (n=7), and isolated IgG4-SC (n=2)). No patient had pancreaticobiliary maljunction on magnetic resonance cholangiopancreatography and/or endoscopic retrograde cholangiopancreatography. AIP and IgG4-SC were diagnosed according to the Diagnostic Criteria for Autoimmune

Pancreatitis (2018) [16] and the Clinical Diagnostic Criteria for IgG4-related Sclerosing Cholangitis (2012) [17], respectively. The median age of the 200 patients with AIP was 66 years (interquartile range (IQR): 59-72 years) and the age range was 25 to 94 years. The ratio of males to females was 2.6:1. Pancreatic enlargement was diffuse (n=104) or localized to the pancreatic head (n=53) or the pancreatic body/tail (n=43). Extrapancreatic lesions were detected in 117 patients with AIP (sclerosing cholangitis (n=84), dacryoadenitis and/or sialoadenitis (n=46), retroperitoneal fibrosis (n=11), and kidney disease (n=2)). Stenosis was detected only in the distal bile duct in 66 patients with AIP and in both the distal and perihilar bile ducts in 18 patients with AIP. One of two patients with isolated IgG4-SC presented with only distal bile duct stenosis while the other patient presented with both distal and perihilar bile duct stenosis. IgG4-related dacryoadenitis and sialadenitis and IgG4-related kidney disease were diagnosed according to the respective diagnostic criteria [18,19]. Other IgG4-related diseases were diagnosed according to the Comprehensive Diagnostic Criteria for IgG4-related Disease (2011) [20]. Steroid therapy was administered to 144 of the patients with AIP, the two patients with isolated IgG4-SC and 30 patients with other IgG4-related diseases.

Methods

The GB of all the patients was examined using abdominal ultrasonography (US, n=159) and/or computed tomography (CT, n=221) before any treatment for IgG4-related diseases was given. The thickness of the GB wall was measured by abdominal US where the cross-sectional area of the GB was largest. In patients who underwent only CT, the maximum thickness of the GB wall was measured. GB wall thickening was defined as a GB wall thickness ≥ 4 mm.

Endoscopic ultrasonography (EUS) was performed in 45 patients with AIP to examine the pancreas, bile duct, and gallbladder. The cystic duct wall was examined in 11 patients.

Intraductal US (IDUS) was performed in 31 patients with AIP with bile duct stenosis and the two patients with isolated IgG4-SC to determine the thickness of the extrahepatic bile duct wall. Cystic duct wall thickness was also examined in 18 patients (14 with, and four without, GB wall thickening).

Extrahepatic bile duct wall thickening was defined as wall thickness ≥ 0.8 mm according to a report by Naitoh et al [21]. The thickness of the cystic duct wall and extrahepatic bile duct wall was examined in nine patients with a normal biliary system on EUS (n=6) and IDUS (n=3). The median thickness of the cystic duct wall was 0.5 mm (IQR: 0.4-0.5 mm), which was close to the median thickness of 0.6 mm (IQR: 0.6-

0.7 mm) of the extrahepatic bile duct wall. Therefore, thickening of the cystic duct wall was defined as a wall thickness ≥ 0.8 mm.

Clinical and imaging features of the patients with AIP and IgG4-SC with and without GB wall thickening, respectively, were also compared.

In total, 48 patients with GB wall thickening received steroid therapy. Follow-up imaging analysis (US (n=17) and/or CT (n=45)) of the GB was performed in 46 patients with AIP and in the two patients with isolated IgG4-SC at a median of 52 days (IQR: 30-82 days) after steroid therapy initiation.

Statistical analyses

Continuous and categorical variables were expressed as the median/IQR and n (%), respectively. The Mann-Whitney U test or Fisher's exact test was used to compare differences between groups of patients with and without GB wall thickening. The paired *t* test was used to evaluate the significance of the difference in GB wall thickness after steroid therapy. $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed with EZR (ver. 1.52), a graphical user interface for R software (The R Foundation for Statistical Computing, version 4.0.2).

The present study was approved by the Institutional Review Board of Tokyo

Metropolitan Komagome Hospital (No. 2609) and the ethics committee of Toho University Omori Medical Center (No. M20227).

Results

GB wall thickening was detected in 58 of 200 (29%) patients with AIP and both patients with isolated IgG4-SC. GB wall thickening was detected in 58 of 86 (67%) patients with IgG4-SC. In all 60 cases, the wall thickening was diffuse, and the inner surface of the wall was smooth (Fig.1A). In contrast, no GB wall thickening was detected among the 56 patients with IgG4-related disease without AIP or IgG4-related SC.

The patients with AIP with and without GB wall thickening showed no significant difference in terms of age at diagnosis, sex ratio, serum IgG4 level or presence of gall stones. Obstructive jaundice was observed more frequently in patients with GB wall thickening (69% vs. 37%, $P<0.001$). Although 37 patients with AIP reported abdominal pain, no patient complained of right hypochondralgia. Bile duct stenosis was detected in 56 of 58 (97%) patients with AIP with GB wall thickening, a rate much higher than the 20% detection rate recorded in patients without GB wall thickening. Enlargement of the pancreatic head was detected in 56 patients with AIP with bile duct stenosis (diffuse

enlargement (n=31) or localized pancreatic head enlargement (n=25)). One of the two, remaining patients with AIP without bile duct stenosis exhibited localized enlargement of the pancreatic head while the other patient exhibited localized enlargement of the pancreatic body and tail. Neither patient had stones or sludge in the GB (Tables 1 and 2).

No significant differences were observed in the clinical or imaging findings among the 86 patients with IgG4-SC with and without GB wall thickening (Table 3).

EUS showed extensive bile duct wall thickening and GB wall thickening in 22 and 13 of 45 patients with AIP, respectively. Cystic duct wall thickening was observed in four patients with thickening of both the extrahepatic bile duct wall and GB wall and one patient with extrahepatic bile duct wall thickening without GB wall thickening (Fig. 3). The frequency of wall thickening in the extrahepatic bile duct and cystic duct was significantly higher in the GB wall thickening group (Table 4).

IDUS revealed extensive extrahepatic bile duct wall thickening in 20 patients with AIP and the two patients with isolated IgG4-SC with GB wall thickening. Cystic duct wall thickening connected to bile duct wall thickening was detected in 11 of 14 (79%) patients with GB wall thickening, but this finding was not observed in any of the four patients without GB wall thickening (Table 5, Fig.2).

GB wall thickening resolved in all 48 patients who underwent steroid therapy (Fig 1B) although the wall thickness did not completely normalize in four patients. The thickness of the GB wall decreased from a median of 4.7 mm (IQR: 4.3-5.2 mm) to 3.0 mm (IQR: 2.4-3.5 mm) (P<0.001). Nine patients experienced a recurrence of AIP and/or IgG4-SC, but no exacerbation of GB wall thickening was observed in any of these patients.

Discussion

IgG4-related disease is a fibro-inflammatory condition involving organ enlargement or nodular/hyperplastic lesions stemming from a high infiltration of lymphocytes and IgG4-positive plasma cells along with fibrosis in a variety of organs. Elevated serum IgG4 levels and responsiveness to steroid are also characteristic, and sometimes several organs are affected simultaneously or metachronously [2, 20]. AIP is the typical phenotype in individuals with IgG4-related disease, and sclerosing cholangitis is most frequently associated with this condition. A nationwide survey in Japan indicated that 49% of patients with AIP had IgG4-SC [22] while 84% of patients with IgG4-SC had AIP [23]. Our preliminary study in 2006 found GB wall thickening via imaging studies in 53% of 19 patients with AIP [2], but the clinical features of these patients were not

recorded.

A previous, histological study of GB lesions in AIP demonstrated that 12 of 20 (60%) patients exhibited intense infiltration of inflammatory cells, and seven patients (35%) exhibited transmural chronic cholecystitis [4]. Our 2006 histopathological study detected transmural GB wall thickening involving fibrosis and abundant IgG4-positive plasma cell infiltration in four of eight patients with AIP [5]. Wang et al. observed dense transmural infiltration in 41% of AIP cases but in only 4% of pancreatic cancer-associated cases and 0% of primary sclerosing cholangitis cases. Furthermore, phlebitis, inflammatory nodules, and dense IgG4-positive plasma cell infiltration in the GB were noted almost exclusively in patients with AIP. The authors concluded that GB involvement in AIP is a primary manifestation of this disease rather than a secondary phenomenon related to biliary obstruction [15].

In the present clinical study of 258 patients with IgG4-related disease, GB wall thickening was detected in 60 patients (23%), including 58 with AIP and two with isolated IgG4-SC. GB wall thickening was detected in 29% of the patients with AIP and 67% of those with IgG4-SC. In contrast, none of the 56 patients with IgG4-related disease without AIP or isolated IgG4-SC exhibited GB wall thickening.

Bile duct stenosis was observed in 58 (97%) of the 60 patients, as a direct result of

bile duct wall thickening. Extensive bile duct wall thickening was the most characteristic finding in the patients with IgG4-SC [3] and was observed in 20 patients with AIP and both patients with isolated IgG4-SC with GB wall thickening who underwent IDUS. Furthermore, cystic duct wall thickening connected to bile duct wall thickening was observed in 11 of 14 (79%) patients with GB wall thickening. GB wall thickening in AIP was closely related to the presence of IgG4-SC. Therefore, we hypothesized that the mechanism of GB wall thickening involved the manifestation of IgG4-related disease in the entire total biliary tract, including the extrahepatic bile duct, cystic duct, and GB; or inflammation in the bile duct wall spreading to the GB wall via the cystic duct.

Several case reports have described IgG4-related cholecystitis that was resected or biopsied because GB cancer was suspected [8-13]. A focal tumor [8] or thickening of the GB fundus wall [9] has been reported in patients with localized AIP in the pancreatic tail without IgG4-SC. In this study, diffuse thickening of the GB wall was detected in one patient with AIP with localized enlargement of the pancreatic head without stenosis of the bile duct and in another patient with AIP exhibiting localized enlargement of the pancreatic body and tail without bile duct stenosis. In contrast, several cases without AIP involvement exhibiting GB masses with bile duct stenosis, in which the patients

underwent resection or biopsy of the gallbladder due to suspicion of advanced gallbladder cancer, have been reported [10-13], but these may have been cases of isolated IgG4-SC that spread to the GB wall. Feely et al. reported two cases of IgG4-related cholecystitis (a focal mass in the fundus and diffuse thickening of the GB wall) that were resected in patients without IgG4-related disease [13]. Ishigami et al. reported newly occurring IgG4-related cholangitis exhibiting diffuse GB wall thickening as an ectopic relapse of IgG4-related disease in a patient undergoing steroid therapy [14]. We therefore propose that there are two types of IgG4-related cholecystitis with different mechanisms: one type is a total biliary manifestation of IgG4-related disease, and the other type is an isolated GB manifestation of IgG4-related disease. The literature and the present study suggest that the former type may tend to involve diffuse thickening of the GB wall whereas the latter tends to lead to mass formation or localized GB wall thickening.

Resected IgG4-related cholecystitis was histopathologically diagnosed by the presence of fibrosis and abundant IgG4-positive plasma cell infiltration in the GB wall. According to the diagnostic criteria, AIP and IgG4-SC are diagnosed based on a combination of radiological, serological, and histopathological findings, the presence of other IgG4-related diseases, and responsiveness to steroid therapy [16,17], but no

clinical diagnostic criteria for IgG4-related cholecystitis currently exist. To diagnose IgG4-related cholecystitis clinically, it must be differentiated from accompanying GB wall thickening in patients with IgG4-related disease. In the present study, gall stones were detected in 18% of the 60 patients with GB wall thickening. However, none of these patients complained of right hypochondralgia, and the GB wall thickening was diffuse, with the inner surface of the walls being smooth. Although GB wall thickening frequently occurs due to pancreaticobiliary reflux in patients with a pancreaticobiliary maljunction, this condition was not detected in any of the patients in the present study. Furthermore, all 48 patients who underwent steroid therapy experienced resolution of GB wall thickening; the condition was diagnosed in these 48 patients as IgG4-related cholecystitis to exclude GB wall thickening due to other causes such as gall stones or cholestasis [24].

The present study is the first to examine clinically a relatively large number of IgG4-related cholecystitis cases and offered a hypothesis of its pathogenesis. GB wall thickening was observed in 29% of the patients with AIP and 67% of those with IgG4-SC. IgG4-SC was also observed in 97% of the patients with GB wall thickening. The GB wall thickening was diffuse, and the inner surface of the wall was smooth. Furthermore, none of the patients complained of right hypochondralgia. Cystic duct

wall thickening was observed in all 11 cases of GB wall thickening examined with IDUS. GB wall thickening resolved in all patients treated with steroids. Clinically, the presence of diffuse GB wall thickening can be consistent with the diagnosis of IgG4-SC and AIP as an instance of extra-organ involvement.

Our data indicated that most cases of GB wall thickening in IgG4-related diseases are closely related to IgG4-SC and may be a manifestation of IgG4-related disease in the entire biliary tract, including the bile duct, cystic duct, and GB.

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Declaration of interest None

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Figure legends

Figure 1. (A) US showing diffuse wall thickening and a smooth inner surface in the gallbladder in a patient with AIP. (B) The gallbladder wall thickening resolved after steroid therapy.

Figure 2. IDUS showing cystic duct wall thickening (arrow-head) connected to the bile duct wall thickening (arrow) in a patient with AIP with gallbladder wall thickening.

Figure 3. EUS showing cystic duct wall thickening (arrow-head) continuous with the bile duct wall thickening (arrow) in a patient with AIP with gallbladder wall thickening.

Table 1 Clinical, laboratory, and imaging findings of AIP with and without gallbladder wall thickening

	Thickening group (N=58)	Non-thickening group (N=142)	P-value
Age, median years (IQR)	67 (61-72)	66 (58-72)	0.312
Sex, male/female (%)	46/12 (79%)	99/43 (70%)	0.222
IgG4, median mg/dl (IQR)	362 (227-753)	332 (248-573)	0.251
Jaundice	40 (69%)	52 (37%)	<0.001
Abdominal pain	7 (12%)	30 (21%)	0.162
Gall stones	10 (17%)	13 (9%)	0.141
Pancreatic enlargement: diffuse/head/body and tail	31/26/1	73/27/42	..
Pancreatic head enlargement (including diffuse type)	57 (98%)	100 (70%)	<0.001
Distal bile duct stenosis	56 (97%)	28 (20%)	<0.001
Perihilar bile duct stenosis	15 (26%)	3 (2%)	<0.001
Extra-biliopancreatic lesions	16 (28%)	38 (27%)	1

AIP, autoimmune pancreatitis; IQR, interquartile range

Table 2 Two AIP patients with gallbladder wall thickening without bile duct stenosis

	Age	Sex	Pancreatic enlargement	Stone or sludge in gallbladder	Steroid therapy	Wall thickness
1	65	Male	Body and tail	-	-	6 mm
2	81	Female	Head	-	+	4.3 mm

AIP, autoimmune pancreatitis

Table 3 Clinical, laboratory, and imaging findings of IgG4-SC with and without gallbladder wall thickening

	Thickening group (N=58)	Non-thickening group (N=28)	P-value
Age, median years (IQR)	68 (61-72)	66 (60-73)	0.695
Sex, male/female (%)	47/11 (81%)	19/9 (68%)	0.186
IgG4, median mg/dl (IQR)	363 (210-769)	358 (245-652)	0.848
Jaundice	40 (69%)	23 (82%)	0.298
Abdominal pain	7 (12%)	8 (29%)	0.073
Gall stones	11 (19%)	4 (14%)	0.765
Distal bile duct stenosis	57 (98%)	28 (100%)	1
Perihilar bile duct stenosis	17 (29%)	3 (11%)	0.062
Junction of cystic duct stenosis	4 (7%)	2 (7%)	1
Extra biliopancreatic lesions	15 (26%)	6 (21%)	0.791

IgG4-SC, IgG4-related sclerosing cholangitis; IQR, interquartile range

Table 4 EUS findings in AIP with and without gallbladder wall thickening

	Total (N=45)	Thickening group (N=16)	Non-thickening group (N=29)	P-value
EUS findings				
Extrahepatic bile duct wall thickening	22/45 (49%)	13/16 (81%)	9/29 (31%)	0.001
Cystic duct wall thickening	5/11 (45%)	4/7 (57%)	1/4 (25%)	0.046

EUS, endoscopic ultrasonography; AIP, autoimmune pancreatitis

Table 5 IDUS findings in AIP and isolated IgG4-SC with and without gallbladder wall thickening

	Total (N=33)	Thickening group (N=22)	Non-thickening group (N=11)	P-value
IDUS findings				
Extrahepatic bile duct wall thickening	31/33 (94%)	22/22 (100%)	9/11 (82%)	0.104
Cystic duct wall thickening	11/18 (33%)	11/14 (50%)	0/4	0.011

IDUS, intraductal ultrasonography; AIP, autoimmune pancreatitis; IgG4-SC, IgG4-related sclerosing cholangitis

Fig1A

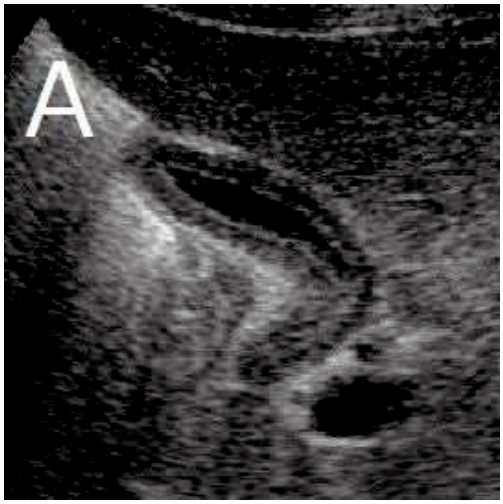

Fig1B

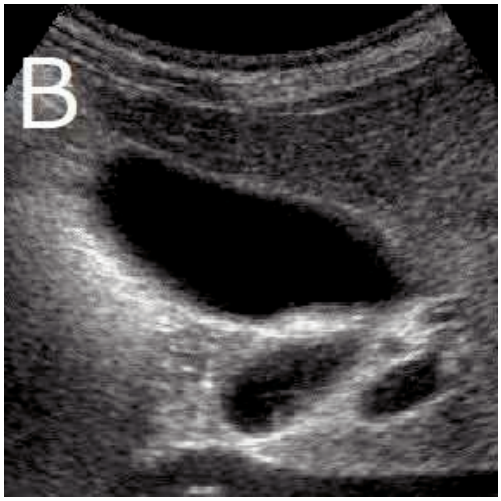

Fig2

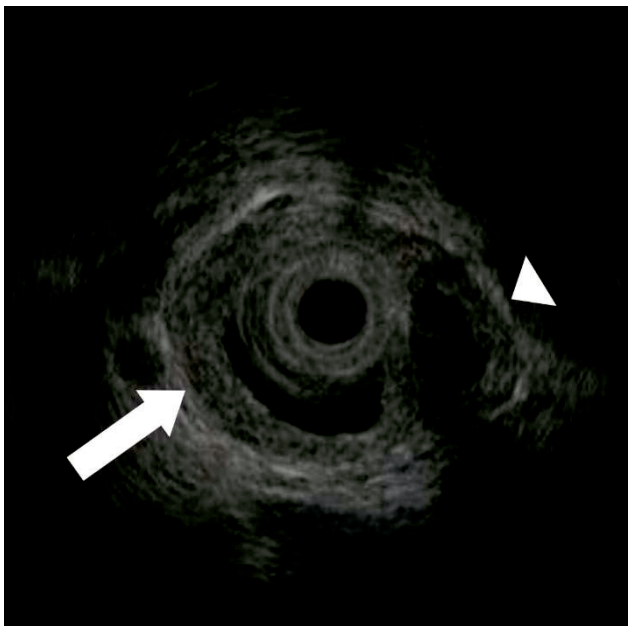

Fig3