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Pancreaticobiliary involvement in treated type 1 autoimmune pancreatitis: Imaging pattern and risk factors for disease relapse

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ABSTRACT

Purpose: To evaluate the imaging pattern of pancreaticobiliary lesions in patients with treated type 1AIP, to determine the incidence of disease relapse and malignancy, and to identify the risk factors.

Method: The institutional review board approval was acquired. All patients gave written informed consent. From a prospective clinico-radiological database since 2012, consecutive patients with type 1 AIP who were treated and followed up (≥18 months) were identified. The presence/absence of pancreaticobiliary lesion(s) development during follow-up were assessed. The etiology was determined and the imaging pattern was compared to the initial attack. Risk factors were identified by univariate and multivariate analysis.

Results: Among 103 patients with treated type 1 AIP, 44 (42.7%) developed pancreaticobiliary lesions during follow up (median time interval to initial diagnosis: 17 months, range 3–62 months), mostly after steroid discontinuation (63.6%) or during maintenance therapy (29.5%). All lesions were disease relapse, which responded to steroid treatment. At relapse, pancreatic involvement was less frequent (81.8% vs 100%, $p = 0.003$), and the pancreas size was smaller ($p < 0.01$), whereas extra-pancreatic bile duct (ExPanBD) involvement was more severe and extensive (both $p < 0.01$). Multivariate analysis revealed ExPanBD involvement at initial diagnosis (hazard ratio 2.437, 95% CI 1.343–7.402, $p = 0.002$) and serum IgG4 response ratio at the induction phase (hazard ratio 0.357, 95% CI 0.055-0.804, $p = 0.011$) as significant independent predictors of relapse.

Conclusions: In treated type 1 AIP, although imaging pattern may differ, pancreaticobiliary lesions are usually manifestations of disease relapse. ExPanBD involvement and poor serum response suggests high risk of relapse.

1. Introduction

Type 1 autoimmune pancreatitis (AIP) is a special type of chronic pancreatitis, which is often accompanied by multiple other organ involvement [1–3]. It is now generally accepted that type 1 AIP is the pancreatic manifestation of a systemic immunoglobulin (Ig) G4-related disease [4]. The disease responds well to steroid treatment with a favorable prognosis. However, the relapse rate is high. In European and Asian patient cohorts, a relapse rate of over 40% (41.2%–47.8%) has been reported [5,6]. Disease relapse often manifests in the pancreas and/or bile ducts, sometimes with other organ involvement as well [1,6]. The diagnosis of disease relapse is not always straightforward. When the original lesions of AIP have already subsided with treatment, sometimes new lesion(s) develop in the pancreas or bile ducts, with a different location and imaging appearance. Such situation is quite challenging: it is mandatory to rule out new neoplastic lesion developed under the ground of AIP. Since AIP often affects elderly male patients, who are exposed to long-term steroid use, development of malignancies

Abbreviations: AIP, autoimmune pancreatitis; IgG4, immunoglobulinG4; ICDC, International Consensus of Diagnostic Criteria; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; MDCT, multi-detector computed tomography; CST, corticosteroid therapy; ExPanBD, extra-pancreatic bile ducts

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during follow-up has been reported [7]. In certain cases, an alternate diagnosis of malignancy should be considered, which disguised as an inflammatory course from the beginning [8,9]. With the above concerns, an extensive clinical work-up, including invasive procedures, is often applied to determine the etiology of the pancreaticobiliary lesions developed in treated AIP patients. A few studies have suggested that during follow-up, the incidence of pancreatic cancer and cholangiocarcinoma in AIP patients is low [5,7]. However, when it comes to the individual patient, it remains challenging to achieve a confident diagnosis at the first place. The knowledge of imaging features and risk factors of pancreaticobilary lesions developed in patients with treated AIP are limited. Therefore, we investigated a prospective cohort of type 1 AIP patients who have received steroid treatment, focusing on the incidence, etiology and imaging pattern of the pancreaticobiliary lesions developed during follow-up. The risk factors for new lesion development were also evaluated, using clinico-radiological data from the baseline and the early stage (induction phase) of treatment.

2. Material and methods

2.1. Patients

This longitudinal cohort study was approved by the institutional review board. All patients have given written informed consent, that their data can be used for scientific evaluation. From a prospectively maintained radiological and clinical database of our institution, consecutive patients who received a diagnosis of type 1 AIP since 2012 were identified. Inclusion criteria were 1) diagnosis of AIP according to the International Consensus of Diagnostic Criteria (ICDC) [4]; 2) regular clinical follow-ups at our institution; 3) imaging studies performed before treatment and during follow-up, including magnetic resonance cholangiopancreatography (MRCP) for ductal evaluation, and contrast-enhanced MRI /CT. Exclusion criteria were 1) less than 18 months of follow-up after initial diagnosis; 2) lack of sufficient data to assess the treatment response and clinical outcome.

The definition of relapse was symptom re-appearance or newly-developed symptoms associated with the disease, and/or imaging findings suggesting pancreatic/extra-pancreatic involvement of IgG4 related disease. An isolated increase in the serum IgG4 concentration was not considered a disease relapse [5,10,11]. Biopsy was performed when the treating physician or the multidisciplinary team panel decided that an alternate diagnosis needs to be ruled out.

2.2. Treatment regimen and follow-up

The corticosteroid therapy (CST) started with prednisolone 0.5–1.0 mg/kg body weight/day (30–60 mg per day) for 1 month, then gradually tapered by 5 mg per 2 weeks until reaching the maintenance dose of 5–10 mg per day. Immuno-suppressive agents were administered in refractory patients. For patients with disease relapse, CST was re-administered at the initial dose.

At the initial diagnosis and during follow-up, serum IgG4 concentration, liver function tests, pancreatic endocrine and exocrine function tests were routinely acquired every 3 months in the first 2 years, and every 6–12 months afterwards. A serum response ratio of IgG4 at the end of the induction phase (3 months after initiation of treatment)was calculated as: (baseline serum IgG4 level - serum IgG4 level at 3-months' follow-up)/ baseline serum IgG4 level.

2.3. Imaging studies

CT examinations were performed on 128-row multidetctor CT scanners (Somatom Definition Flash, Siemens Healthinners, Forchheim, Germany). The scanning parameters were: tube voltage, 120 kVp; effective amperage settings, 150 mAs; gantry rotation time, 0.5 s; table increment, 46.8 mm per rotation; matrix, 512 × 512. Slice thickness 3 mm. After unenhanced scan of the upper abdomen, non-ionic contrast material (Ultravist, 370 mg I/ml, Bayer AG, Berlin, Germany) with 1.5 ml/kg of body weight was injected intravenously at a rate of 3.0 ml/s. Pancreatic arterial phase (PAP) was initiated 15 s after aortic enhancement of 100 HU. The portal venous phase and delayed phase was initiated with a 30-second and 90-second delay after PAP, respectively.

MRCP and contrast-enhanced MRI were performed on a 3 T MR imaging system (MAGNETOM Skyra, Siemens Healthineers, Erlangen, Germany). Isotropic 3D MRCP (TR/TE variable/812 ms, flip angle 100 degrees, slice thickness 1 mm) and thick-slab 2D MRCP was both performed. The other sequences included volume-interpolated breath-hold (VIBE) T1-weighted imaging (TR/TE, 4.11/1.31–2.54 ms, flip angle 12 degrees, FOV 380 × 380, slice thickness 3 mm), turbo-spin-echo (TSE) fat-saturated (fs) T2WI (TR/TE, 2390/81 ms, FOV, 400 × 400, slice thickness 6 mm), Half-Fourier acquisition single-shot turbo spin echo (HASTE) T2WI in coronal and axial plane (TR/TE 2000/92 ms, FOV, 300 × 300, slice thickness 4 mm), and diffusion-weighted imaging (DWI) with b values of 0 and 800 mm^2/sec (TR/TE 3000/53 ms, FOV, 400 × 400, slice thickness 4 mm). A multi-phase contrast-enhanced study was performed after injecting 0.1 mmol per body weight gadobenate dimeglumine (MultiHance, Bracco, Italy) intravenously at a rate of 2 ml/sec through a power injector, followed immediately by a 20 mL saline flush.

2.4. Image analysis

Two radiologists (16 years and 7 years of experience in interpreting abdominal CT and MR, respectively) retrospectively reviewed image data on a local PACS (GE Healthcare, USA). Patient identity, clinical and laboratory findings and treatment history were blinded.

Imaging evaluation was carried out in two steps:

Step 1: Imaging data from the same patient at different time points were taken as independent studies, all were evaluated in random order. The two readers determined the abdominal organ involvement in consensus, taking imaging data from the same patient at different time points as independent studies. The details as follows: The presence/absence of pancreas/bile ducts involvement, and the imaging pattern (diffuse/focal involvement of pancreas; solitary distal/solitary proximal/multiple-segment involvement of bile ducts). Besides, on MRCP studies, the entire pancreaticobiliary system was divided into 8 segments, including pancreatic head, body and tail; intra-pancreatic distal bile duct (InPanBD), extra-pancreatic extra-hepatic bile duct (ExPanExHBD, including cystic duct and gallbladder), hilar bile duct (Hilar BD), the right intra-hepatic bile duct (R-IHBD) and left intra-hepatic bile duct (L-IHBD). The latter 4 segments together comprise extra-pancreatic bile ducts (ExPanBD). The readers recorded the involvement of each specific segment. Other abdominal organ involvement (kidney, aorta, mesentery lesions, peri-pancreatic arteries) and hilar, peri-pancreatic and retroperitoneal lymph node enlargement was also recorded.

One of the readers also took the following measurements: the anterior-posterior diameter of the pancreatic head, body and tail, the maximum thickness of the involved bile duct wall, the maximum diameter of the bile duct lumen of the intra-hepatic bile duct and extra-hepatic bile duct. Each measurement was performed 3 times and the results were averaged.

Step 2: Imaging studies from the same patient were presented to the readers in the chronological order, still with patient identity and clinical information masked. The readers reviewed the image, determined whether there was pancreaticobiliary involvement during follow-up, and compare the image features to the initial attack.

2.5. Statistical analysis

Descriptive data was displayed in terms of percentages and means with standard deviations if they were normally distributed. For patients

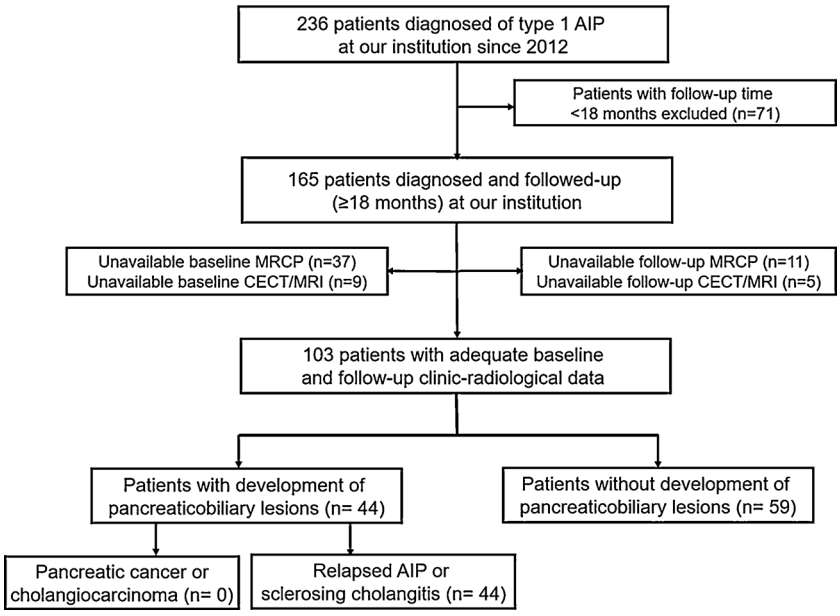

Fig. 1. Flowchart showing enrollment and outcomes of patients with treated type 1 autoimmune pancreatitis (AIP). A total of 236 patients with type 1 AIP has been diagnosed and followed up since 2012. Patients who had a follow-up time of less than 18 months until the time of the study were excluded (n = 71). Patients without available image data of MRCP and enhanced abdominal CT/MRI at our institution at baseline and follow-up were also excluded (n = 62). Finally 103 patients fulfilled the study criteria and 44 of them developed pancreaticobiliary lesions during follow-up, all were proven to be disease relapse.

with relapsed disease, imaging and clinical data at relapse were compared with the initial attack using paired Student's t-test, McNemar's test or Fisher's exact test, as appropriate. Gender, age, clinical findings, laboratory results and radiological features were compared between patients with and without disease relapse, to identify risk factors for relapse. For variables reaching significance level at univariate analysis, further multivariate binary logistic regression analysis was performed, using the backward likelihood ratio method. Statistical analyses were performed using SPSS 17.0 (IBM Corp., Armonk/NY, USA). A double-sided $p < 0.05$ was considered to indicate a statistically significant difference.

3. Results

3.1. Incidence and etiology of pancreaticobiliary lesions developed during follow-up

The flowchart of patient enrollment is shown in Fig. 1. The final cohort consisted of 103 patients with type 1 AIP, who received steroid treatment and underwent regular follow-up (82 male, median age 58 years, range 32–84 years). The median follow-up time was 38 months (range: 18–75 months). Their imaging studies included 283 CTs and 347 MRs. Among those patients, 44 (42.7%) developed pancreaticobiliary lesions during follow-up, after the original lesions had resolved. The majority of lesions developed after steroid discontinuation (28/44, 63.6%), while the remaining lesions developed during steroid tapering (3/44, 6.8%) or during maintenance therapy (13/44, 29.5%). The median time interval to the initial diagnosis was 17 months (range: 3–62 months). Biopsies were performed in 15 patients to determine the etiology of the newly-developed lesions. All lesions were responsive to a new cycle of CST. Radiological follow-up after short-term steroid treatment (range 13–38 days, median 22 days) confirmed lesion resolution/partial resolution in all cases. None of those patients had proven pancreatic cancer, pancreatic endocrine tumor or cholangiocarcinoma during the time of the study. Four patients were diagnosed with malignancy elsewhere during follow-up, including 1 colon cancer, 1 rectal cancer, 1 thyroid cancer and 1 lung cancer.

3.2. Clinical data and imaging pattern at initial diagnosis and relapse

Clinical presentation and laboratory findings at the initial diagnosis and at disease relapse is shown in Table 1. The most common

Table 1
clinical data and abdominal organ involvement at initial diagnosis and relapse.

	Initial diagnosis	Relapse	P value
Symptoms			
Painless jaundice	27 (61.4%)	20 (45.5%)	0.065
Abdominal discomfort	11 (25.0%)	9 (20.5%)	0.625
Weight loss	7 (15.9%)	6 (13.6%)	1.000
Serum IgG4 elevation	41 (93.2%)	40 (90.9%)	1.000
Serum CA19-9 elevation	13 (43.3%)*	10 (22.7%)	0.250 **
Abdominal organ involvement			
Pancreas	44(100%)	36 (81.8%)	**0.008**
Bile ducts	36 (81.8%)	32 (72.7%)	0.567
Kidney	5 (11.4)	10 (22.7%)	0.125
Mesentery	3 (6.8%)	2 (4.5%)	1.000
Aorta	0	1 (2.3%)	1.000
Peri-pancreatic arteries			
Splenic artery	11 (25.0%)	5 (11.4%)	0.070
Celiac artery	2 (4.5%)	2 (4.5%)	1.000
SMA	4 (9.1%)	3 (6.8%)	1.000
Lymph nodes enlargement	26 (59.1%)	23 (52.3%)	0.549

* Serum CA19-9 was tested in a subgroup of patients (n = 30).
** Fisher's exact test performed for 30 patients who had serum CA19-9 value available at initial diagnosis and relapse.

presentation at initial diagnosis was painless jaundice, abdominal discomfort and weight loss. During relapse, the majority of patients (27/44, 61.4%) reported re-appearance of symptoms. Three patients (6.8%) had new symptoms, all presented as painless jaundice. The remaining 14 (34.1%) patients reported no symptom, but imaging revealed pancreaticobiliary lesion development. Therefore, our cohort has a symptomatic relapse rate of 29.1% and clinically silent relapse in 13.6% patients, whose lesions were evident by radiological studies.

The vast majority of patients had elevated serum IgG4 at initial diagnosis and disease relapse (93.2% and 90.9%, respectively). In most patients, a relative rise of serum IgG4 concentration was observed when pancreaticobiliary lesions developed compared to test result from last time. The median value serum IgG4 increase was 2680 mg/dL, ranging: -1250 to 26,500 mg/dL,. Serum CA19-9 was elevated in 43.3% and 22.7% patients at initial diagnosis and relapse, respectively.

At initial diagnosis, all patients had pancreatic involvement, and 81.8% had bile duct involvement. At relapse, pancreatic involvement became less frequent (81.8%, p = 0.008), while incidence of bile duct involvement remained high (72.7%). In 5 (11.4%) patients, new organ

Table 2
Imaging pattern of pancreaticobiliary lesions at initial diagnosis and relapse.

	Initial diagnosis	Relapse	P value
Pancreas			
Imaging pattern			**< 0.001**
Diffuse	34 (77.3%)	12 (33.3%)	
Focal	10 (22.7%)	24 (66.7%)	
Segments involved			
Head	40 (90.1%)	24 (55.8%)[#]	**< 0.001**
Body	36 (81.8%)	25 (56.8%)	**0.020**
Tail	37 (84.1%)	28 (63.6%)	0.051
Size of pancreas (mm)[*]			
Head	34.5 ± 7.2	27.6 ± 6.4	**0.004**
Body	25.0 ± 5.8	17.3 ± 5.5	**< 0.001**
Tail	27.3 ± 6.3	20.2 ± 5.5	**< 0.001**
Bile ducts			
Imaging pattern			**0.002**
Solitary distal BD	13 (36.1%)	6 (18.8%)	
Solitary proximal BD	0	9 (28.1%)	
Multiple BD involvement	23 (63.9%)	17 (53.1%)	
Segments involved			
InPBD	36 (81.8%)	29 (67.4%)[#]	0.065
ExPBD	23 (52.3%)	26 (59.1%)	0.629
ExPExH-BD	14 (31.8%)	19 (43.2%)	0.227
Hilar BD	13 (29.5%)	15 (34.1%)	0.727
R-IHBD	6 (13.6%)	8 (18.2%)	0.754
L-IHBD	4 (9.1%)	7 (15.9%)	0.508
Number of bile duct segments involved[**]	1(1-5)	3(1-5)	**0.019**
Maximal bile duct wall thickness (mm)	2.9 ± 1.1	4.5 ± 2.1	**< 0.001**
Maximal IHBD lumen width (mm)	6.5 ± 4.3	8.6 ± 5.7	0.132
Maximal ExHBD lumen width (mm)	14.5 ± 6.1	11.7 ± 5.2	0.093

InPBD = intra-pancreatic bile duct, ExPBD = extra-pancreatic bile duct, ExPExH-BD = extra-pancreatic extra-hepatic bile duct, Hilar BD = hilar blie duct, R-IHBD = right intra-hepatic bile duct, L-IHBD = left intra-hepatic bile duct.

[#] one patient has received surgery and removed the pancreatic head.

[*] size was measured as anterior-posterior diameter on axial CT/MR images, presented as mean ± standard deviation.

[**] presented as median (range).

was involved at relapse, and in 39 (88.6%) patients, lesions developed in the same organs involved at initial attack.

Imaging pattern of the pancreatic and biliary lesions at initial diagnosis and relapse is shown in Table 2. Concerning the specific segments of the pancreaticobiliary system, in 15 (34.1%) patients, new segments were involved at relapse. In 29 (65.9%) patients, lesions developed in segments that had already been involved at initial attack.

At relapse, the majority (66.7%) of pancreatic involvement manifested as a focal lesion (Fig. 2). This differs from the initial attack, where diffuse pancreatic enlargement was more common ($p < 0.001$). The size of the pancreas was smaller at relapse, compared to the initial attack (for pancreatic head, body and tail, all $p < 0.01$).

For the bile ducts, multiple strictures involving both distal and proximal bile ducts was the most common manifestation both at initial diagnosis and relapse (63.9% and 53.1%, respectively). At relapse, solitary proximal bile duct stricture was also common (28.1%), which, on the contrary, was very rare at the initial diagnosis ($p = 0.002$) (Fig. 3). At relapse, the thickening of the involved bile duct was more severe compared to the initial attack (4.5 ± 2.1 mm vs 2.9 ± 1.1 mm, $p < 0.001$).

3.3. Risk factors for relapse

Clinical factors and imaging features of patients at the initial presentation, and the organ response score and serum response ratio at the induction phase were compared between groups with (n = 44) and without disease relapse (n = 59) in Table 3. Univariate analysis showed that the relapsed group had more male patients, had higher serum IgG4 level at the initial diagnosis, and showed more frequent ExPanBD involvement. The value of maximal thickness of involved bile ducts was higher in the relapsed group. Patients who had relapsed disease also showed a lower response ratio of serum IgG4 level during the initial induction phase. Multivariate analysis identified ExPanBD involvement at initial diagnosis (Odds ratio 2.437, 95% CI 1.343–7.402, $p = 0.002$) and serum IgG4 response ratio at induction phase (Odds ratio 0.357, 95% CI 0.055-0.804, $p = 0.011$) as significant independent predictors of relapse.

4. Discussion

As a relatively new disease entity, our knowledge of AIP has substantially increased in the past few decades [12–14]. The diagnostic criteria has been well established, and the cardinal imaging features on CT/MRI that characterize AIP against neoplastic lesions have been intensively studied [1,4,11,15–20]. However, only a few papers have addressed the evolution of the disease and the post-treatment imaging appearance [1,11,16,17]. Even if the patient had an established diagnosis of IgG4-related AIP, it can be challenging to characterize the new pancreaticobiliary lesions developed after treatment, without being familiar with their image pattern. Great efforts are often made to rule out a neoplasm, which turned out to be unnecessary in many cases. In a prospective patient cohort of treated type 1 AIP patients, we found that pancreaticobiliary lesion development during follow-up was quite common (42.7%). All those lesions responded to CST, suggesting disease relapse. There was no cancer of bile duct or pancreas in this cohort with a median follow-up time of 38 months. This finding suggests that the relapse rate of type 1 AIP was high, and the pancreatic and biliary lesions developed in treated patients were much more likely manifestation of disease relapse, rather than neoplasms of the pancreaticobiliary system. Although no pancreaticobiliary cancer developed in our cohort during follow-up, it is possible that a few cases may finally have pancreatic or bile duct cancer with an extended follow-up time.

Our finding is in alignment with several previous studies. In a multicenter study of type 1 AIP patients from 10 different countries, Hart et al reported a relapse rate of 56% for patients with AIP and IgG4-related sclerosing cholangitis. The diagnosis of pancreatic cancer and cholangiocarcinoma during follow-up was rare (0.5% and 0.3%, respectively), and mostly over 3 years after the AIP diagnosis [21]. In a Korean cohort of type 1 AIP patients with a median follow-up time of 60 months, the relapse rate was 47.8%. None of those patients had cancer from the pancreaticobiliary system during follow-up, although 5 patients (3.6%) had new cancer from other parts of the body [5]. Similarly, in a UK cohort of 115 patients with a median follow-up time of 33 months, relapse occurred in 50%, and pancreaticobiliary cancer was found in only three patients (2.6%) [7]. These data altogether, and the fact that the relapsed pancreatic and bile duct lesions respond well to CST, suggested that in such patients, close radiological follow-up after re-starting CST might replace the invasive procedures for lesion characterization.

On the other hand, although the incidence of pancreaticobiliary malignancy was low (0, 0.8% and 2.6% in the aforementioned studies [5,7,21]), it should not be overlooked. Awareness of the imaging pattern of disease relapse is helpful to enhance the diagnostic confidence. At relapse, lesion migration was common. New organs can be involved (11.4%), but more often, lesions occur in the same organ with location change (34.1%). Relapsed AIP and IgG4-SC has a different imaging pattern compared to the initial attack. The pancreas involvement became less frequent, and when involved, the lesion often appears like a focal mass on the background of pancreatic atrophy. For the biliary system, solitary proximal bile duct stricture was more common at relapse, and the involved bile duct also became thicker, often mimicking hilar cholangiocarcinoma. Multifocal involvement and thinner bile duct walls were imaging features favoring the diagnosis of IgG4-SC against infiltrative bile duct cancer [20]. For the relapsed IgG4-SC, however,

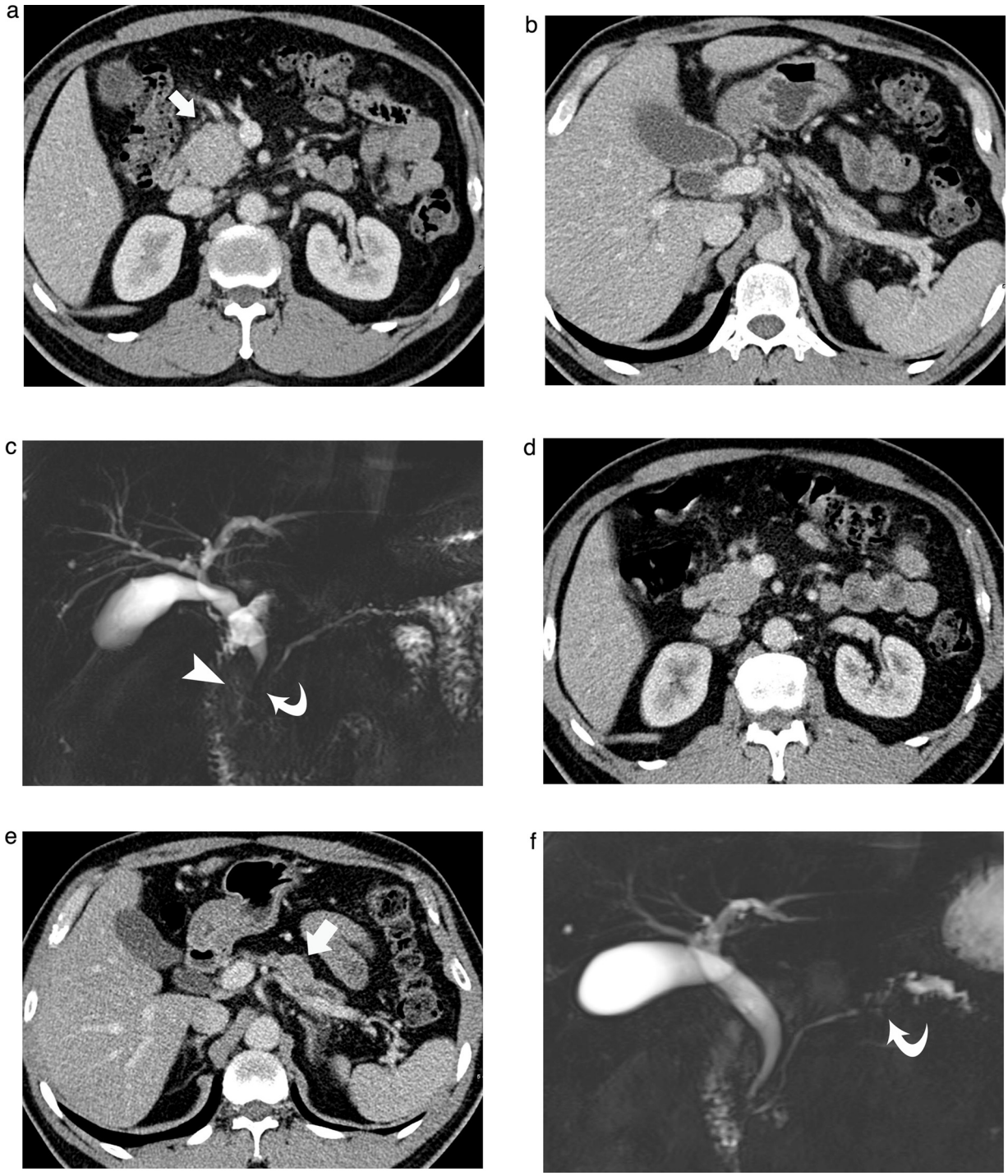

Fig. 2. 58-year-old man with IgG4-related autoimmune pancreatitis. (a–c): images acquired at initial diagnosis. (a) the pancreatic head was enlarged, with a mass-like appearance (straight arrow). (b) Upstream pancreatic parenchyma was atrophied with slight pancreatic duct dilation. (c) MRCP image demonstrated stricture of intra-pancreatic bile duct (arrowhead), as well as main pancreatic duct in the pancreatic head region (curved arrow). After corticosteroid treatment, the lesion resolved (images not shown). (d–f) 3 years later, new pancreatic lesion developed in a different location. (d) the pancreatic head appeared normal. (e) a solid lesion developed in the pancreatic body (straight arrow). (f) MRCP showed pancreatic duct obstruction in the pancreatic body and significant upstream dilation (curved arrow), while bile duct and pancreatic duct in the pancreatic head remained normal. The patient underwent biopsy to rule out a neoplastic lesion of the pancreas, which was negative. The lesion resolved after re-initiation of steroid therapy.

there might be a substantial overlap of such imaging features. In such cases, the previous diagnosis of IgG4-AIP strongly suggests the benign nature of bile duct lesion.

Through multivariate analysis, presence of ExPanBD involvement at initial diagnosis and poorer serum IgG4 response at the induction phase suggests high risk of relapse. Accompanying IgG4-SC at initial diagnosis has been found to be a predictor for relapse [7,21]. Our study, together with several recent studies from Korea and China, have found the Ex-PanBD involvement, rather than bile duct involvement in general, to be more specific for predicting relapse [5,11,22]. It is very frequent that IgG4-SC associated with AIP shows a stricture of the distal BD, which might be caused by compression of the inflamed swollen pancreas,

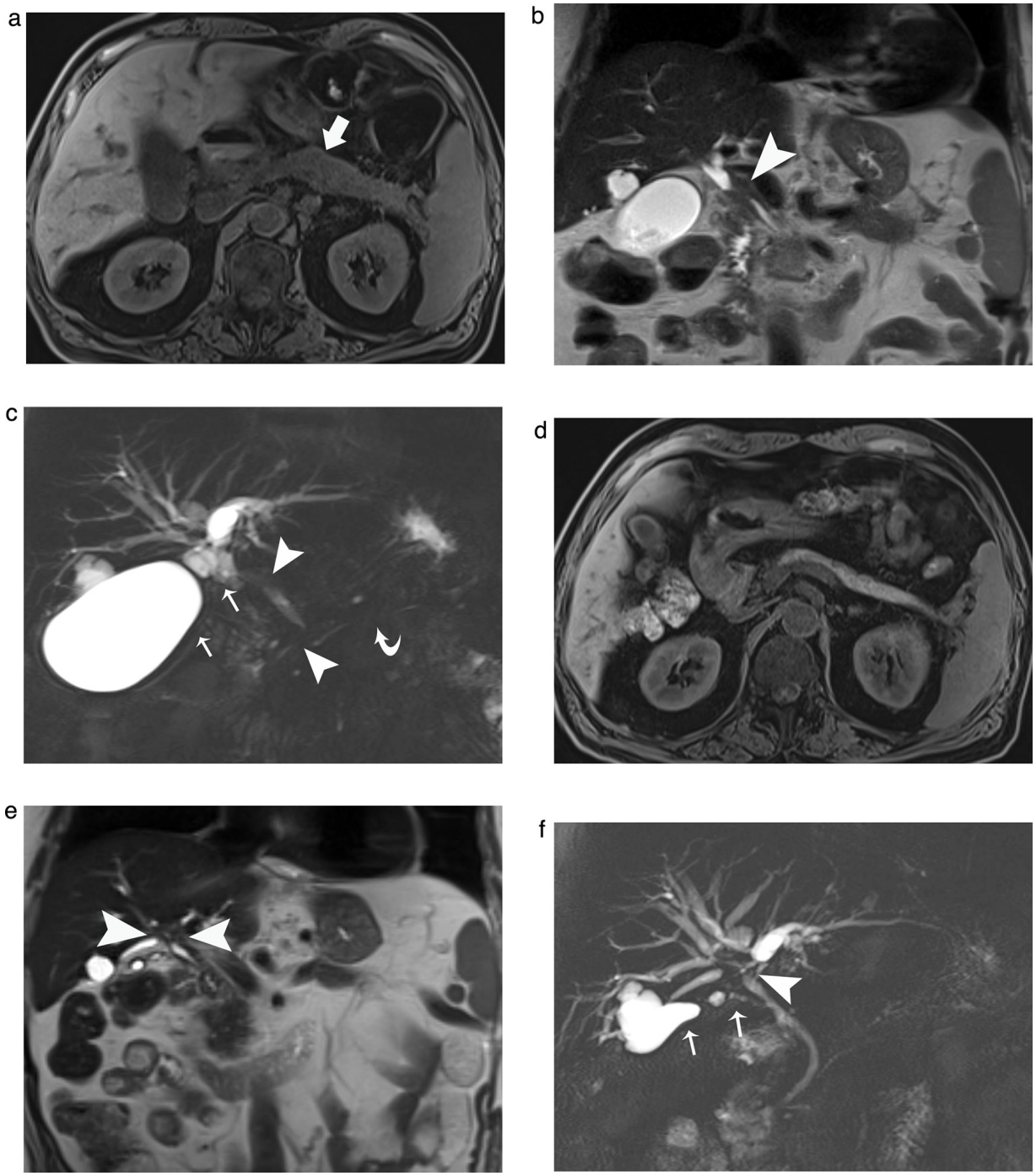

Fig. 3. 79-year-old man with IgG4-related autoimmune pancreatitis. (a–c): images acquired at initial diagnosis. (a) T1 weighted fat-saturated (T1w fs) image showed the pancreas was diffusely enlarged, with decreased signal intensity (straight arrow). (b)T2 weighted Half-Fourier acquisition single-shot turbo spin echo (T2w HASTE) image showed circumferential bile duct wall thickening in the extra-pancreatic extra-hepatic segment (arrowhead). (c) MRCP image showed multiple strictures involving both the distal and proximal bile duct (arrowheads). Cystic duct opening was involved, both cystic duct and gallbladder was distended (thin straight arrows). Also note the long-segment pancreatic duct stricture (curved arrow). After corticosteroid treatment, the lesions all resolved and pancreas became atrophied (images not shown). (d–f) 20 months later, new lesion developed in the hilum. (d) T1w fs image showed the pancreas remained atrophied. (e) T2w HASTE image showed bile duct lesion migrated proximally to involve the hilar bile duct, which manifested as circumferential wall thickening (arrowhead). (f) MRCP showed hilar bile duct obstruction (arrowhead) and dilation of intrahepatic bile ducts. Note that cystic duct and gallbladder was not involved this time (thin straight arrows).

instead of active inflammation of the bile duct wall [23]. On the contrary, the involvement of extra-pancreatic bile ducts indicates a more extensive and severe disease and high risk of relapse.

There have been controversial views concerning the role of serum IgG4 level in predicting disease relapse. In a recent review paper, Okazaki et al has described that persistently high serum IgG4 level after steroid therapy may be predictor for relapse [24], based on several Japanese studies. Wallace et al has found baseline serum IgG4 level to be a predictor for IgG4 related disease [10]. In other recent studies which involved over 100 type 1 AIP patients, serum IgG4 level has not been identified as an independent risk factor [5,22,25]. In our study, it turned out that both the organ involvement pattern at baseline and the serum response at the induction phase have significant prognostic value. A high serum IgG4 response ratio, indicating a good response at

Table 3
Clinical factors and imaging features of patients who experienced disease relapse, compared to the non-relapsed patients.

	Relapse (n = 44)	Non-relapse (n = 59)	P value
Age (years)	56(34-84)	58(32-76)	0.83
Gender (M:F)	40:4	42:17	**0.014**
Baseline serum IgG4*	7620(1460-63800)	5050(229-35600)	**0.02**
Pancreas involvement pattern			0.487
Diffuse	34 (77.3%)	42 (78.0%)	
Focal	10 (22.7%)	17 (22.0%)	
Peripancreatic capsule	25 (56.8%)	31 (52.5%)	0.666
Splenic vein stenosis with collateral	17 (38.6%)	29 (47.5%)	0.288
Bile duct involvement pattern			0.117
Solitary distal BD	13 (36.1%)	24 (61.7%)	
Solitary proximal BD	0	1 (2.1%)	
Multiple BD involvement	23 (63.9%)	18 (36.2%)	
InPanBD involvement	36 (81.8%)	41 (69.5%)	0.154
ExPanBD involvement	23 (52.3%)	19 ((32.2%)	**0.04**
ExPanExHBD	14 (31.8%)	10	0.077
Hilar BD	13 (29.5%)	9	0.08
R-IHBD	6 (13.6%)	4	0.245
L-IHBD	4 (9.1%)	4	0.665
Number of bile duct segments involved*	1(1-5)	1(1-5)	0.129
Maximal bile duct wall thickness (mm)	2.9 ± 1.1	2.2 ± 1.0	**0.013**
Kidney involvement	5	11	0.313
Renal parenchyma	5	10	0.427
Renal pelvis	1	3	0.465
Mesentery	3 (6.8%)	3 (5.1%)	0.710
Aorta	0	1 (1.7%)	0.386
Peri-pancreatic arteries			
Splenic artery	11 (25.0%)	9 (15.3%)	0.216
Celiac artery	2 (4.5%)	2 (3.4%)	0.764
SMA	4 (9.1%)	3 (5.1%)	0.424
Lymph nodes enlargement	26 (59.1%)	31 (52.5%)	0.508
Abdominal organ response score	0.87 ± 0.81	0.82 ± 0.78	0.37
Serum IgG4 response ratio	0.59 ± 0.18	0.68 ± 0.12	**0.008**

the induction phase, is a protective factor for disease relapse. Maintenance therapy has been recognized as a protective factor from disease relapse [11,22,26,27]. However, in our cohort, maintenance therapy was routinely performed, but relapse rate during long-term follow-up remains unsatisfactory, especially when those clinically-silent relapses with new lesion development were taken into account. A combined evaluation of baseline condition and early response at induction phase might thus provide more information for relapsing risks, thus enabling an optimized treatment strategy. Patients at low risk of relapse might cease CST earlier, decreasing the risk of long-term steroid use; and patients at high risk of relapse might be targets of stronger treatments. Ancillary drugs and novel therapies might hold the promise to further decrease the relapse rate [28,29], and might be applied early in those patients at high risk of relapse.

Our study has several limitations. First, this was a single center study of Asian patients. Multicenter studies are needed to extend the validity of these findings. Second, although our cohort was relatively large for this rare disease, we were not able to determine the risk factors and imaging features of pancreatic or bile duct cancer developed on AIP. According to previous studies, a few patients developed pancreatic and biliary cancer after 3 years of follow-up [21]. A larger scale study with longer follow-up time is needed for this purpose. Third, this was an observational study, and we didn't compare the effect of different therapies on disease relapse. Last but not least, since the pancreaticobilary lesions can migrate to a different location, the quantitative comparison of maximal bile duct thickness between initial attack and relapse might not be very accurate.

5. Conclusion

Patients with treated type 1 AIP often develop pancreaticobiliary lesions during follow-up, which is usually manifestation of disease relapse. The imaging pattern of the relapsed lesions differs from the initial attack. ExPanBD involvement at initial diagnosis and poorer serum response at the induction phase suggest a high risk of relapse.

Declaration of Competing Interest

None.

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