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Case Report

Type 1 autoimmune pancreatitis may develop in gastric-type intraductal papillary mucinous neoplasm

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Abstract: A subtype of autoimmune pancreatitis (AIP) is associated with increased serum IgG4, and IgE levels and steroid responsiveness, suggesting abnormal immunity, including allergy or autoimmunity. This subtype also exhibits dense infiltration of IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis. Recognized as lymphoplasmacytic sclerosing pancreatitis (LPSP; type 1 AIP), this is a pancreatic manifestation of IgG4-related diseases (IgG4-RD). IgG4-RD can occur simultaneously with malignancies, which might also be applicable to AIP. However, the relationship between AIP and pancreatic carcinoma needs to be clarified. Recently, there are 4 reported cases of the coexistence of intraductal papillary mucinous neoplasm (IPMN) and AIP. We report another case of a 68-year-old Japanese man, where AIP developed in IPMN 4 years after the initial radiological detection of branch- and gastric-type IPMN. We believe that the 4 previously reported cases also result from the coexistence of AIP and branch- and gastric-type IPMN. Two cases exhibited the occurrence of AIP during IPMN follow up similar to our case. These findings suggest that IPMN, particularly the branch- and gastric-type IPMN, might induce AIP. Further studies are necessary in order to conclusively define the relationship between IPMN and AIP.

Keywords: Autoimmune pancreatitis, intraductal papillary mucinous neoplasm, mural nodule, pancreatoduodenectomy, type 1

Introduction

There are two subtypes of autoimmune pancreatitis (AIP) recognized as types 1 (lymphoplasmacytic sclerosing pancreatitis; LPSP) and 2 (idiopathic duct-centric chronic pancreatitis; IDCP), respectively [1]. Apart from the type 2 AIP encountered in Western countries, characteristics of type 1 AIP, such as increased serum IgG4 and IgE levels and steroid responsiveness, are suggestive of abnormal immunity (e.g. allergy or autoimmunity) [1, 2]. Other characteristics of type 1 AIP are elderly male preponderance, pancreatic enlargement, irregular narrowing of the main pancreatic duct, dense infiltration of IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis [1, 2]. Type 1 AIP is regarded as the pancreatic manifestation of IgG4-related disease (IgG4-RD), because extrapancreatic manifestations of IgG4-RD (e.g. sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis) are sometimes accompanied by type 1 AIP [3].

Some cases of AIP associated with pancreatic carcinoma have been reported, but a relationship between AIP and pancreatic carcinoma has yet to be elucidated [4-7]. Although any intraductal papillary mucinous neoplasm (IPMN) did not accompany AIP in 114 surgically resected cases [8], there have recently been 4 cases documenting coexistence of IPMN and AIP in the English language literature [9-12]. Herein, we report the 5th case and discuss the relationship between them.

Clinical summary

A 68-year-old Japanese man was referred to our hospital due to the presence of a cystic lesion in the pancreas detected by ultrasonography upon check up. The physical examination and laboratory tests did not reveal any abnormality. On contrast enhanced computed tomography (CT), a cystic lesion was confirmed at the head of the pancreas (**Figure 1A**, **1B**). On magnetic resonance cholangiopancreatography (MRCP), a multilocular lesion measuring 20 ×

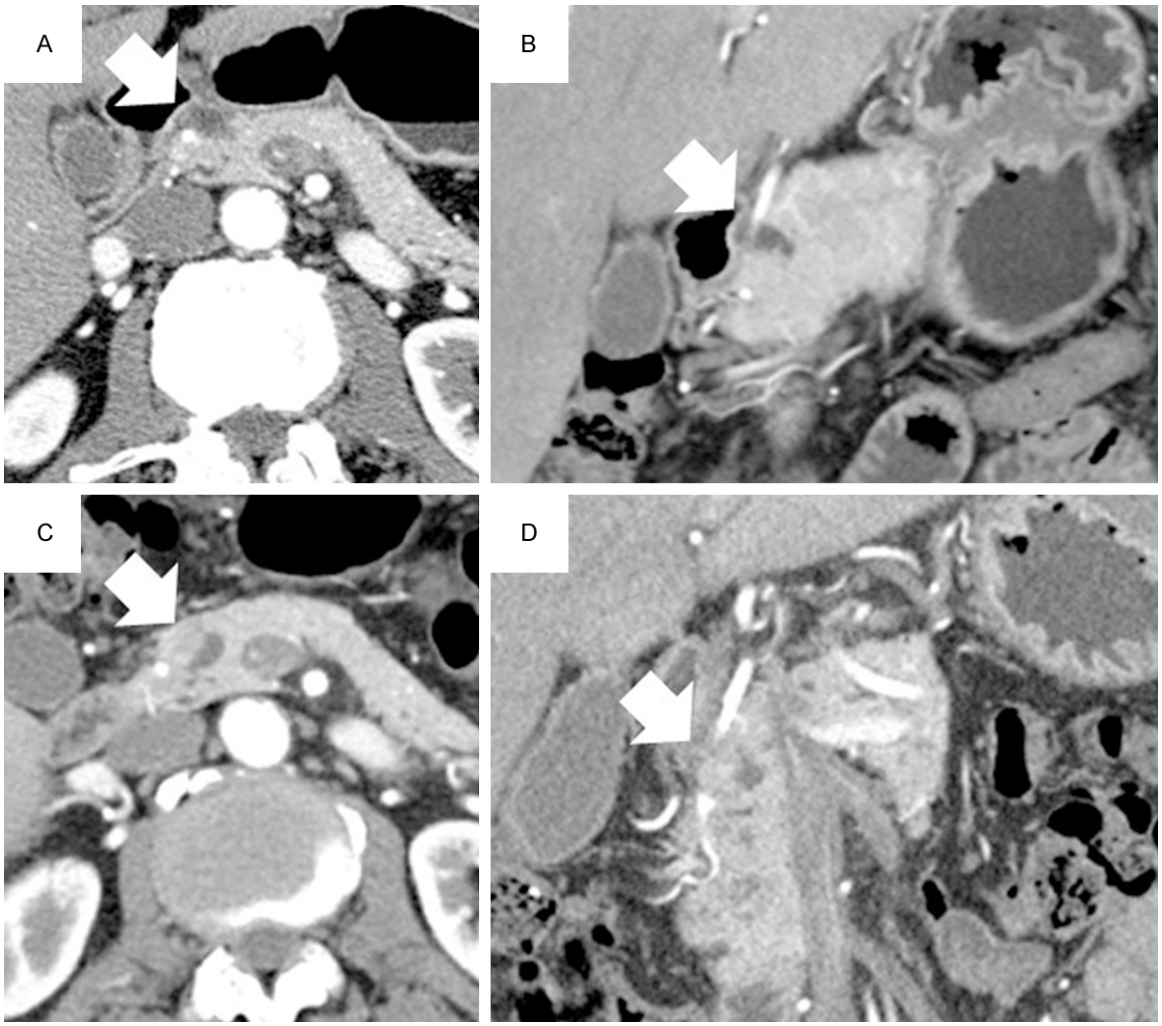

Figure 1. Contrast enhanced computed tomography findings. (A) Axial and (B) coronal views of a cystic lesion (arrow) that was confirmed at the head of the pancreas. (C) Axial and (D) coronal views of the cystic lesion. Four years after (A) and (B) were visualized, a mural nodule (arrow), measuring 12 × 10 × 8 mm, appeared in the lesion.

12 × 8 mm, and involving the branch pancreatic duct was visualized (**Figure 2A**) and identified as IPMN. Regular follow up was started. After 1 year, the lesion size increased to 24 × 14 × 10 mm on MRCP (**Figure 2B**). Two years after the initial radiological examination, there were no changes in size on MRCP (**Figure 2C**). Four years after the initial radiological examination, a mural nodule, measuring 12 × 10 × 8 mm, appeared in the lesion on contrast enhanced CT (**Figure 1C**, **1D**). The size of the cystic part of the lesion markedly decreased on MRCP (**Figure 2D**). Invasive carcinoma arising from branch type IPMN was suspected. At this point, the patient had no complaints. Subsequently, pancreatoduodenectomy was performed. Since the pathological diagnosis was type 1 AIP arising in branch type IPMN, serum IgG4 was measured using preserved preoperative serum sample and fresh postoperative serum sample. The values of IgG4 from the preoperative and postoperative samples were 44.4 mg/dL and 55.4 mg/dL, respectively (normal range: 4.8-105 mg/dL). Postoperatively, the patient did not have any complaints and physical and radiological examination revealed no abnormal finding in the other organs.

Pathological findings

Macroscopically, the cut surface revealed a whitish mass with a cystic portion at the periphery, which involved peripnacreatic fat (**Figure 3**).

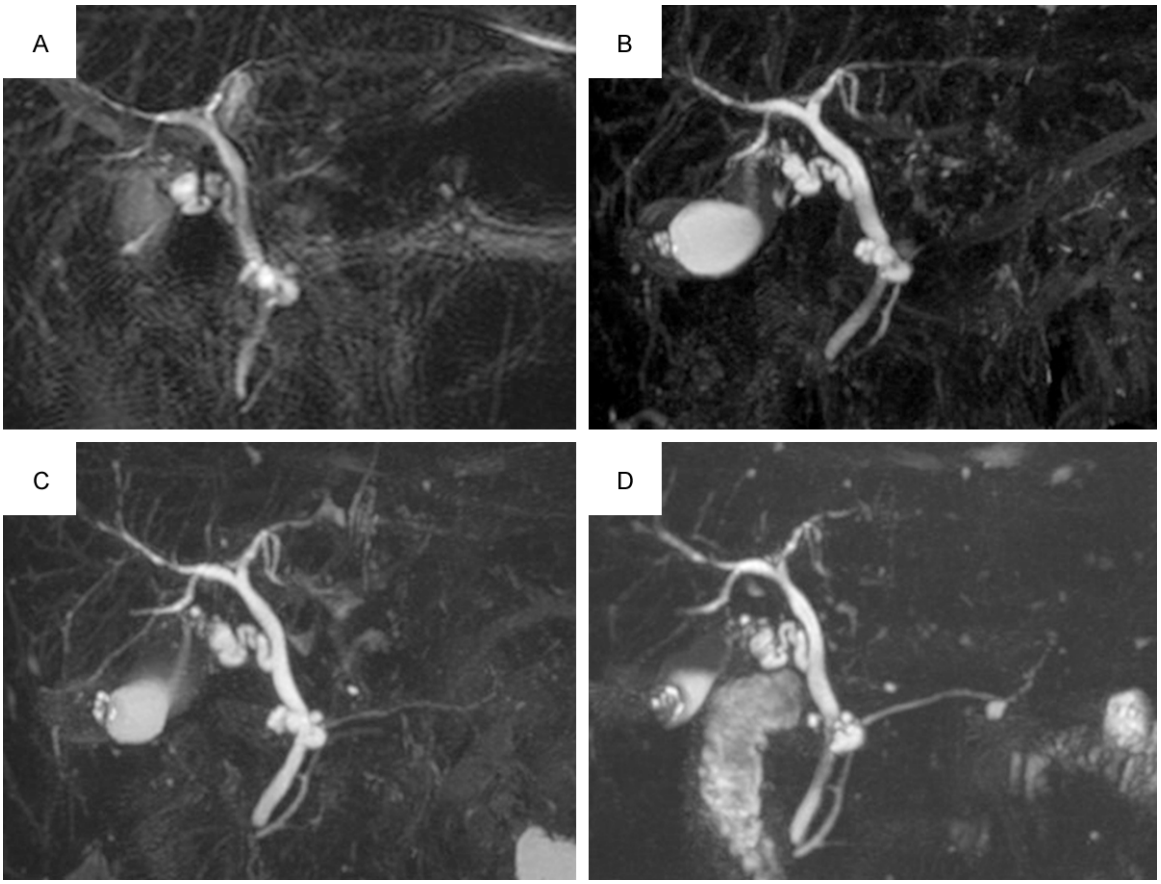

Figure 2. Magnetic resonance cholangiopancreatography findings. (A) The lesion measured 20 × 12 × 8 mm and involved the branch pancreatic duct. (B) One year after (A) was identified, the size of the lesion increased to 24 × 14 × 10 mm. (C) Two years after (A) was identified, the size of the lesion remained unchanged. (D) Four years after (A) was identified, the size of the cystic part of the lesion markedly decreased.

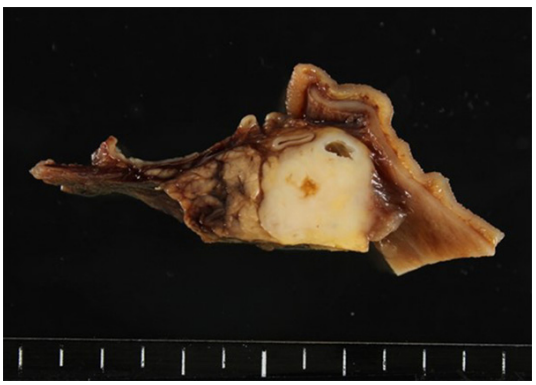

Figure 3. Macroscopic findings. The cut surface revealed a whitish mass with a cystic portion identified at the periphery and involvement of the peripancreatic fat.

Microscopically, there was severe lymphoplasmacytic infiltration with lymphoid follicle formation in the mass. Fibrosis was variably present in the background. Cystic portion was noted at the periphery (**Figure 4A**) with storiform fibrosis frequently observed (**Figure 4B**). Obliterative phlebitis was also noted with Elastica van Gieson staining (**Figure 4C**). The cystic portion was lined with mucin-containing epithelium with mild to moderate nuclear atypia (**Figure 4D**); typical papillary proliferation was not observed. Mucin-containing epithelium growing into smaller ducts was observed at the periphery of the mass (**Figure 4E**). The mucin-containing epithelium was supposed to involve the branch pancreatic duct with intact main pancreatic duct. The diagnosis of autoimmune pancreatitis involving branch type IPMN was rendered. Lymphoplasmacytic infiltration was not found in other parts of the pancreas and bile duct.

Immunohistochemcially, IgG-positive plasma cells were abundant (**Figure 4F**). IgG4-positive

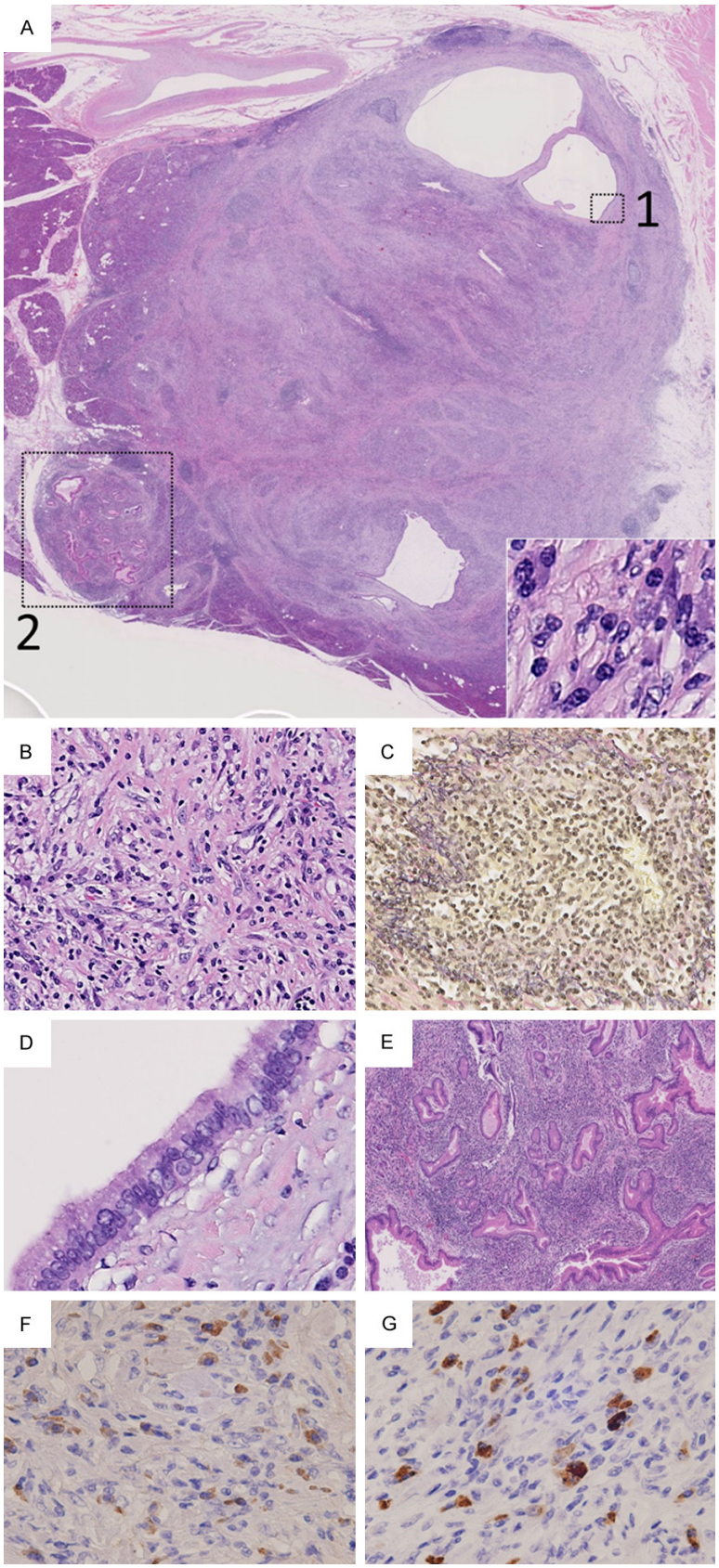

Figure 4. Histopathological and immunohistochemical findings. (A) There was severe lymphoplasmacytic infiltration with lymphoid follicle formation in the mass. Fibrosis was variably present in the background. Cystic portion was noted at the periphery (× 12.5). Inset: high-power view of lymphoplasmacytic infiltration (× 400). (B) Storiform fibrosis was often observed (× 200). (C) Obliterative phlebitis was observed with Elastica van Gieson staining (× 200). (D) High-power view of the dotted box 1 in (A). The cystic portion was lined with mucin-containing epithelium with mild to moderate nuclear atypia (× 400). (E) Middle-power view of the dotted box 2 in (A). Mucin-containing epithelium that extended into the smaller ducts was observed at the periphery of the mass (× 200). (F) Immunohistochemistry revealed numerous IgG-positive plasma cells (× 400). (G) Immunohistochemistry revealed abundant IgG4-positive plasma cells, exceeding 10 such cells per 1 high-power field (× 400).

plasma cells were numerous and exceeded 10 cells per 1 high power field at any part of the mass (**Figure 4G**). The ratio of IgG4-positive plasma cells/IgG-positive plasma cells was approximately 50%. Based on the international consensus diagnostic criteria (ICDC) formulated by the International Association of Pancreatology [13], the diagnosis of type 1 AIP was confirmed. The mucin-containing epithelium was positive for MUC5AC and MUC6 and negative for MUC1 and MUC2. Thus, the IPMN was regarded as gastric type.

Discussion

The diagnosis of type 1 AIP in our case was confirmed according to the recently pro-

Table 1. Cases showing overlap of autoimmune pancreatitis (AIP) with intraductal papillary mucinous neoplasm (IPMN)

Case	Reported year	Country	Age (years)	Sex
1 [9]	2013	Japan	64	Male
2 [10]	2013	Japan	76	Male
3 [11]	2013	Japan	79	Male
4 [12]	2013	Japan	70	Female
Present case	2015	Japan	68	Male

Location of IPMN	Follow-up period of IPMN	Type of IPMN
Head	None	Branch and Gastric type
Head	4 years	Branch and possibly Gastric type*
Body and Tail	None	Branch and Gastric type
Head	3 years	Branch and probably Gastric type*
Head	4 years	Branch and Gastric type

Type of AIP	Serum IgG4	Treatment	IgG4-related disease in other organs
Type 1, diffuse	Preoperative, 27.7 mg/dL	Pancreatoduodenectomy	N.A.
Type 1, focal	Postoperative, 1260 mg/dL	Pancreatoduodenectomy	None
Type 1, focal	Preoperative, 627 mg/dL	Pancreatoduodenectomy	None
Type 1, focal	N.A.	Pancreatoduodenectomy	N.A.
Type 1, focal	Preoperative, 44 mg/dL	Pancreatoduodenectomy	None

*Our opinion. N.A.: not available.

posed ICDC [13]. Without elevation of serum IgG4 level and typical radiological findings, histopathology of the pancreas alone is sufficient for diagnosis if 3 or more of the following 4 findings are observed: (1) Dense infiltration of plasma cells and lymphocytes, particularly in the periductal regions; (2) Peculiar storiform fibrosis; (3) Venulitis with lymphocytes and plasma cells often leading to obliteration of the affected veins; and (4) Abundant [> 10 cells per high power field (HPF)] IgG4-positive plasma cells [13]. In our case, all of these 4 findings were observed. With respect to the diagnosis of IPMN, the typical papillary structure was not identified. However, the presence of mucin-containing cells immunopositive for MUC5AC and MUC6 and extension of mucin-containing cells to smaller ducts, which is known as pancreatic intraepithelial neoplasia (PanIN)-like complex [14], supportive of gastric-type IPMN.

Pancreatoduodenectomy for coexistent IPMN and AIP is unavoidable and the appropriate choice, although it was found to be a benign lesion postoperatively. Preoperative endoscopic ultrasound guided fine needle aspiration (EUS-FNA) was not performed in this case because of the absence of a consensus regarding its usefulness for the assessment of potential malignancy in IPMN, especially in the absence of a common diagnostic criteria for the pathological evaluation of a sample that was obtained using this technique [15]. In addition, complications, including injury to adjacent organs, hemorrhage, and the seeding of malignant cells into the peritoneum, have been reported [16]. With respect to AIP, surgical resection is sometimes selected, especially in cases of focal AIP due to the difficulty of distinguishing it from other solid pancreatic masses on multidisciplinary examinations [10].

Although some reports suggest a high relative risk of pancreatic carcinoma in AIP, there is no conclusive association between AIP and pancreatic carcinoma [7, 17]. IgG4-RD can be accompanied by the simultaneous occurrence of malignancies, which might also apply to AIP [17]. On the other hand, there is a well studied report, in which AIP and pancreatic carcinoma are suggested not to be associated [18]. Meanwhile, there are no negative reports on the relationship between AIP and IPMN; the possibility of the IPMN triggering AIP or AIP-like tissue reaction has been suggested [11].

Apart from a debate on the relationship between AIP and neoplasia, two types of pan-

creatic cysts (uni- and multilocular) have long been identified in cases with AIP [19]. When treated with steroids, unilocular cysts were shrunk or vanished. In contrast, mulitilocular cysts did not demonstrate noticeable steroid responses [19]. Pancreatic carcinoma often accompanied AIP with multilocular cysts, while AIP with unilocular cysts did not harbor pancreatic carcinoma [19]. Unilocular cysts, including the pseudocysts, can possibly be formed, because of a highly active inflammatory process [20]. Conversely, we speculated that some of the multilocular cysts might represent unrecognized IPMN that lack the easily recognizable and typical papillary structure, due to its unresponsiveness to steroids and coexistent pancreatic carcinoma.

We closely examined the previously reported 4 cases exhibiting coexistence of AIP and IPMN and summarized these cases in **Table 1** with some of our own interpretation [9-12]. We interpreted epithelial proliferation in one case as neoplastic proliferation indicating gastric-type IPMN, based on the microscopic pictures provided in the report [10]. We also interpreted the subtype of IPMN in another case as the gastric type, based on the microscopic pictures as well as the description of immunopositivity and immunonegativity of IPMN for MUC5AC and MUC2, respectively [12]. As a result, we noticed that all of the 4 cases supposedly coexisted with AIP and the branch- and gastric-type IPMN. Similar to our case, 2 out of 4 cases exhibited development of AIP during the follow up of IPMN [10, 12]. The occurrence of AIP prior to IPMN was not observed in any of the cases. Interestingly, one case demonstrated two IPMNs, which were both superimposed by AIP. The AIP was only observed in the vicinity of IPMNs [12]. Two IPMNs discretely involved with AIP is not coincidental since these findings suggest that IPMN could induce AIP, which is likely to develop as an inflammatory reaction against IPMN. However, further accumulation of cases and extensive studies are needed in order to conclude the relationship between IPMN and AIP.

In conclusion, there has been debate on the relationship between AIP and neoplasia, such as pancreatic carcinoma and IPMN. With respect to pancreatic carcinoma, varying opinions that support and deny its association with AIP still exists. Conversely, there are no reports that deny the association between IPMN with AIP. Some authors believe there is an association between them despite the limited number of recognized cases describing their coexistence (5 cases, including our case) and the scarcity of extensive studies on their coexistence. Based on our examination, there have been 4 previously reported cases of the coexistence of AIP and branch- and gastric-type IPMN, which are similar to our case. In addition to our case, the 2 other AIP cases occurred during follow up of IPMN. These findings suggest that IPMN, particularly branch- and gastric-type IPMN, might induce AIP.

Disclosure of conflict of interest

None.

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