

Intraductal Tubulopapillary Epithelial Proliferation Associated with Type 1 Autoimmune Pancreatitis

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ABSTRACT

A 70-year-old man was referred to our hospital with exacerbation of diabetes. His blood tests showed elevated levels of serum IgG4 and HbA1c. Computed tomography of the pancreatic body demonstrated a weakly enhanced mass, 2 cm in size, with indistinct borders. Magnetic resonance cholangiopancreatography revealed a narrowing of the main pancreatic duct (MPD) at the pancreatic body, a markedly dilated upstream duct, and a slightly dilated downstream duct. Endoscopic ultrasonography demonstrated an iso-hypoechoic heterogeneous mass, protruding and spreading in the pancreatic duct. The histology of a fine needle aspiration sample demonstrated fibrous tissue containing abundant IgG4-positive plasma cells and atypical epithelial cells. The imaging findings and histology were not typical for either pancreatic ductal adenocarcinoma or type 1 autoimmune pancreatitis (AIP), but these were not completely excluded, and a distal pancreatectomy was performed. Histological examination showed an intraductal tubulopapillary epithelial proliferation, which contained cytoplasmic mucin (MUC5AC and MUC6), and severe IgG4-positive lymphoplasmacytic infiltration in the interstitium around the MPD. Next-generation sequencing using DNA extracted from the tumor revealed no mutation of *K-ras*, *GNAS*, or *TP53*. The entire lesion was ultimately diagnosed as AIP with an intraductal tubular and papillary epithelial hyperplasia producing gastric-type mucin. Some recent reports have described AIP development in the background of intraductal papillary mucinous neoplasms, and some have hypothesized a paraneoplastic occurrence of IgG4-related disease. The current case indicates issues in the clinical diagnosis of rare variants of AIP, and raises questions about the relationship between AIP and pancreatic epithelial lesions.

Key words: autoimmune pancreatitis – intraductal tumor – IgG4 – *K-ras* – diagnosis.

Abbreviations: AIP: Autoimmune pancreatitis; CT: computed tomography; EUS: Endoscopic ultrasonography (EUS); EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; FDG-PET: ¹⁸F-fluorodeoxyglucose-positron emission tomography; ICDC: international consensus diagnostic criteria; IPMN: intraductal papillary mucinous neoplasm; MPD: main pancreatic duct.

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INTRODUCTION

Autoimmune pancreatitis (AIP) is a pancreatic disorder characterized by immunological abnormalities. Type 1 AIP, in particular, is regarded as a subtype of the IgG4-related systemic diseases that include dacryoadenitis, sclerosing cholangitis, and retroperitoneal fibrosis [1, 2]. Some literature has demonstrated an association between the development of type 1 AIP and that of pancreatic

epithelial neoplasms, including invasive ductal carcinoma [3-6] and intraductal papillary mucinous neoplasms (IPMNs) [4, 7-9]. Moreover, even in non-AIP cases, an abnormal level of IgG4-positive plasmacytic aggregation has been observed in the tissues surrounding pancreatic cancers [10] and IPMNs [11]. We report a case of type 1 AIP that was accompanied by an intraductal tumor-like lesion, consisting of tubular and papillary epithelial proliferation. Atypical clinical images impeded accurate preoperative diagnosis in this case.

CASE REPORT

In June 2016, a 70-year-old man was referred to our hospital with exacerbation of diabetes. He was a former smoker (10 cigarettes a day from age 20 to 39) and he had a medical

history of hypertension and diabetes mellitus. His serum tests showed elevated levels of IgG4 (265 mg/dL, normal: 4.8–105 mg/dL) and HbA1c (9.2%, normal: 4.6–6.2%); serum tumor markers (carcinoembryonic antigen, carbohydrate antigen 19-9, DUPAN-2, and SPAN-1) were all within the normal range. Dynamic computed tomography (CT) at the equilibrium phase revealed a weakly enhancing, ill-demarcated mass, 20 × 18 mm in size, at the pancreatic body (Fig. 1). Magnetic resonance imaging revealed the mass lesion as a low-intensity signal on T1-weighted images and a slightly high-intensity signal on both T2-weighted and diffusion-weighted images. Magnetic resonance cholangiopancreatography demonstrated narrowed pancreatic ducts in the pancreatic body, accompanied by marked upstream dilatation of the main pancreatic duct (MPD) and a small downstream dilatation (Fig. 2). Endoscopic ultrasonography (EUS) revealed an iso-hypoechoic heterogeneous nodule protruding within the MPD, possibly suggesting an intraductal tumor associated with an invasive mass. Multiple small cysts were also recognized around the mass (Fig. 3). ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET) [12] demonstrated an abnormal uptake at the level of pancreatic body (SUV max: 4.61), but no extrapancreatic lesions. These imaging findings were atypical for pancreatic cancer, IPMN, or AIP. Hence, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) was performed using a 22G needle (EchoTip, Cook Medical, Bloomington, IN) to obtain histological evidence of the pancreatic mass [13]. Histology of the EUS-FNA sample demonstrated fibrous tissue containing abundant IgG4-positive plasma cells (≥10 cells/high power field) and atypical epithelial cells. Taken together, the imaging and histological findings led to a suspicion of invasive cancer derived from the intraductal tumor and occupying the MPD, accompanied by abundant infiltration of IgG4-positive lymphoplasmacytic cells or with type 1 AIP. A distal pancreatectomy was performed.

Macroscopically, the resected pancreas showed a white mass with indistinct borders in the pancreas body and multiple small cysts around the mass. Histological examination showed a nodular lesion with both tubular and high papillary epithelial proliferation, mainly in the MPD (Fig. 4a). These intraductal epithelial cells were negative for MUC2 expression and positive for both MUC5AC and MUC6 (gastric-type mucin core protein). The possibility of gastric-type IPMN could not be

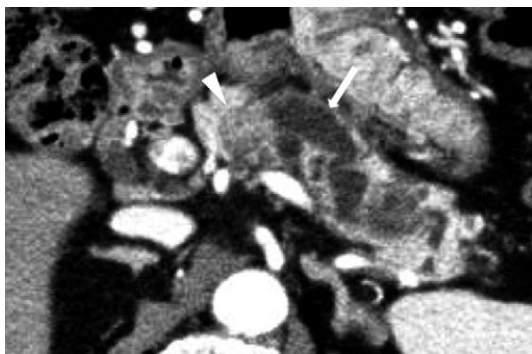


Fig. 1. Enhanced CT images showing a weakly enhanced, ill-demarcated mass at the pancreatic body, 20×18 mm in size (arrow head), and a marked dilation of the upstream main pancreatic duct (arrow).

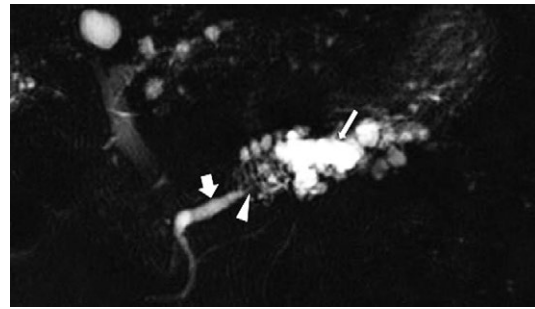


Fig. 2. Magnetic resonance cholangiopancreatography demonstrating narrowed pancreatic ducts at the pancreatic body (arrow head), a dilated upstream duct (thin arrow), and a faintly dilated downstream duct (thick arrow).

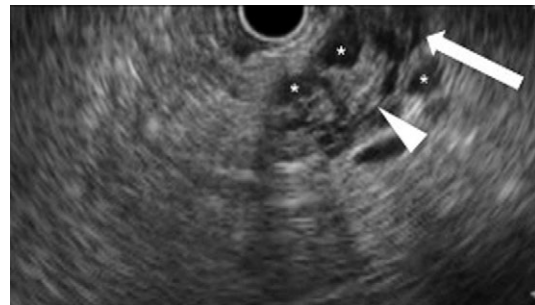


Fig. 3. Endoscopic ultrasonography showing an iso-hypoechoic heterogeneous nodule, protruding within the main pancreatic duct (MPD; arrow head), a dilated upstream MPD (arrow), and multiple small cysts around the nodule (asterisk).

completely discounted, but we diagnosed epithelial hyperplasia based on the following findings: 1) very low-grade histological atypia, especially nuclear atypia; 2) inconsistent amounts of mucin production by the site; 3) abundant tubular formation in the bottom regions, as well as in the top of the club-shaped epithelial projection; and 4) many epithelial cells containing cytoplasmic granules, quite atypical for IPMN (Fig. 4b, 4c). Severe IgG4-positive lymphoplasmacytic infiltration was recognized in the interstitium of the epithelial projection and its surrounding pancreas (average 96 cells per high powered field) (Fig. 5a). Storiform fibrosis and obliterative phlebitis were also found around the MPD (Fig. 5b, 5c). These histological findings fully met the international consensus diagnostic criteria (ICDC) for type 1 AIP [14].

Consequently, the entire lesion was diagnosed as type 1 AIP accompanied with tubular and papillary epithelial hyperplasia producing gastric-type mucin. We determined the neoplastic or hyperplastic nature of this epithelial proliferation by whole-exome sequencing [15] using DNA extracted from the intraductal protrusion. We observed three representative areas within the lesion in Hematoxylin-Eosin section, each consisting of >1000 cells (containing epithelial, interstitial and inflammatory cells), as viewed by light microscopy at 200×. The average proportion of the epithelial cells per total cells was 47% (range: 34–60%), which was far beyond the sensitivity of current DNA sequencing (mutant DNA concentration: ≥5%). No mutation was recognized in APC, K-ras, GNAS, CDKN2A/p16, TP53, or DPC4.

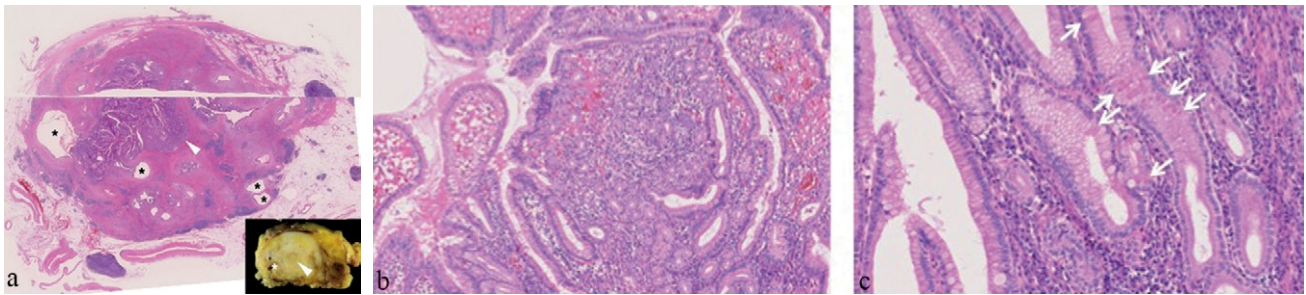


Fig. 4. Histological aspect of the pancreatic lesion. Loupe finding of the pancreatic epithelial proliferation mainly in the main pancreatic duct (arrow ahead), multiple cystic dilation of the branch ducts (asterisk) surrounded by dense fibrosis and lymph follicles (H&E; 1.25×) (inset: macroscopic view of the fixed pancreatic cut surface) (a). Magnified view of the epithelial lesion in the main pancreatic duct showing club-shaped epithelial projections with abundant inflammatory cell infiltration (40×)(b) and epithelial cells containing eosinophilic cytoplasmic granules (100×)(c).

DISCUSSION

In the current case, based on the ICDC for AIP [2, 14], the inflammatory lesion around the tubulopapillary epithelial component was diagnosed as definitive type 1 AIP (Fig. 5). However, diagnosis of the intraductal epithelial component was difficult using only the clinical images and histology. The epithelial projection was depicted by enhanced CT as a weakly enhanced and ill-demarcated mass (Fig. 1), and as an iso-hypo echoic heterogeneous mass protruding into the MPD (Fig. 3). Multiple small cysts were seen around the mass. The pancreatic duct was narrowed in a reticular pattern within the mass area and markedly dilated upstream (Fig. 1-3). These findings were atypical for either IPMN or pancreatic ductal adenocarcinoma. EUS-FNA was not conclusive, although the findings suggested an accompanying type 1 AIP. Distal pancreatectomy was unavoidable because of the existence of the intraductal mass suspicious of an epithelial tumor and the markedly dilated upstream MPD suggestive of cancer invasion. Other than cases with IPMN [7, 8, 16, 17], so far, several atypical variants of AIP have been reported; i.e., a case mimicking endocrine tumor with enlarged pancreatic ducts

[18], a case with a huge pancreatic cyst [19], and a case with colonic stenosis due to inflammatory infiltration [20]. Even an AIP case containing cholesterol granuloma and mimicking IPMN has been reported [21]. In such cases, steroid trial can be offered to prevent unnecessary surgery. Koshita et al. [22], reported a case of branch-type IPMN involving type 1 AIP, diagnosed by EUS-FNA and successfully treated with steroids. However, in such atypical cases, exclusion of malignancy by EUS-FNA is mandatory, before a therapeutic trial [1, 2, 14].

The intraductal tubulopapillary component was diagnosed by pathology as a gastric-type epithelial hyperplasia for the reasons described above. In addition to the wide interstitial cells, the key findings of a low grade of histological atypia [23], glandular formation within the club-shaped epithelial projection, cytoplasmic granules, and incoherent mucin production were uncharacteristic of IPMN (Fig. 4b, 4c). The tumor location was also atypical for gastric-type IPMN, which frequently develops in the branched duct [23]. Autoimmune pancreatitis with the null mutations of *K-ras* and *GNAS* were also suggestive of epithelial hyperplasia rather than IPMN, as IPMN often shows these somatic mutations (*K-ras* mutation: 50–73% [24, 25] and *GNAS* mutation: 40–89% cases of IPMN) [24, 26].

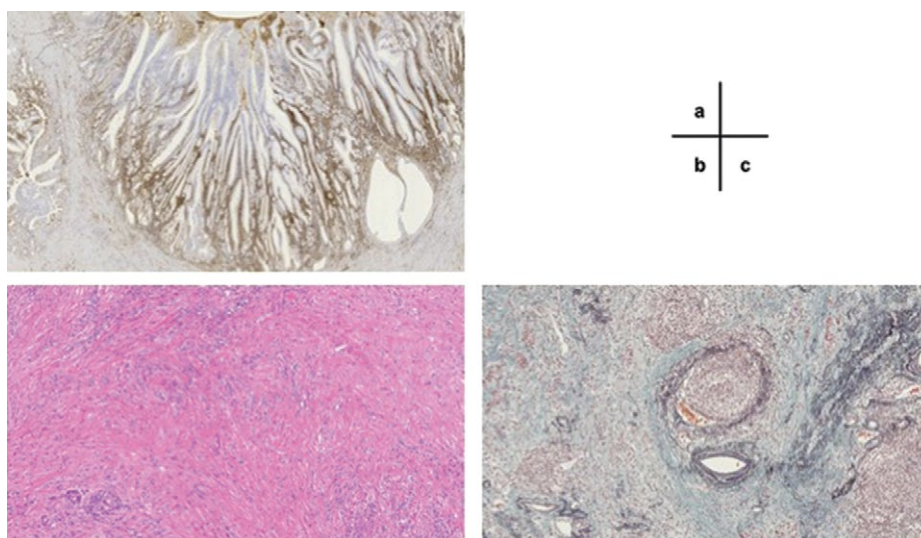


Fig. 5. Histological findings confirming type 1 autoimmune pancreatitis. Severe IgG4-positive lymphoplasmacytic infiltration within the proliferative epithelial lesion and the surrounding pancreas (IgG4, 25×)(a); storiform fibrosis (H&E; 40×) (b); and obliterative phlebitis around the main pancreatic duct (MPD)(Elastica Van Gieson, 40×)(c).

However, previous data has raised issues regarding the development of pancreatic epithelial neoplasms and AIP [16, 17, 27] or an AIP-like anomaly [11, 28]. One suggestion is that IPMN develops in the background of chronic inflammation caused by AIP [7]. Others have suggested that AIP develops during the follow-up of IPMN [8, 9]. A similar phenomenon has been discussed in the development of AIP and pancreatic cancer (i.e., pancreatic cancer develops during the follow-up of AIP) [4, 6]; a paraneoplastic occurrence of AIP has also been speculated [29, 30]. Shiokawa et al. [29] reported that patients diagnosed with AIP are at high risk for cancer and that cancer resection was possible with the remission of AIP (i.e., there are patients in whom AIP appears as a paraneoplastic syndrome). In the present case, no malignant tumor was found in the pancreas or in other organs. Hence, based on the histological and molecular findings, we speculated that this was a reactive epithelial hyperplasia due to long-term inflammation. Kinugawa et al. [31] detected promoter methylation of several cancer-related genes (*NPTX2*, *TFPI2*, *Cyclin D2*, *FOXE1*, *ppEnk*, etc.) [32], but no *K-ras* mutation in AIP tissues. Intensive chronic inflammation due to AIP may be associated with pancreatic tumorigenesis arising from a route that differs from the usual pathway.

CONCLUSION

We experienced a case of type 1 AIP accompanied with protrusion into the intraductal tubule and papillary epithelium, mainly in the MPD. These findings caution clinicians to bear in mind current rare and atypical variants of AIP in future diagnoses. The mechanism by which these lesions develop needs further investigation.

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Authors' contributions: S.F., H.M., H.I., and H.H. performed the endoscopic and radiological examinations and their evaluations; T.I. performed surgery and managed the patient; K.S. made pathological diagnosis; S.F. and H.M. wrote the manuscript and H.O. supervised it. All authors read and approved the final version of the manuscript.

REFERENCES

- Okazaki K, Tomiyama T, Mitsuyama T, Sumimoto K, Uchida K. Diagnosis and classification of autoimmune pancreatitis. *Autoimmun Rev* 2014;13:451-458. doi:10.1016/j.autrev.2014.01.010
- Matsubayashi H, Kakushima N, Takizawa K, et al. Diagnosis of autoimmune pancreatitis. *World J Gastroenterol* 2014;20:16559-16569. doi:10.3748/wjg.v20.i44.16559
- Matsubayashi H, Matsunaga K, Uesaka K, et al. A case of pancreatic carcinoma with suspected autoimmune pancreatitis. *Clin J Gastroenterol* 2009;2:59-63. doi:10.1007/s12328-008-0045-9
- Matsubayashi H, Iwai T, Matsui T, et al. Pancreatic cystic lesions with atypical steroid response should be carefully managed in cases of autoimmune pancreatitis. *J Gastroenterol Hepatol* 2016;31:270-276. doi:10.1111/jgh.13051
- Hirano K, Tada M, Sasahira N, et al. Incidence of malignancies in patients with IgG4-related disease. *Intern Med* 2014;53:171-176. doi:10.2169/internalmedicine.53.1342
- Ikeura T, Miyoshi H, Uchida K, et al. Relationship between autoimmune pancreatitis and pancreatic cancer: a single-center experience. *Pancreatol* 2014;14:373-379. doi:10.1016/j.pan.2014.04.029
- Naitoh I, Nakazawa T, Notohara K, et al. Intraductal papillary mucinous neoplasm associated with autoimmune pancreatitis. *Pancreas* 2013;42:552-554. doi:10.1097/MPA.0b013e31826cc2fc
- Nakaji S, Hirata N, Fujii H, et al. A case of focal autoimmune pancreatitis (AIP) mimicking an intraductal papillary mucinous neoplasm (IPMN). *Clin J Gastroenterol* 2013;6:329-333. doi:10.1007/s12328-013-0392-z
- Umamura S, Naitoh I, Nakazawa T, et al. Autoimmune pancreatitis presenting a short narrowing of main pancreatic duct with subsequent progression to diffuse pancreatic enlargement over 24 months; natural history of autoimmune pancreatitis. *JOP* 2014;15:261-265. doi:10.6092/1590-8577/2393
- Dhall D, Suriawinata AA, Tang LH, Shia J, Klimstra DS. Use of immunohistochemistry for IgG4 in the distinction of autoimmune pancreatitis from peritumoral pancreatitis. *Hum Pathol* 2010;41:643-652. doi:10.1016/j.humpath.2009.10.019
- Tabata T, Kamisawa T, Hara S, et al. Intraductal papillary mucinous neoplasm of the pancreas and IgG4-related disease: a coincidental association. *Pancreatol* 2013;13:379-383. doi:10.1016/j.pan.2013.04.197
- Matsubayashi H, Furukawa H, Maeda A, et al. Usefulness of positron emission tomography in the evaluation of distribution and activity of systemic lesions associated with autoimmune pancreatitis. *Pancreatol* 2009;9:694-699. doi:10.1159/000199439
- Matsubayashi H, Matsui T, Yabuuchi Y, et al. Endoscopic ultrasonography guided-fine needle aspiration for the diagnosis of solid pancreaticobiliary lesions: Clinical aspects to improve the diagnosis. *World J Gastroenterol* 2016;22:628-640. doi:10.3748/wjg.v22.i2.628
- Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 2011;40:352-358. doi:10.1097/MPA.0b013e3182142fd2
- Urakami K, Shimoda Y, Ohshima K, et al. Next generation sequencing approach for detecting 491 fusion genes from human cancer. *Biomed Res* 2016;37:51-62. doi:10.2220/biomedres.37.51
- Bateman AC, Culver EL, Sommerlad M, Chetty R. Intraduct papillary mucinous neoplasm of the pancreas: a tumour linked with IgG4-related disease? *J Clin Pathol* 2013;66:671-675. doi:10.1136/jclinpath-2013-201516
- Urata T, Naito Y, Izumi Y, et al. Localized type 1 autoimmune pancreatitis superimposed upon preexisting intraductal papillary mucinous neoplasms. *World J Gastroenterol* 2013;19:9127-9132. doi:10.3748/wjg.v19.i47.9127
- Neuzillet C, Lepere C, El Hajjam M, et al. Autoimmune pancreatitis with atypical imaging findings that mimicked an endocrine tumor. *World J Gastroenterol* 2010;16:2954-2958. doi:10.3748/wjg.v16.i23.2954
- Matsubayashi H, Matsui T, Ono H. Pancreatic Duct Drainage for the Treatment of a Huge Pancreatic Cyst Associated With Autoimmune Pancreatitis. *Clin Gastroenterol Hepatol* 2015;13:e151-e152. doi:10.1016/j.cgh.2015.03.020
- Matsubayashi H, Kishida Y, Yoshida Y, et al. Autoimmune pancreatitis with colonic stenosis: an unusual complication and

- atypical pancreatographic finding. *BMC Gastroenterol* 2014;14:173. doi:[10.1186/1471-230X-14-173](https://doi.org/10.1186/1471-230X-14-173)
21. Takahashi Y, Yokoyama N, Sato D, Otani T, Mitsuma K, Hashidate H. Diagnosis of autoimmune pancreatitis with cholesterol granuloma mimicking intraductal papillary-mucinous carcinoma: A case report. *Int J Surg Case Rep* 2017;33:62-66. doi:[10.1016/j.ijscr.2017.02.053](https://doi.org/10.1016/j.ijscr.2017.02.053)
 22. Koshita S, Noda Y, Ito K, et al. Branch Duct Intraductal Papillary Mucinous Neoplasms of the Pancreas Involving Type 1 Localized Autoimmune Pancreatitis with Normal Serum IgG4 Levels Successfully Diagnosed by Endoscopic Ultrasound-guided Fine-needle Aspiration and Treated without Pancreatic Surgery. *Intern Med* 2017;56:1163-1167. doi:[10.2169/internalmedicine.56.8017](https://doi.org/10.2169/internalmedicine.56.8017)
 23. Furukawa T, Klöppel G, Volkan Adsay N, et al. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. *Virchows Arch* 2005;447:794-799. doi:[10.1007/s00428-005-0039-7](https://doi.org/10.1007/s00428-005-0039-7)
 24. Tan MC, Basturk O, Brannon AR, et al. GNAS and KRAS Mutations Define Separate Progression Pathways in Intraductal Papillary Mucinous Neoplasm-Associated Carcinoma. *J Am Coll Surg* 2015;220:845-854. e1. doi:[10.1016/j.jamcollsurg.2014.11.029](https://doi.org/10.1016/j.jamcollsurg.2014.11.029)
 25. Matsubayashi H, Watanabe H, Yamaguchi T, et al. Multiple K-ras mutations in hyperplasia and carcinoma in cases of human pancreatic carcinoma. *Jpn J Cancer Res* 1999;90:841-848.
 26. Furukawa T, Kuboki Y, Tanji E, et al. Whole-exome sequencing uncovers frequent GNAS mutations in intraductal papillary mucinous neoplasms of the pancreas. *Sci Rep* 2011;1:161. doi:[10.1038/srep00161](https://doi.org/10.1038/srep00161)
 27. Vaquero EC, Salcedo MT, Cuatrecasas M, et al. Autoimmune pancreatitis type-1 associated with intraduct papillary mucinous neoplasm: report of two cases. *Pancreatology* 2014;14:316-318. doi:[10.1016/j.pan.2014.04.032](https://doi.org/10.1016/j.pan.2014.04.032)
 28. Hedayat AA, Lisovsky M, Suriawinata AA, Longnecker DS. Association of IgG4 response and autoimmune pancreatitis with intraductal papillary-mucinous neoplasms. *Pancreatology* 2017;17:263-266. doi:[10.1016/j.pan.2017.02.004](https://doi.org/10.1016/j.pan.2017.02.004)
 29. Shiokawa M, Kodama Y, Yoshimura K, et al. Risk of cancer in patients with autoimmune pancreatitis. *Am J Gastroenterol* 2013;108:610-617. doi:[10.1038/ajg.2012.465](https://doi.org/10.1038/ajg.2012.465)
 30. Hirano K, Isayama H, Tada M, Koike K. Association between autoimmune pancreatitis and malignancy. *Clin J Gastroenterol* 2014;7:200-204. doi:[10.1007/s12328-014-0486-2](https://doi.org/10.1007/s12328-014-0486-2)
 31. Kinugawa Y, Uehara T, Sano K, et al. Methylation of Tumor Suppressor Genes in Autoimmune Pancreatitis. *Pancreas* 2017;46:614-618. doi:[10.1097/MPA.0000000000000804](https://doi.org/10.1097/MPA.0000000000000804)
 32. Matsubayashi H, Canto M, Sato N, et al. DNA methylation alterations in the pancreatic juice of patients with suspected pancreatic disease. *Cancer Res* 2006;66:1208-1217. doi:[10.1158/0008-5472.CAN-05-2664](https://doi.org/10.1158/0008-5472.CAN-05-2664)