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RESEARCH

# Clinicopathological study of surgically treated non-neoplastic diseases of the pancreas with special reference to autoimmune pancreatitis

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## Abstract

**Purpose** After the popularization of serum immunoglobulin G4 (IgG4) measurement and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in our institute, surgical resection for non-neoplastic diseases of the pancreas became less common. Although the incidence of such false-positive cases was clarified in the 10-year period after the introduction of these measures (2009–2018), these data were not compared with the 30 years before 2009 (1979–2008). This study was performed to determine the percentage of autoimmune pancreatitis (AIP) that was included during the latter period and how the numbers of false-positive cases differed between the two periods.

**Methods** From 1979 to 2008, 51 patients had clinical suspicion of pancreatic carcinoma (false-positive disease). Among these 51 patients, 32 non-alcoholic patients who had tumor-forming chronic pancreatitis (TFCP) were clinically, histologically, and immunohistochemically compared with 11 patients who had TFCP during the latter 10-year period.

**Results** Retrospective IgG4 immunostaining of false-positive TFCP revealed 14 (35.0%) cases of AIP in the former 30 years versus 5 (45.5%) in the latter 10 years. There were 40 (5.9%) cases of TFCP among 675 patients in the former 30 years and 11 (0.9%) among 1289 patients in the latter 10 years.

**Conclusions** When the TFCP ratio of pancreatic resections and the AIP ratio of false-positive TFCPs were compared between the two periods, the TFCP ratio was 5.9% versus 0.9% and the AIP ratio was 35.0% versus 45.5%, respectively. It can thus be speculated that IgG4 measurement and EUS-FNA are absolutely imperative for the diagnosis of TFCP.

**Keywords** Autoimmune pancreatitis (AIP) · Tumor-forming chronic pancreatitis (TFCP) · Immunoglobulin G4 (IgG4) staining · Surgical treatment · Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA)

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## Introduction

Throughout the last decade, the precision of clinical images (i.e., computed tomography (CT), ultrasound (US), and magnetic resonance imaging) for the diagnosis of pancreatic tumors has progressed considerably. Moreover, the popularization of measuring serum immunoglobulin G4 (IgG4) [1] and performing endoscopic US-guided fine-needle aspiration (EUS-FNA) [2–4] has contributed to a marked decrease in the resection of non-neoplastic (false-positive) diseases.

After 2009, serum IgG4 measurement and EUS-FNA were introduced for the preoperative diagnosis of pancreatic tumors in our institute. Moreover, IgG4 immunostaining [5] began to be routinely performed for the pathological diagnosis of non-neoplastic specimens. Although cases of autoimmune pancreatitis (AIP) were confirmed to have been included among patients with false-positive disease during a recent 10-year period (2009–2018) in our institute, such data remain unknown for the 30-year period before 2009 (1979–2008).

The present study was performed to elucidate the percentage of AIP that was included among surgically treated non-neoplastic (false-positive) diseases of the pancreas prior to the popularization of serum IgG4 measurement and EUS-FNA and to determine how patients with false-positive diseases differed between the two time periods.

## Materials and methods

From 1979 to 2008, 675 patients (618 with neoplastic diseases and 57 with non-neoplastic diseases) underwent pancreatic resection, and from 2009 to 2018, 1289 patients (1278 with neoplastic diseases and 11 with non-neoplastic diseases) underwent pancreatic resection at the Cancer Institute of the Japanese Foundation of Cancer Research (Table 1). US, enhanced CT, and endoscopic retrograde pancreatography were the main preoperative imaging modalities used, and after 2009, serum IgG4 measurement and EUS-FNA were introduced in the preoperative diagnosis of pancreatic tumors. False positive had been defined as histological diagnosis for the resected specimen was non-neoplastic, i.e., non-malignant contrary to our preoperative diagnosis. During the former 30 years, 57 pancreatic resections were performed for non-neoplastic diseases in 51 patients with clinical suspicion of pancreatic carcinoma (40 with tumor-forming disease and 11 with stenosis of the larger pancreatic duct without apparent tumor-forming disease) and 6 patients with non-neoplastic disease (alcoholic chronic pancreatitis (ACP)) (3 with pancreatolithiasis, 2 with a pseudocyst/abscess, and 1 with a pancreatic duct–portal vein fistula). During the latter 10 years, 11 of the 1289 patients who underwent pancreatic resections had non-neoplastic (false-positive) diseases. We clinically, histologically, and immunohistochemically compared the 40 cases of non-neoplastic (false-positive) pancreatic disease during the former 30 years and the 11 cases of non-neoplastic (false-positive) pancreatic disease during the latter 10 years with special reference to

**Table 1** Breakdown of false-positive cases by etiology: 1979–2008 vs. 2009–2018

| Etiology | 1979–2008 | 2009–2018 | Total |
|---|---|---|---|
| Number of resection | | | |
| Total number | 675 | 1289 | 1964 |
| Neoplastic disease | 615 | 1278 | 1896 |
| Non-neoplastic disease | 57 (8.4%) | 11 (0.9%) | 68 (3.5%) |
| Non-neoplastic disease | | | |
| Clinically suspicious (false-positive) | 51 (7.6%) | 11 (0.9%) | 62 (3.2%) |
| Known benign disease (ACP) | 6 | 0 | 6 |
| False-positive | | | |
| Tumor-forming | 40 (5.9%) | 11 (0.9%) | 51 (2.6%) |
| ACP | 8 | 0 | 8 |
| NACP | 32 | 11 | 43 |
| Stenosis of larger pancreatic duct without apparent tumor forming | 11 | 0 | 11 |
| TFCP (NACP) | | | |
| Total number | 32 (4.7%) | 11 (0.9%) | 43 (2.2%) |
| Unknown etiology | 18 (2.7%) | 6 (0.5%) | 24 (1.2%) |
| AIP | 14 (2.1%) | 5 (0.4%) | 19 (1.0%) |

*ACP*, alcoholic chronic pancreatitis; *NACP*, non-alcoholic chronic pancreatitis; *TFCP*, tumor-forming chronic pancreatitis; *AIP*, autoimmune pancreatitis

AIP. These 51 patients with tumor-forming chronic pancreatitis (TFCP) ranged in age from 31 to 82 years (average age, 64 years), and the male: female ratio was3.3:1.0.

All resected pancreatic tissues were fixed in 10% formalin and sliced serially at 5- to 8-mm intervals along the plane at right angles to the main pancreatic duct (MPD). All slices were processed according to standard procedures for preparation of sections stained with hematoxylin and eosin (HE), and IgG4 immunostaining was performed in most cases except for eight with stenosis of the larger pancreatic duct. Histological diagnosis of Type 1 AIP was judged by at least 3 of the following according to the international consensus diagnostic criteria (ICDC) for AIP [6],

(1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration
(2) Obliterative phlebitis
(3) Storiform fibrosis
(4) Abundant (> 10 cells/HPF) IgG4-positive cells

By contrast, it was judged to be positive for Type 2 AIP when idiopathic duct-centric chronic pancreatitis (IDCP) according to the international consensus diagnostic criteria (ICDC) for AIP [6]: Both of the following.

(1) Granulocytic infiltration of duct wall (GEL) with or without granulocytic acinar inflammation
(2) Absent or scant (0–10 cells/HPF) IgG4-positive cells

Through a combination of the Mayo Clinic HISORt criteria (histology, imaging, serology, other organ involvement, and response to steroid therapy) [5] in the USA and the Asian diagnostic criteria [7], the goal of the International Association of Pancreatology was to develop an international consensus in 2011 [6].

The 51 patients with false-positive disease (40 in the former 30 years and 11 in the latter 10 years) who underwent pancreatic resection were classified into two groups according to the anatomical distribution of the disease as defined by the ICDC for AIP [6]: patients with segmental/focal disease ($n=39$) and patients with diffuse disease ($n=12$). Diffuse disease was defined as a widespread pancreatic lesion covering an area of more than one-third the length of the MPD. Of the 12 patients with diffuse disease, 5 had head-to-body lesions and 7 had body-to-tail lesions.

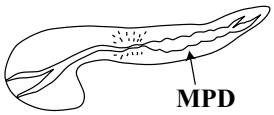
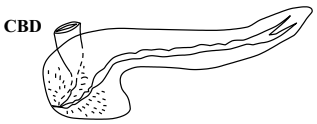
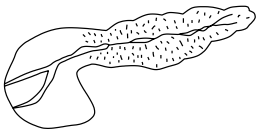
## Results

As shown in Table 1, we divided the patients who underwent pancreatic resection during the past 40 years into two periods: the former 30 years (1979–2008) and the latter 10 years (2009–2018). We investigated the breakdown of false-positive cases using IgG4 immunostaining of the resected specimens in each period, considering that serum IgG4 measurement and/or EUS-FNA were routinely performed from 2009 onward for the diagnosis of pancreatic tumors at our institute. During the former 30 years, there were 51 (7.6%) false-positive cases among 675 pancreatic resections; among these 51 cases, 40 were TFCP (excluding 11 cases of stenosis of the larger pancreatic duct without apparent tumor-forming disease) (unknown etiology, $n=18$; AIP, $n=14$; alcoholic chronic pancreatitis (ACP), $n=8$). During the latter 10 years, there were 11 (0.9%) false-positive cases among 1289 pancreatic resections (unknown etiology, $n=6$; AIP, $n=5$). The AIP/TFCP ratio was 14/40 (35.0%) and 5/11 (45.5%), respectively.

The anatomical distribution of the 51 cases of TFCP (false-positive disease) treated by pancreatic resection is shown in Table 2. According to the ICDC definitions [6], 39 patients had focal/segmental disease and 12 had diffuse disease, and AIP was present in 12 (30.8%) of the 39 patients with focal/segmental disease (30.8%) and in 7 (58.3%) of the 12 patients with diffuse disease. The anatomical distribution among the patients with focal/segmental disease was the head of the pancreas in 21 patients, the body in 10, and the tail in 8. The anatomical distribution among the patients with diffuse disease was the head-body in five patients and the body-tail in seven.

The detailed clinical information of the 19 patients with AIP is provided in Table 3 according to the year of the operation. One patient had type 2 AIP and the remaining 18 patients had type 1. When we classified the disease distribution of AIP into two groups (i.e., diffuse and segmental/focal) according to the ICDC for AIP [6], we identified 7 (37%) cases of diffuse disease among the 19 cases of AIP, and all 7 were included in the cases before 2009. With respect to the radiologic findings suspicious for carcinoma excluding tumor-forming disease, 9 of 14 cases before 2009 had an abnormality at the MPD or/and common bile duct (Case Nos. 1–14 in Table 3), whereas 4 of 5 cases after 2009 had encasement of large vessels (Case Nos. 15–19 in Table 3). The serum IgG4 concentration was within the reference range in three (60%) of five cases of AIP after 2009. EUS was performed for three of five AIP cases after 2009, in which only one case was diagnosed with TFCP. But FNA was not performed for this case and he was ultimately operated because of strong suspicion of malignancy by other diagnostic modalities. Cholangitis was associated with diffuse disease in three (43%) of seven cases, among which two cases were metachronous (Case Nos. 2 and 13) and one case was synchronous (Case No. 7).

**Table 2** Anatomical distribution of tumor-forming pancreatitis in 51 patients with false-positive disease with a focus on AIP (n = 19)

| Disease distribution | | No. of patients (No. of patients with AIP) |
|---|---|---|
| Focal/segmental | | 39 (12) |
| |   | |
| |   | |
| | Head | 21 (5) |
| | Body Tail | 10 (5) |
| | | 8 (2) |
| Diffuse | | 12 (7) |
| |  | |
| | Head-body | 5 (3) |
| | Body-tail | 7 (4) |

**AIP, autoimmune pancreatitis; MPD, main pancreatic duct; CBD, common bile duct**

## Clinical imaging and microscopic appearance of representative cases

### Case 1·focal enlargement (Table 3-no.10, Fig. 1)

In an 81-year-old man with focal pancreatitis (apparent obstructive pancreatitis), enhanced CT demonstrated a round low-attenuation mass of 2-cm diameter in the pancreatic body (Fig. 1a). Segmental interruption of the MPD in the pancreatic body was evident by magnetic resonance cholangiopancreatography (Fig. 1b). A low-power view of the MPD stenosis showed marked lymphoplasmacytic infiltration into the thickened wall, which was positively stained with IgG4 (Fig. 1c, d).

### Case 2·diffuse enlargement (Table 3-no.7, Fig. 2)

In a 50-year-old man with diffuse pancreatitis accompanied by areas of focal cholangitis in the liver, two enhanced CT images showed small low-attenuation areas in the liver and a diffuse low-attenuation area from the pancreatic body to the tail (Fig. 2a, b). A low-power view of an HE-stained section at the body of the pancreas showed marked lymphoplasmacytic infiltration surrounding the MPD (Fig. 2c) and marked infiltration of IgG4-positive plasma cells through the wall of the MPD (Fig. 2d). Additionally, a low-power view of an HE-stained section, which was taken from the indurations at the lateral segment of the liver showed marked lymphoplasmacytic infiltration in the Glisson sheath adjacent to the liver tissue (Fig. 2e) and marked infiltration of IgG4-positive plasma cells in the Glisson sheath (Fig. 2f).

### Case 3·Type 2 AIP (Table 3-no.5, Fig. 3)

In a 50-year-old man with segmental pancreatitis around the duodenum, enhanced CT showed an ill-demarcated, low-attenuation area in the dorsal part of the pancreatic head. Endoscopic retrograde pancreatography showed filling defects in the MPD, leading to suspicion of protein plugs. Many neutrophils had invaded the epithelium of the MPD on histopathological examination (Fig. 3a, b), and type 2 AIP was therefore diagnosed. The low-attenuation area in the CT scan corresponded to fibrosis associated with an abscess (Fig. 3c) or xanthogranuloma formation containing cholesterin crystal crests (Fig. 3d).

## Discussion

For a long time prior to the popularization of serum IgG4 measurement and EUS-FNA, we occasionally encountered patients with TFCP among them undergoing resection for suspected pancreatic malignancy [8–10]. When we received pathological reports of benignancy in patients with suspected malignancy, we reviewed the clinical images and surgical indications and examined the pathological etiology of the tumor-forming lesions. Since the emergence of new concepts such as AIP [11–13], it has been clarified that

**Table 3** Clinical findings of patients with AIP who underwent operations for false-positive diagnosis

| Case no | Age (years) | Sex | Year of operation | Type of AIP | Disease distribution | Chief complaint | Radiologic finding suspicious of carcinoma excluding tumor-forming disease | IgG4 value (4.8–105 ng/dL) | EUS (-FNA) | Outcomes diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 48 | M | 1979 | 1 | Seg/focal(T) | Hematemesis | Stenosis of MPD | - | - | 3 m Alive |
| 2 | 68 | M | 1982 | 1 | Diffuse(B-T) | Epigastralgia | Long stenosis of MPD | - | - | 7y Dead* |
| 3 | 57 | M | 1984 | 1 | Seg/focal(H) | Vomiting | Stenosis of duct of Santorini | - | - | 15y7m Alive |
| 4 | 31 | M | 1987 | 1 | Diffuse(B-T) | Epigastralgia | Long stenosis of MPD | - | - | 3 m Alive |
| 5 | 53 | M | 1993 | 2 | Seg/focal(H) | Backache | Intraductal tumor of MPD | - | - | 3y Alive |
| 6 | 69 | M | 1997 | 1 | Seg/focal(H) | - (US) | Rapid growth of tumor | - | - | 5y Alive |
| 7 | 50 | M | 1999 | 1 | Diffuse(B-T) | Backache | Encasement of SPA/SPV | - | - | 9y Dead** |
| 8 | 73 | M | 2000 | 1 | Diffuse(B-T) | Jaundice | Encasement of GDA | - | - | 6y Alive |
| 9 | 59 | M | 2005 | 1 | Diffuse(H-B) | - (US) | Stenosis of CBD, long stenosis of MPD | - | - | 16y Alive |
| 10 | 81 | M | 2005 | 1 | Seg/focal(B) | - (US) | Obstruction of MPD | - | - | 6y7m Alive |
| 11 | 76 | M | 2007 | 1 | Seg/focal(H) | Jaundice | Stenosis of CBD | 459 | - | 12y4m Alive |
| 12 | 82 | F | 2007 | 1 | Diffuse(H-B) | Jaundice | Obstruction of CBD | - | - | 4y Alive |
| 13 | 59 | M | 2008 | 1 | Diffuse(B-T) | - (MRI) | Encasement of SPA/SPV | 212 | - | 9y6m Alive |
| 14 | 61 | F | 2008 | 1 | Seg/focal(B) | Epigastralgia | Considerably high uptake value of tumor (PET-CT) | - | - | 3y8m Alive |
| 15 | 72 | F | 2010 | 1 | Seg/focal(B) | Nausea | Encasement of SPA | 12.3 | - | 8 m Alive |
| 16 | 64 | M | 2011 | 1 | Seg/focal(B) | - ($^{\text{Deterioration}}$of DM) | Encasement of SPA/SPV | 48.3 | TFCP (no FNA) | 7y2m Alive |
| 17 | 68 | M | 2012 | 1 | Seg/focal(H) | Epigastralgia | Encasement of SMV/PV | 226 | IDC (no FNA) | 9y7m Alive |
| 18 | 58 | F | 2013 | 1 | Seg/focal(T) | - (CT) | Encasement of SPA | 37.1 | - | 7y10m Alive |
| 19 | 69 | F | 2017 | 1 | Seg/focal(B) | Lumbago | Hypervascular tumor (NET?) | 154 | NET (NPT) | 3y7m Alive |

Associated extrapancreatic diseases: Case 2, IgG4-related sclerosing cholangitis (metachronous); Cases 7 and 13, IgG4-related sclerosing cholangitis (synchronous)

*AIP*, autoimmune pancreatitis; *IgG4*, immunoglobulin G4; *M*, male; *F*, female; *Type 1 AIP*, lymphoplasmacytic sclerosing pancreatitis; *Type 2 AIP*, idiopathic duct-centric chronic pancreatitis; *Seg*, segmental; *H*, head; *B*, body; *T*, tail; *US*, ultrasound; *MRI*, magnetic resonance imaging; *DM*, diabetes mellitus; *CT*, computed tomography; *PET*, positron emission tomography; *MPD*, main pancreatic duct; *SPA*, splenic artery; *SPV*, splenic vein; *GDA*, gastroduodenal artery; *CBD*, common bile duct; *PV*, portal vein; *NET*, neuroendocrine tumor; *EUS-FNA*, endoscopic ultrasound guided fine-needle aspiration; *TFCP*, tumor-forming chronic pancreatitis; *IDC*, invasive ductal cancer; *NPT*, normal pancreatic tissue

*Autoimmune cholangitis. **Lung cancer

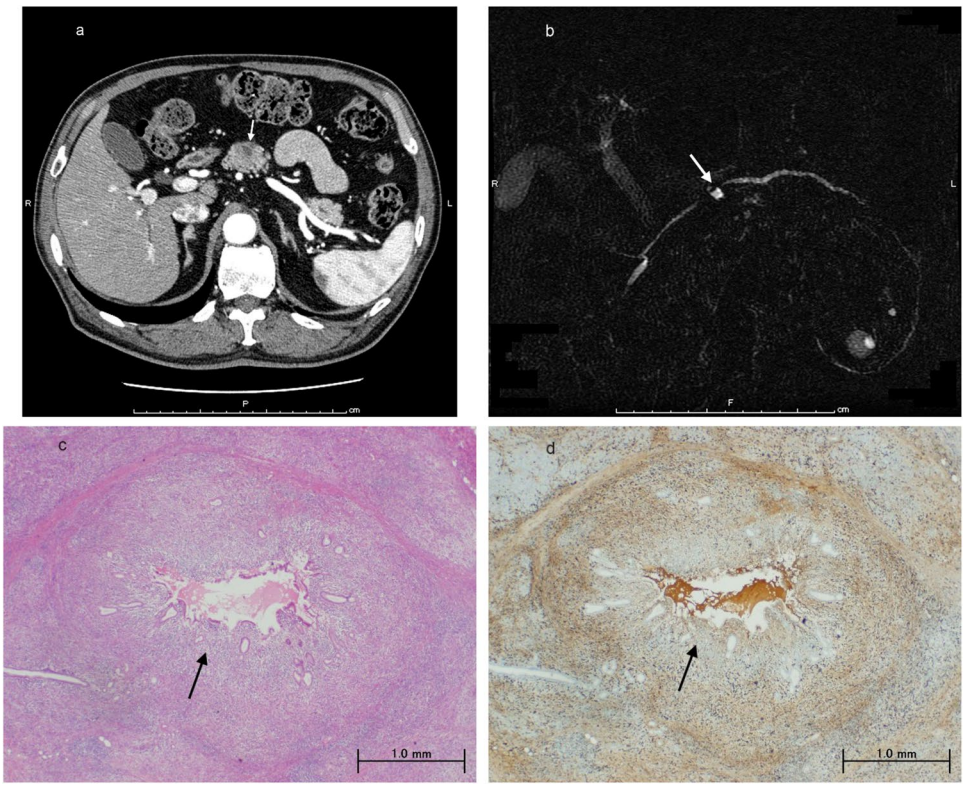



**Fig. 1** Images of a patient with a deep pancreatic focal lesion with apparent obstructive pancreatitis. a Enhanced CT scan showing a round low-attenuation tumor of 2 cm in diameter in the pancreatic body (arrow). b Segmental interruption of the MPD (arrow) is seen in the pancreatic body on magnetic resonance cholangiopancreatography. Low-power view of MPD stenosis (arrow) showing c marked lymphoplasmacytic infiltration into the thickened wall and d positive staining for IgG4

some patients with AIP have been included among those with TFCP. We therefore focused on determining how many patients with AIP were included among those with TFCPs prior to the practical use of IgG4 immunostaining in our institution. Because retrospective histological reviews were rarely performed [14], we also investigated tissue blocks of TFCP obtained during the 30 years before 2009. IgG4 immunostaining revealed 14 (43.8%) cases of AIP among 32 cases of TFCP without ACP, which is similar to the findings reported by Kobayashi et al. [15] (i.e., 6 (66.7%) cases of AIP among 9 cases of TFCP). This suggests that nearly half of TFCP cases are AIP. Moreover, IgG4 immunostaining of non-neoplastic diseases (i.e., false-positive specimens) in patients with ACP and stenosis of the larger pancreatic duct during the same time period revealed 14 (27.5%) cases of AIP among 51 non-neoplasms, which is almost identical to the findings in four surgical series in which AIP was present in 31/159 (19.5%), 11/47 (23.4%), 6/23 (26.1%), and 10/33 (30.3%) patients who underwent resection non-neoplastic pancreatic disease, respectively [9, 10, 16, 17]. Consequently, it seems likely that nearly 30% of false-positive cases are AIP.

It was speculated that the emergence of serum IgG4 measurement and EUS-FNA for the diagnosis of AIP has surely reduced the incidence of non-neoplastic pancreatic resection. This was clearly demonstrated in our series: 40 (5.9%) cases of TFCP were present among 675 pancreatic resections during the 30 years before 2009, whereas 11 (0.9%) cases of TFCP were present among 1289 pancreatic resections during the 10 years after 2009. However, recognition of other features of AIP might also contribute to make a proper diagnosis. For example, diffuse pancreatic swelling is characteristic of AIP, but unusual for pancreatic cancer. Wide recognition of the difference might give rise to reduce the number of resected AIP cases with diffuse pancreatic swelling after 2008. In this way, it is evident that the increased use of the ICDC for AIP [6] and greater precision of diagnostic imaging (i.e., CT, US, and magnetic resonance imaging) have contributed to a marked decrease in TFCP resection during the last decade.

Interestingly, the ratio of AIP/unknown etiology among cases of TFCP during the two periods in the present study was very similar at 0.78 (14/18) in the former 30 years and 0.83 (5/6) in the latter 10 years. It is obviously difficult to explain the reasons why ratio of AIP is similar between the two groups before 2009 and after 2008. But it is possible to speculate them to some extent when 5 cases of AIP after 2008 are clinically analyzed. They have the following three factors difficult to differentiate from unknown etiology TFCP or pancreatic cancer. (1) Four cases of 5 are small tumor at the body or tail of the pancreas, where EUS-FNA was occasionally difficult to obtain appropriate biopsy

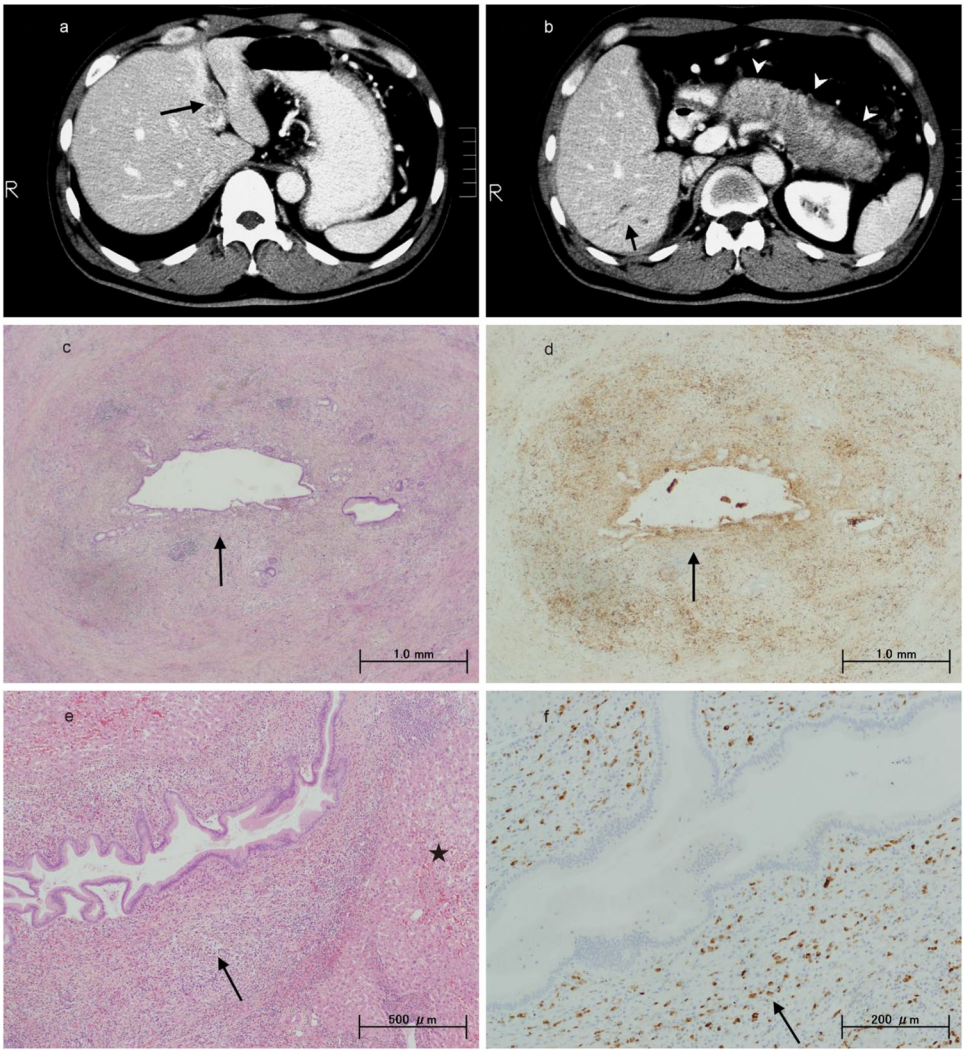



**Fig. 2** Images of a patient with diffuse pancreatitis accompanied by areas of focal cholangitis in the liver. Two enhanced CT images showing a small low-attenuation areas in the liver (arrows) and b a diffuse low-attenuation area from the pancreatic body to the tail (arrowheads). c A low-power view after HE staining showing marked lymphoplasmacytic infiltration surrounding MPD stenosis (arrow). d A low-power view after histochemical staining shows marked IgG4-positive plasma cell infiltration surrounding the MPD and close to the MPD epithelium (arrow). e A low-power view of an intraoperative liver biopsy specimen obtained from the low-attenuation area in Segment IV seen by CT, showing marked lymphoplasmacytic infiltration (arrow) in the Glisson sheath adjacent to the liver tissue (solid star). f Note the marked infiltration of IgG4-positive plasma cells (arrow) in the Glisson sheath

specimen. (2) Four cases of 5 had apparent encasement of large vessels (Splenic artery/vein, Portal vein, etc.) in preoperative clinical images. (3) Three cases of 5 had normal IgG4 level. It is presumed that although larger lesions of AIP are decreased after the recognition of AIP, smaller lesions of AIP which have the above three factors hard to differentiate from unknown etiology TFCP or pancreatic cancer, will be contained with some probability within false-positive TFCP. Even if the numbers of resected AIP can be further decreased, the ratio of AIP in false-positive TFCP resections may be nearly unchangeable in the near future.

We found no reports of the anatomical distribution of lesions in non-neoplastic pancreatic resection. Moreover, the relationship between the anatomical distribution and AIP has rarely been reported [15]. We found AIP in 7 (58.3%) of 12 diffuse (head-to-body or body-to-tail) lesions and in 12 (30.8%) of 39 focal/segmental lesions. The percentage of patients with AIP was higher among those with diffuse lesions; thus, it is likely that AIP is more often observed in larger lesions. Although these larger lesions are generally easy to diagnose by serum IgG4 measurement or EUS-FNA, how to diagnose focal, small lesions remains controversial [18–20]. Small lesions do not always show remarkable elevation of the serum IgG4 concentration, and it may be anatomically difficult to obtain a specimen by EUS-FNA. In previous studies involving such cases, the diagnostic performance was significantly higher when both cytological and Tru-Cut biopsy [21] and cell-block examination [22] were carried out than when only cytological examination was performed. During the latter 10 years of the present study, popularization of EUS-FNA for differential diagnosis of pancreatic tumors advanced remarkably, and this is certain to facilitate further reduction in the performance of non-neoplastic pancreatic resection in the near future.

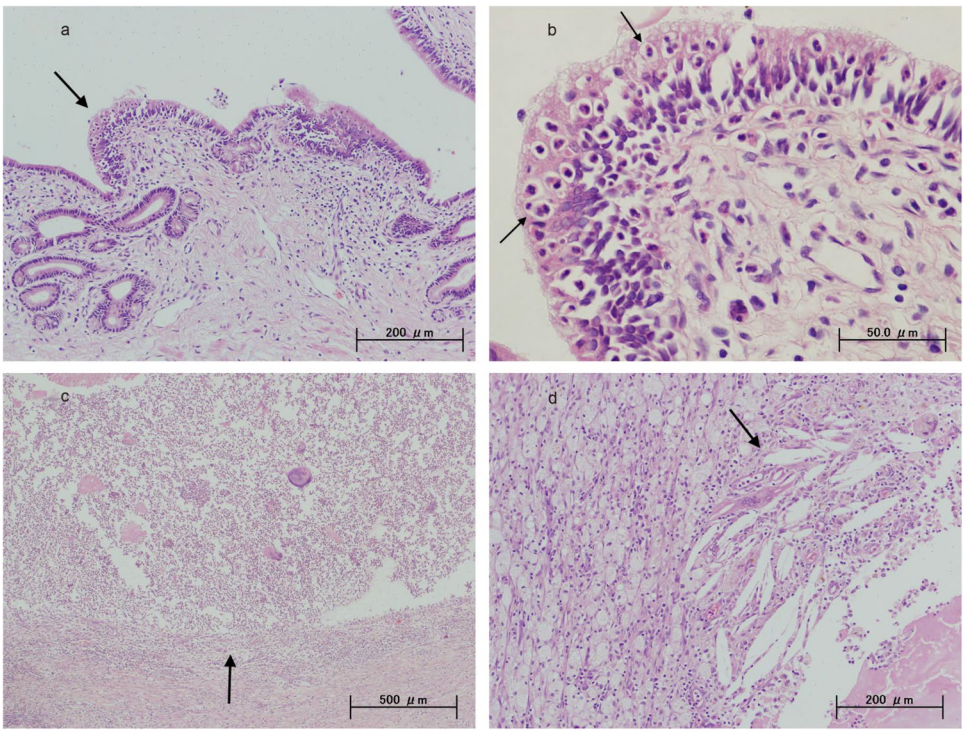



**Fig. 3** Images of a patient with paraduodenal segmental pancreatitis (type 2 AIP). Numerous neutrophils (arrow) invading the epithelium of the MPD in the pancreatic head in the a low- and b high-power views. c High-power view of the so-called groove in the pancreatic head showing abscess formation (arrow) with marked infiltration of neutrophils and lymphocytes. d High-power view of the region near the abscess showing xanthogranuloma formation containing cholesterin crystallization (arrow). Marked infiltration of foamy cells can be seen

It is interesting that tumor-forming ACP was found in 8 cases before 2009, but not after 2008. In order to pursue the reasons of this change, preoperative clinical images of the 8 cases were reviewed. Pancreatolithiasis in the main pancreatic duct and/or large branches of the pancreas was observed in seven cases of 8 ACP tumors. Moreover, peri-/intra-pancreatic pseudocyst and/or abscess was seen in five cases of them. When these findings are observed in preoperative images, we had changed to doubt more strongly tumor-forming ACP than pancreatic cancer and identify its histology by EUS-FNA. We think that this reflection led to marked decrease of ACP resections.

In conclusion, retrospective IgG4 immunostaining of false-positive TFCP tissue blocks obtained during the 30 years before 2009 revealed 14 (35.0%) cases of AIP among 40 cases of TFCP, whereas 5 (45.5%) cases of AIP were found among 11 cases of TFCP during the 10 years after 2009 (i.e., the period during which serum IgG4 measurement and EUS-FNA were implemented). The false-positive TFCP ratio was 5.9% (40/675) in the former 30 years and only 0.9% (11/1289) in the latter 10 years. It can thus be speculated that serum IgG4 measurement and EUS-FNA are absolutely imperative for the diagnosis of TFCP.

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## Declarations

**Ethics approval** The protocol for this research project was approved by our institutional ethics review committee on 17 August 2015 (approval number 2015–1062), and the study confirms to the provisions of the Declaration of Helsinki.

**Informed consent** All patients consented to the use of their clinical data for research purposes when the operations were performed.

**Competing interests** The authors declare no competing interests.

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