

[ CASE REPORT ]

# Multilocular Cyst of Type 1 Autoimmune Pancreatitis Masquerading as Cancerization of Intraductal Papillary Mucinous Neoplasm

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## Abstract:

A small proportion of intraductal papillary mucinous neoplasms (IPMNs) are accompanied by type 1 autoimmune pancreatitis (AIP); however their clinical courses and image characteristics have not been fully reported. A 65-year-old woman was referred to our hospital for the examination of a pancreatic head cyst that had shown exacerbation for two years. Several images demonstrated a multilocular cyst with a symmetrically thickened, enhanced, cyst wall. Cancerization of IPMN was suspected, and pancreatoduodenectomy was performed. The resected specimens showed a multilocular cyst with solid areas. The solid areas demonstrated pathological findings that corresponded with type 1 AIP. Papillary epithelia suggestive of IPMN was recognized in some parts of the cystic wall.

**Key words:** autoimmune pancreatitis, intraductal papillary mucinous neoplasms, IgG4, diagnosis

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## Introduction

To date, a few studies have highlighted the pathological findings of coexisting intraductal papillary mucinous neoplasm (IPMN) and type 1 autoimmune pancreatitis (AIP) (1-3). However, the clinical course and imaging features of AIP-associated IPMN have not been fully reported. Tumorigenesis associated with IgG4-related disease is controversial as a chicken-or-egg question (4, 5), and it is still difficult to make an accurate imaging-based diagnosis.

We herein report a case of IgG4-related, branch duct-type IPMN (BD-IPMN), that was preoperatively diagnosed as cancerized IPMN based on the imaging changes over two years of screening.

## Case Report

A 65-year-old woman was referred to our hospital for the examination of a pancreatic head cyst, which showed an ex-

acerbation on follow-up images. She had been diagnosed with diabetes mellitus at 45 years of age, but had no history of autoimmune disease. She had a family history of cancer: her mother had pancreatic cancer, and her father and brother had colorectal cancers. Two years previously, enhanced computed tomography (CT) incidentally depicted a 3.5 cm multicellular cyst without a mural nodule in the head of the pancreas (Fig. 1A). Endoscopic retrograde cholangiopancreatography (ERCP) revealed a cyst communicating with the pancreatic duct (Fig. 2). The cytology of the aspirated pancreatic juice was class III (epithelial cells with mild to moderate atypia, no malignancy) according to the Japanese criteria. The cyst was diagnosed as a BD-IPMN and was followed up regularly.

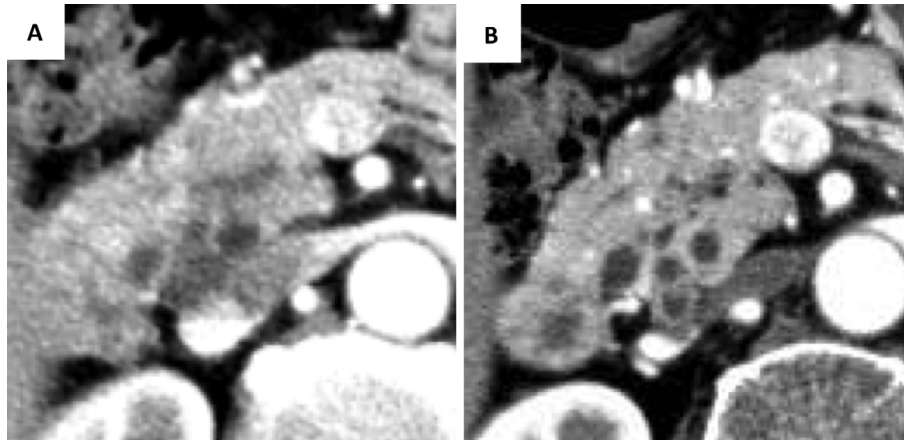
At referral, a full-body CT scan (Fig. 1B) showed that the cyst remained unchanged in size, but the cyst wall was strongly enhanced and thickened in comparison to with two years previously. Mural nodules, capsule-like rim, and extra-pancreatic lesions were not recognized; however, the main pancreatic duct (MPD) was mildly dilated diffusely. <sup>18</sup>F-

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**Figure 1.** Serial computed tomography showing a multilocular cyst at the pancreas head in the initial examination (A), and an enhanced and thickened cystic wall two years later (B).



**Figure 2.** Endoscopic retrograde cholangiopancreatography showing the dilated main pancreatic duct (MPD), communicating with the pancreas head branch, and a filling defect floating inside the MPD.

fluorodeoxyglucose-positron emission tomography (FDG-PET) revealed a faint uptake at the pancreas head (SUV<sub>max</sub>: 3.25) and multiple mediastinum lymph nodes (SUV<sub>max</sub>: 3.87). Diffusion-weighted magnetic resonance imaging (MRI) showed a high-intensity signal at the cyst wall (Fig. 3). Endoscopic ultrasonography (EUS) demonstrated a multilocular cyst with a markedly thickened, low-echoic wall. Each locule was circular and symmetric with homogeneous internal echo, like a lotus root (Fig. 4). The patient's laboratory data, including her serum tumor marker levels, were normal [carcinoembryonic antigen (CEA): 1.9 ng/mL; normal: <5.0 ng/mL, and cancer antigen 19-9 (CA19-9): 23 U/mL; normal: <37 U/mL]. Obvious IgG4-related lesion was not recognized throughout the images.

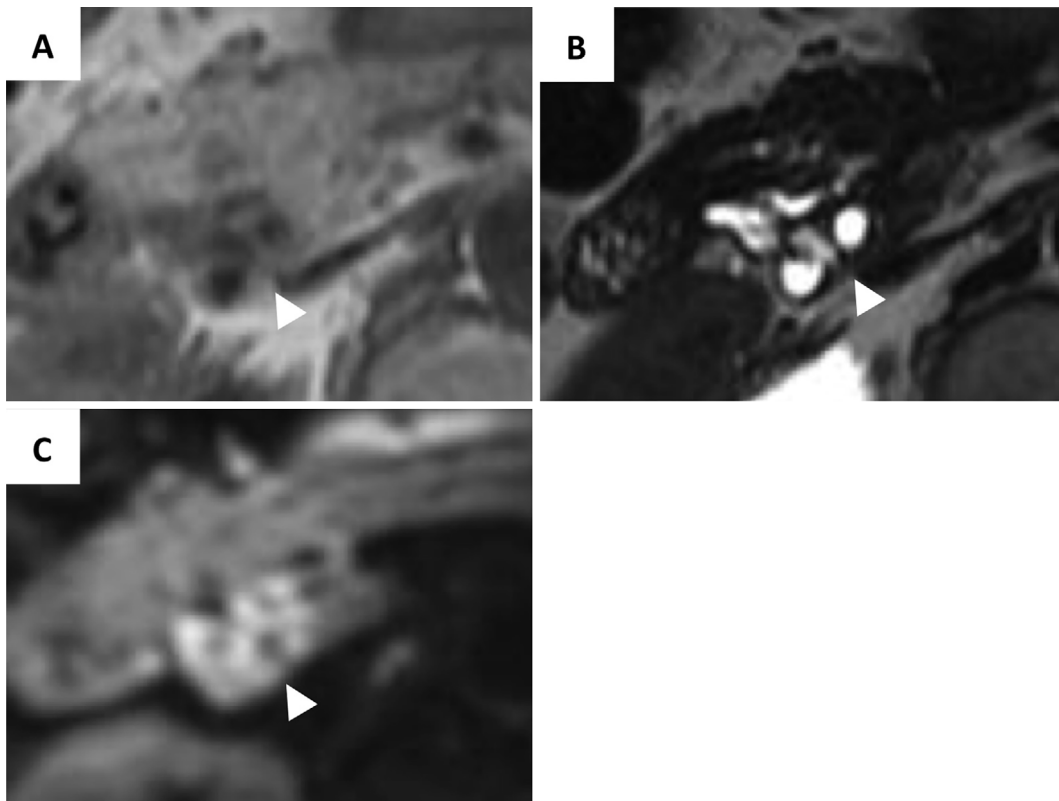
Cancerization of the IPMN was suspected based on the obvious cyst wall thickening, and pancreatoduodenectomy was performed. Macroscopically, the resected specimens demonstrated a multilocular cyst with whitish solid areas nearby (Fig. 5A, B). Microscopically, papillary epithelium producing gastric-type mucin, suggestive of intraductal pap-

illary mucinous adenoma (IPMA), was recognized in a small part of the cyst (Fig. 5C, D). Immunostaining of the papillary epithelial cells revealed that they were positive for MUC5AC and MUC6, but negative for MUC1 and MUC2 (Fig. 5D). The thickened cyst wall and whitish solid areas were composed of proliferative fibrous tissue with abundant lymphoplasmacytic infiltration (IgG4-positive cells: >30 per high power field), storiform fibrosis, and obliterative phlebitis (Fig. 5E-H). These histological findings fully met the international consensus diagnostic criteria (ICDC) for type 1 AIP. The distribution of the type 1 AIP-associated pathological findings was limited to around the pancreatic head cyst (Fig. 5A, B).

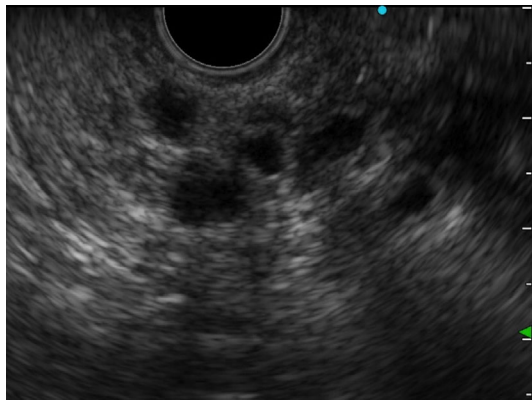
Her serum IgG4 level was analyzed for the first time two months after surgery, and was found to be slightly elevated (163 mg/dL, normal: 4.5-117 mg/dL). No evidence of recurrence and/or emergence of an IgG4-related lesion has been recognized on enhanced abdominal and pelvic CT for ten months since surgery, without the administration of steroids or immunosuppressive therapy. Her serum IgG4 level has also remained stable (165 mg/dL). Eosinophilia was not recognized throughout the course.

## Discussion

Type 1 AIP is sometimes [10% (6)-22% (7)] accompanied by pancreatic cystic lesions. These lesions are mostly unilocular and respond well to corticosteroid therapy. They are therefore thought to develop as a result of pancreatic juice stasis due to the narrowing of the pancreatic duct. However, some steroid-refractory cysts or multilocular cysts are histologically proven to be IPMN (7). Most recent cases of AIP are accurately diagnosed and are not surgically resected; thus, the actual incidence of IPMN in cases with AIP is unclear. Meanwhile, 17% (1)-19% (2) of resected IPMNs showed abundant IgG4-positive plasma cells around the cyst and 4% (1)-5% (2) showed a full spectrum of type 1 AIP histology (lymphoplasmacytic infiltration, abundant IgG4-positive cells, storiform fibrosis, and obliterative phlebitis).



**Figure 3.** Magnetic resonance imaging. A T1-weighted image showing a low-intensity signal around the multilocular cyst (A). A T2-weighted image showing multiple locules depicted with high-intensity signals (B). A diffusion-weighted image showing reduced diffusing capacity at the cystic wall (C).



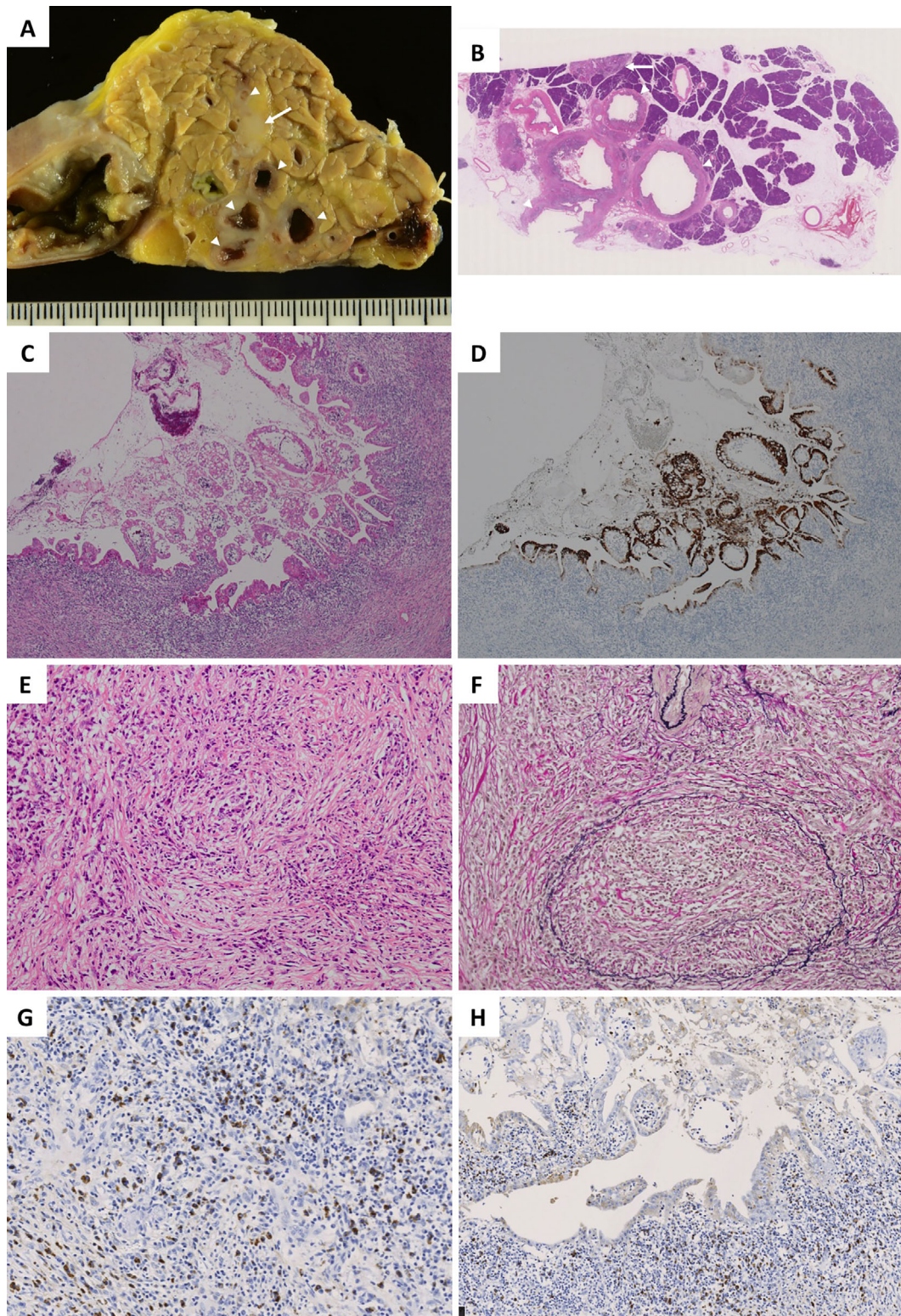
**Figure 4.** Endoscopic ultrasound showing multiple locules with circular, symmetric wall thickening, like a lotus root.

In this case, type 1 AIP developed during the follow-up of BD-IPMN. Surgery was performed, as the thickening of the cyst wall was mimicking the cancerization of IPMN. To date, only a few studies (1-3) and several case reports have described the coexistence of pancreatic cysts [e.g., IPMN (8-10) or IPMN-like lesions (11, 12)] and IgG4-related pathology (infiltration by type 1 AIP or IgG4-positive cell) (1, 7-14). Among the 9 reported cases with coexisting type 1 AIP and BD-IPMN (Table), 5 simultaneous cases were detected (cases: 1, 2, 5, 6 and 8) and 4 cases of AIP developed during follow-up for an IPMN or IPMN-like lesion (case: 3, 4, 7, and 9) (8, 9). Although the number of

reported cases was limited, macroscopically visible IgG4-related lesions appeared in the background of IPMNs or IPMN-like lesions, but not in the opposite order.

The Japanese multicenter retrospective cohort study demonstrated a high incidence of systemic tumor development in patients with AIP; thus, IgG4-related disease is thought to be a paraneoplastic syndrome caused by potentially neoplastic lesions (4). A pathological observation study by Strehl et al. (15) demonstrated that IgG4-positive cells tend to gather more aggressively in autoimmune conditions than in other inflammatory conditions and also in pericancerous tissues to some degree (15). In our case, IgG4-positive cells infiltrated around the ductal epithelium and formed so-called ductitis (Fig. 5), similar to the previous studies (1, 7-14). All of these aspects are suggestive of and compatible with the development of autoimmunity against the mucin-secreting pancreatic epithelia, or IPMN. The occurrence of this autoimmunity may trigger or promote carcinogenesis from intra-ductal epithelial lesions to cancers through long-term continuous inflammation, like the sequence from chronic pancreatitis to pancreatic cancer (5). Whether this IgG4-positive cell infiltration will progress into the full spectrum of type 1 AIP histology remains a question. If this occurs, the trigger should be identified.

The preoperative diagnosis of coexistent AIP and IPMN is extremely difficult, and most cases have been surgically resected. This is probably due to their rarity and low recognition of the disease by clinicians. Furthermore, eight previ-



**Figure 5.** Pathology. The cut surface of the resected pancreas showing a multilocular cyst with a homogeneous whitish thickened wall (arrowheads) and a solid area (arrows) (A), confirmed by loupe finding [Hematoxylin and Eosin (H&E) staining] (B). Papillary epithelial projections secreting mucin, like intraductal papillary mucinous neoplasm (IPMN) (H&E staining,  $\times 40$ ) (C), diffusely positive for MUC5AC (MUC5AC,  $\times 40$ ) (D). Storiform fibrosis (H&E staining,  $\times 100$ ) (E) and obliterating phlebitis (H&E staining,  $\times 100$ ) (F) recognized in the solid area around the multilocular cyst. Abundant IgG4-positive lymphoplasmacytic infiltration was positively detected not only in the solid area (IgG4,  $\times 100$ ) (G), but also in the papillary epithelia covering the cyst (IgG4,  $\times 200$ ) (H).

**Table. Cases of Type 1 Autoimmune Pancreatitis (AIP) Associated with Intraductal Papillary Mucinous Neoplasm (IPMN) or IPMN-like Lesion.**

Case no.	Ref. no.	Age (year old)	Sex	Follow-up of IPMN	Initial findings (site)	Morphological change	Serum IgG4 (mg/dL)	Extrapancreatic lesions	Treatment	Pathology
1	10	64	M	none	segmental narrowing of the PD (Ph), multiple cysts (Pu), and biliary stricture	none	27.7	none	surgery	BD-IPMN and type 1 AIP
2	1	79	M	none	segmental stenosis of the PD (Pb) and multiple cysts (Pbt)	none	627	none	surgery	IPMN and type 1 AIP
3	8	70	F	yes	two cysts (Ph)	solid lesions appearing in or around the cysts	unknown	none	surgery	BD-IPMN and type 1 AIP
4	11	76	F	yes	a cyst (Ph)	a mural nodule appearing in the cyst	1,240*	none	surgery	IPMN-like lesion and type 1 AIP
5	3	75	M	unknown	a solid lesion (Ph) and the dilated PD	unknown	unknown	pulmonary nodules, retroperitoneal nodes, bulky ampulla	surgery	BD-IPMN and type 1 AIP
6	3	74	M	unknown	a solid lesion (Ph) and the dilated PD	unknown	unknown	solitary indeterminate lung nodule, peripancreatic nodes	surgery	BD-IPMN and type 1 AIP
7	9	68	M	yes	multiple cysts (Pt)	a solid lesion appearing in the Pb	46.5	none	steroid	type 1 AIP**
8	12	70	M	none	a solid lesion and surrounding multiple cysts (Pb)	none	265	none	surgery	IPMN-like lesion and type 1 AIP
9	Ours	65	F	yes	a multilocular cyst (Ph)	circular-symmetric wall thickening and solid masses appearing around the cyst	163*	none	surgery	BD-IPMN like lesion and type 1 AIP

\*Serum IgG4 was examined after the surgery. \*\*Pathology was confirmed by endoscopic ultrasound guided-fine needle aspiration. IPMN: intrapapillary mucinous neoplasm, AIP: autoimmune pancreatitis, M: male, F: female, PD: pancreatic duct, BD: brach duct, Ph: pancreas head, Pu: pancreatic uncinuate portion, Pb: pancreas body, Pt: pancreas tail

ously reported cases appeared in various formations (Table): multiple cystic lesions accompanying segmental pancreatic duct stenosis [cases: 1 (10) and 2 (1)] or with a nodule (case: 8) (12); a solid lesion with a dilated pancreatic duct (cases: 5 and 6) (3); the development of a nodule in the BD-IPMN [cases: 3 (8) and 4 (11)], and the appearance of a nodule distant from the BD-IPMN (case: 7) (9). Our case developed circular-symmetric wall thickening around the multilocular cyst, a lotus-root like appearance, and added a unique imaging option to this series. Interestingly, the circular-symmetric wall thickness is a characteristic morphological change of IgG4-related sclerosing cholangitis (16). As BD-IPMNs mostly form multilocules (17), similar cases will be increasingly reported in the future.

The most accurate diagnostic approach for pancreatic mass lesions is histological confirmation by EUS-FNA (18); however, care should be taken as there is a risk of dissemination in cases of cystic lesions (17). Koshita et al. (9) reported a case of type 1 AIP accompanied by BD-IPMN that was safely diagnosed by EUS-FNA without surgical resection (case: 7). Pancreatic juice cytology is also helpful; how-

ever, the sensitivity for malignancy is limited (33-67%) and some patients develop post-ERCP pancreatitis (3-25%) (19, 20). Of course, serum IgG4 and other organ involvement are crucial diagnostic items, but not conclusive. Evaluation based on the steroid response is the final strategy if malignancy is fully excluded (21); inflammatory lesions will shrink but IPMNs will not (7).

### Conclusion

We reported a case of BD-IPMN in which the patient developed type 1 AIP during follow-up. The case showed a unique morphological change, with a lotus root-like appearance. Clinicians should be aware of the disease concept of AIP and carefully diagnose atypical cases.

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

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