

Synchronous pancreatic solid pseudopapillary neoplasm and intraductal papillary mucinous neoplasm

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Abstract

Solid pseudopapillary neoplasm (SPN) is a rare and low-grade malignant pancreatic neoplasm composed of poorly cohesive monomorphic neoplastic cells forming solid and pseudopapillary structures with frequent hemorrhagic-cystic degeneration. Intraductal papillary mucinous neoplasm (IPMN) is a pancreatic exocrine tumor composed of intraductal papillary growth of mucin containing neoplastic cells in the main pancreatic duct or its major branches. In the case presented here, a 53-year-old, Japanese man was found to have multiple

cystic lesions and dilatation of the main pancreatic duct in the neck of the pancreas. Histological examination revealed a main-duct and branch-duct type IPMN, of the gastric-type, involving the neck of the pancreas, associated with a 0.5 cm SPN in the caudal side of the IPMN. We diagnosed this case as synchronous SPN and IPMN. As far as we know, only one other case of synchronous SPN and IPMN has been reported. Both the present case and the previously reported case showed abnormal nuclear expression of β -catenin in SPN, whereas IPMN showed no abnormal nuclear expression. These results suggest that β -catenin abnormality is not a common pathogenetic factor of synchronous SPN and IPMN.

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Key words: Intraductal papillary mucinous neoplasms; Solid pseudopapillary neoplasms; Pancreatic neoplasms; Synchronous neoplasms; Pancreas; Beta-catenin

Core tip: We report the second case of synchronous solid pseudopapillary neoplasm (SPN) and intraductal papillary mucinous neoplasm (IPMN) of the pancreas in a 53-year-old Japanese man. IPMN was classified as a "combined" type due to the involvement of both the main and branch ducts, and it showed a gastric subtype with low-grade dysplasia. Adjacent to the caudal side of IPMN, a 0.5-cm solid SPN was present. The SPN showed abnormal nuclear expression of β -catenin in SPN, whereas IPMN showed no abnormal nuclear expression. This result suggested that β -catenin abnormality is not a common pathogenetic factor of synchronous SPN or IPMN.

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nous neoplasm. *World J Gastroenterol* 2013; 19(21): 3358-3363 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v19/i21/3358.htm> DOI: <http://dx.doi.org/10.3748/wjg.v19.i21.3358>

INTRODUCTION

Solid pseudopapillary neoplasm (SPN) is a rare and low-grade malignant pancreatic neoplasm composed of poorly cohesive, monomorphic cells forming solid and pseudopapillary structures with frequent hemorrhagic-cystic degeneration, which predominantly occurs in young women. Immunohistochemically, SPN usually expresses vimentin, α -1-antitrypsin, CD56, progesterone receptor, CD10, and nuclear/cytoplasmic β -catenin^[1-3].

Intraductal papillary mucinous neoplasm (IPMN) is a macroscopic pancreatic exocrine tumour that grows primarily within the main pancreatic duct or its major branches, and mainly occurs in older men. IPMNs are composed of intraductal papillary growth of mucin-containing neoplastic cells that are classified into 4 major subgroups: gastric, intestinal, pancreatobiliary, and oncocytic types^[4,5]. Gastric-type IPMN consists of innocuous, tall columnar cells that resemble gastric foveolar epithelium and express mucin (MUC) 5AC, but are negative for MUC1, MUC2, and CDX2^[4,5]. Intestinal-type IPMN consists of neoplastic cells that resemble intestinal villous neoplasms with MUC2, MUC5AC, and CDX2 expression, but without MUC1 expression^[4,5]. Pancreatobiliary-type IPMN consists of thin, branching papillae with high-grade dysplasia and is at least focally positive for MUC1 and MUC5AC, but is negative for MUC2 or CDX2^[4,5]. Oncocytic-type IPMN is characterised by complex and arborizing papillae lined by cuboidal cells with granular eosinophilic cytoplasm, which usually express MUC5AC and MUC6, but are negative for MUC2 and CDX2^[4,5].

Although IPMNs have been reported to occur synchronously with a variety of primary pancreatic neoplasms such as pancreatic ductal adenocarcinomas, endocrine neoplasms, or serous cyst adenomas^[6-9], the synchronous occurrence of SPN with other pancreatic neoplasms has only been reported in a single case report associated with an IPMN^[10]. In the current study, we present the histological and clinical features of a second case of synchronous “early” SPN and IPMN, with a review of the literature.

CASE REPORT

A 53-year-old Japanese man with multiple pancreatic cystic lesions, which were detected at a local hospital, was referred to the Tokai University Hospital for further examination. Upon inspection, he had no complaints, and no abnormal physical findings were reported. Laboratory data, including tumour markers, carcinoembryonic antigen, or carbohydrate antigen 19-9, showed no abnormal findings. Computed tomography showed multiple cystic

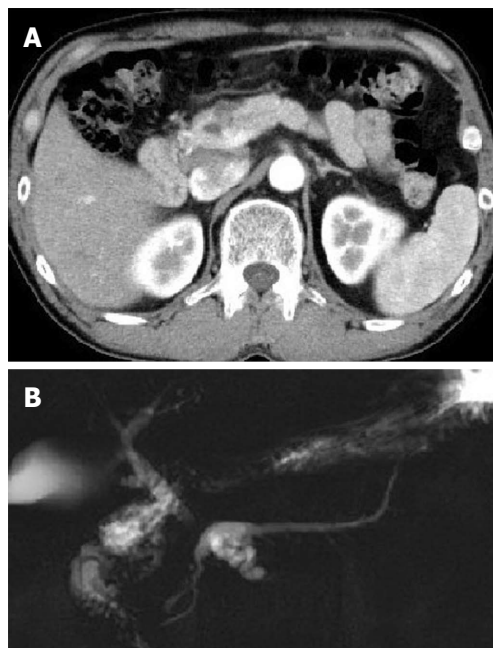


Figure 1 Computed tomography and magnetic resonance cholangiopancreatography imaging. A: Multiple cystic lesions measuring 23 mm are indicated in the neck of the pancreas; B: Multiple cystic dilations of pancreatic branch duct connecting to the dilated main pancreatic duct are indicated in the neck of the pancreas.

lesions measuring 2.3 cm in the neck of the pancreas (Figure 1A). Magnetic resonance cholangiopancreatography imaging showed multiple cystic dilations of the pancreatic branch ducts connecting to the dilated main pancreatic duct in the neck of the pancreas (Figure 1B). Endoscopic retrograde pancreaticography showed a dilated main pancreatic duct in the neck of the pancreas, measuring 6 mm in diameter, with multiple nodular defects. Distal pancreatectomy and splenectomy were performed. At present, the patient is alive and well 25 mo after the operation.

Tissues

The resected specimen was fixed in 10% formalin, routinely embedded in paraffin, sectioned at 4- μ m, and stained with haematoxylin and eosin.

Immunohistochemistry

The sections were deparaffinised in xylene and rehydrated in a graded ethanol series. The primary antibodies and their dilutions and sources are summarized in Table 1. If necessary, antigen retrieval was performed by autoclaving the samples for 15 min in a sodium citrate buffer at pH 6.0 (β -catenin, CD56, chromogranin A, E-cadherin, MUC1, MUC2, MUC5AC, MUC6, vimentin, and Ki67) or by treatment with 0.1% trypsin at 37 °C for 30 min (synaptophysin). The antibodies were detected using EnVision Plus (Dako, Glostrup, Denmark; for β -catenin, CD56, chromogranin A, E-cadherin, MUC1, MUC2, MUC5AC, MUC6, vimentin, synaptophysin, and Ki67), or Horseradish Peroxidase-conjugated polyclonal goat anti-rabbit

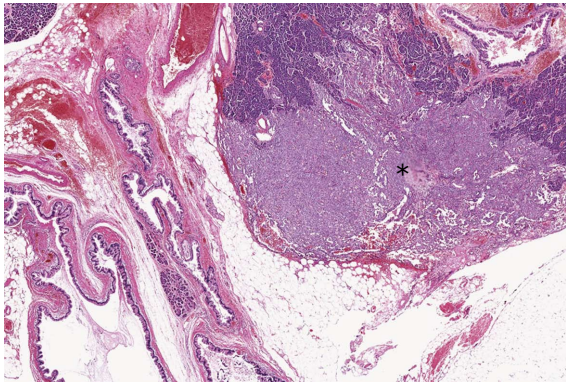


Figure 2 Microscopic findings (low-power view). A small and irregularly shaped solid lesion of solid pseudopapillary neoplasm (asterisk) can be observed near the cystically dilated branch ducts of intraductal papillary mucinous neoplasm (hematoxylin and eosin stain, × 10).

immunoglobulin (Dako; for alpha-1-antitrypsin), with 3,3'-diaminobenzidine as the chromogen. Assays for pancytokeratin, progesterone receptor (PR), and CD10 were performed using Ventana Benchmark XT (Ventana Medical Systems, Tucson, AZ, United States) equipped with the Ultra View Detection Kit. Antigen retrieval was performed by treatment with CC1 (Ventana; for PR and CD10) or protease 1 (Ventana; for pancytokeratin).

On gross examination, the distal pancreatectomy specimen showed a dilatation of the main pancreatic duct, with multiple cystic dilatations of the branch ducts, filled with mucus and containing papillae, in the neck of the pancreas. A whitish and solid lesion measuring 0.5 cm × 0.3 cm in size, located adjacent to the caudal side of the cystically dilated branch ducts, was identified.

Microscopically, 2 distinct primary pancreatic neoplasms were present (Figure 2): (1) a typical central and branch-duct type IPMN, with the cyst lined by tall and pale columnar cells with only low-grade dysplasia, and pyloric-gland adenoma-like papillary projections (Figure 3A). Immunohistochemically, the neoplastic cells showed gastric-type phenotype with MUC5AC (Figure 3B) and MUC6 positivity, and MUC1 and MUC2 negativity. β -catenin immunostaining showed membranous expression, but did not show abnormal nuclear expression (Figure 3C). On the basis of current World Health Organization (WHO) criteria^[4], we diagnosed the patient with gastric-type IPMN with low-grade dysplasia; and (2) a small, SPN, adjacent to the IPMN, which showed an ill-defined demarcation, with focal extension to the pancreatic parenchyma. The tumor showed a prevalent solid pattern, with focal degenerative changes and rough pseudopapillary structures (Figure 3D). The neoplastic cells had eosinophilic cytoplasm and small, round nuclei with finely dispersed chromatin. We failed to find perineural infiltration, peripancreatic invasion, or calcification. Immunohistochemically, the neoplastic cells expressed CD56, vimentin, alpha-1-antitrypsin, CD10, progesterone receptor (Figure 3E), nuclear/cytoplasmic β -catenin (Figure 3F), focal positivity for synaptophysin and negativity

Table 1 Immunohistochemical findings

	Clone	Source	Dilution	IPMN	SPN
Pancytokeratin	AE1, AE3, and PCK26	Ventana	Prediluted	(+)	(-)
Alpha-1 anti-trypsin	Polyclonal	Dako	1:100	(-)	(+)
CD10	56C6	Leica	1:50	(-)	(+)
CD56	1B6	Leica	1:30	(-)	(+)
MUC1	Ma695	Leica	1:50	(-)	(-)
MUC2	Ccp58	Leica	1:100	(-)	(-)
MUC5AC	CLH2	Leica	1:100	(+)	(-)
MUC6	CLH5	Leica	1:100	(+)	(-)
Vimentin	V9	Dako	1:100	(-)	(+)
Synaptophysin	27G12	Leica	1:50	(-)	(-/+)
Chromogranin A	DAK-A3	Dako	1:20	(-)	(-)
β -catenin ¹	17C2	Leica	1:100	(-)	(+)
E-cadherin	36B5	Leica	1:20	(+)	(-)
Progesterone receptor	1E2	Ventana	Prediluted	(-)	(+)
Ki67	MIB1	Dako	1:50	< 1%	< 1%

¹Nuclear labelling. Ventana Medical Systems, Tucson, AZ, United States; Dako, Glostrup, Denmark; Leica Microsystems, Newcastle upon Tyne, United Kingdom. +: Positive; -: Negative; -/+ : Focal positive; MUC: Mucin; IPMN: Intraductal papillary mucinous neoplasm; SPN: Solid pseudo-papillary neoplasm.

for chromogranin A, and E-cadherin and cytokeratin AE1 and 3. The immunohistochemical profiles of the 2 neoplasms are summarized in Table 1.

As our results show, the SPN was located near the IPMN. However, neither transition nor collision between IPMN and SPN were identified. Therefore, we diagnosed the present case as synchronous SPN and IPMN of the pancreas. The surgical margins were free of both types of tumors. No lymph node metastasis was identified.

DISCUSSION

We reported a case of synchronous small, radiologically undetected SPN, in a patient operated on for a radiologically evident IPMN of the pancreas. To our knowledge, this association has only been previously reported by Imamura *et al*^[10]. They reported a patient who presented with a 3-cm, solid SPN in the head of the pancreas that invaded the mesocolon with a synchronous IPMN constituted by 2 multilocular cystic lesions in the head of the pancreas. In other words, the 2 cases showed mirror clinicopathologic traits.

In general, SPN occurs predominantly in young women (91%) and is rare in men (9%)^[11]. Interestingly, however, both our case and Imamura's occurred in men^[10]. Several authors have reported the clinicopathologic correlations between genders and SPN. Takahashi *et al*^[12] reported that the cases of SPN in men tend to exhibit solid components without prominent degenerative changes. Tien *et al*^[13] reported no significant differences in patient age, size, neoplasm location, or malignancy rate between the genders in SPN. By contrast, Machado *et al*^[14] reported that cases of SPN in men are more aggressive and that the patients are older. According to the literature review of 1014 SPN patients (women, 877; men, 137)

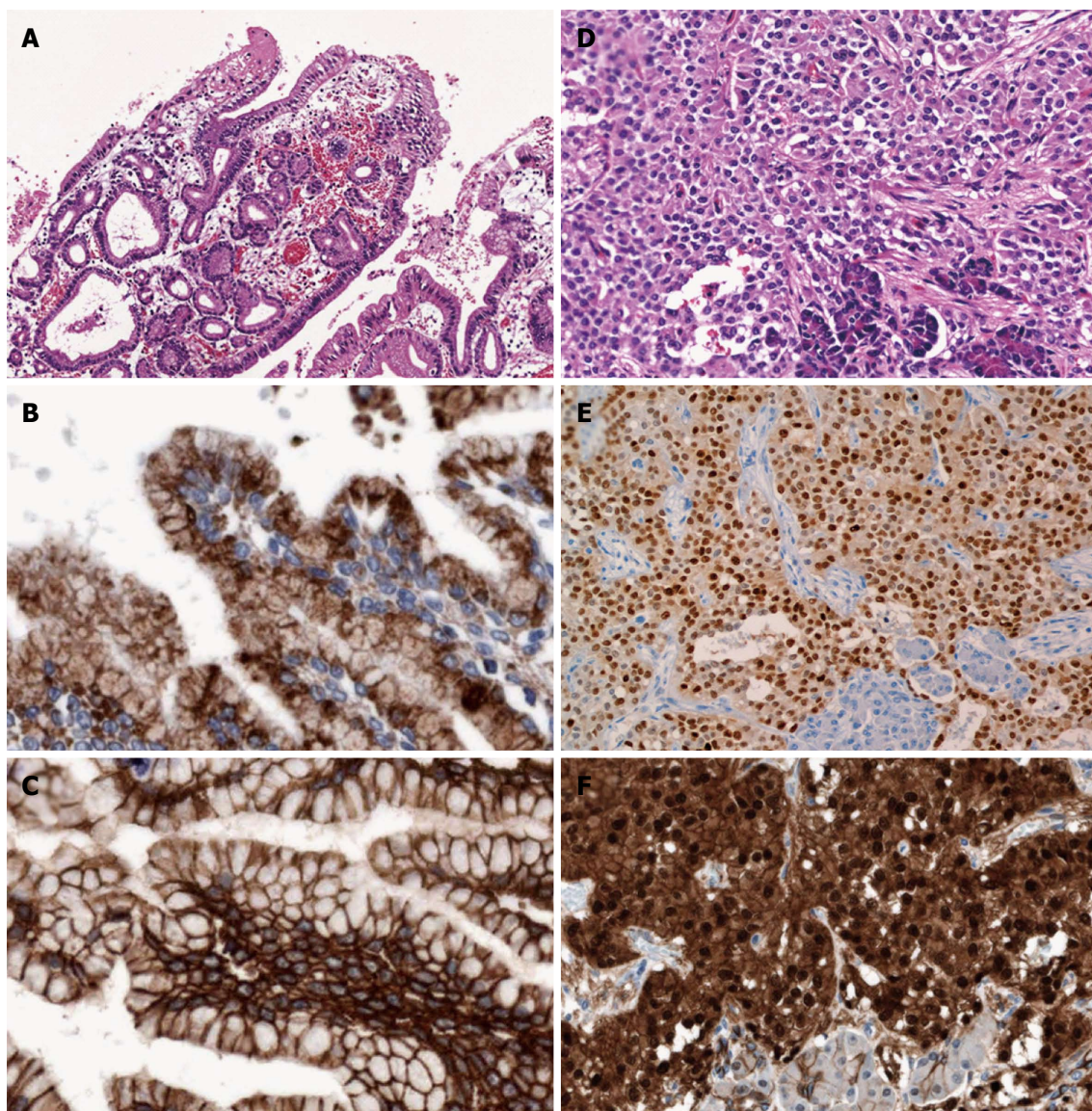


Figure 3 Microscopic and immunohistochemical findings. A: High-power view of intraductal papillary mucinous neoplasm (IPMN). The dilated main and branch pancreatic ducts show intraductal papillary mucinous neoplasm (IPMN). The dilated main and branch pancreatic ducts show intraductal papillary mucinous neoplasm (IPMN). The dilated main and branch pancreatic ducts show intraductal papillary mucinous neoplasm (IPMN). B: Mucin 5AC-positivity in the gastric-type papillary projections of IPMN (×400); C: β -catenin shows membranous and cytoplasmic expression, but does not show abnormal expression in the nuclei of IPMN (×400); D: High-power view of solid pseudopapillary neoplasm (SPN). The neoplastic cells show sheet-like or pseudopapillary proliferation and infiltrate among acinar cells (HE, ×200); E: Progesterone receptor nuclear labeling in the neoplastic cells of SPN (×200); F: Abnormal nuclear and cytoplasmic β -catenin expression in neoplastic cells of SPN (×400).

by Lin *et al*^[15], men were on average 5 years older, had a twofold higher incidence of metastases (women, 4.3%; men, 10.2%) and invasive malignancy (women, 12.4%; men, 24.4%), and showed a threefold higher death rate (women, 3.6%; men, 11.4%). There is no difference in immunohistochemical profiles between the genders in SPN cases^[12,13].

The SPN reported by Imamura *et al*^[10] showed a solid appearance with calcification, but no cystic degeneration. Although our case showed a prevalent solid pattern, cystic degeneration with haemorrhage was only observed microscopically; whereas foci of calcification were not present. The Imamura's SPN case was considered malignant for the presence of perineural infiltration, the invasion of the anterior peripancreatic soft tissue, adipose

tissue of the transverse mesocolon, and the duodenum^[10]. By contrast, our case was limited to the pancreas, without peripancreatic extension or perineural infiltration. However, since it was not proven to be a predictor of malignancy, the current WHO classification considers all SPNs as low-grade malignant neoplasms^[4].

SPNs usually form large masses, with mean diameter of 6 cm and range of 0.5–34.5 cm^[11]. Our case, measuring 0.5 cm in diameter, is one of the smallest reported SPNs^[11]. Small SPNs generally show less cystic change, less sharp demarcation, and frequently no capsule^[11]. Our case, indicating a prevalent solid pattern and ill-demarcated margins, fits well with the concept of an “early” stage of development. Nonetheless, it presents foci of cystic degeneration with papillary formations.

According to the current WHO classification^[4], the IPMN in the present case should be classified as low-grade dysplasia. Imamura *et al*^[10] diagnosed the IPMN component in their case as intraductal papillary mucinous adenoma (IPMA). Under the current WHO classification guidelines, IPMA is now designated as IPMN with low-grade dysplasia^[4]. Imamura *et al*^[10] did not mention the subtype of IPMN applicable to their case. We assume that it might have been a gastric type, based on the features of their figures and the MUC5AC positivity, and MUC1 and MUC2 negativity.

In both our case and Imamura's case, the SPNs were adjacent to the IPMNs, without any transition or collision between the 2 neoplasms^[10].

The occurrence of SPN and IPMN offers an interesting opportunity to investigate the role of β -catenin gene mutation in the pathogenesis of both lesions. In fact, almost all SPNs harbour somatic point mutations in exon 3 of CTNNB1, the gene that encodes β -catenin, which results in abnormal nuclear expression of β -catenin on immunohistochemistry^[1]. The role of β -catenin gene mutations in IPMN is more controversial. β -catenin nuclear protein accumulation has been reported in one patient with familial adenomatous polyposis^[16] and in a small series of IPMNs. In the latter study, 7 of 18 IPMNs indicated abnormal β -catenin nuclear protein accumulation (1 of 8 adenomas, 2 of 3 borderline, and 4 of 7 carcinomas)^[17]. Both the present case and Imamura *et al*^[10] showed abnormal nuclear expression of β -catenin in SPN, whereas IPMN showed only membranous expression, but no abnormal nuclear expression. These results suggest that, at least in these 2 patients, there is no correlation between the β -catenin abnormalities, exclusively found in SPNs, and the development of synchronous IPMNs.

In conclusion, we present a second case of synchronous SPN and IPMN of the pancreas. Unlike SPNs that usually occur in adolescent girls or young women, the 2 synchronous SPNs and IPMNs occurred in old, male patients (53 and 66 years, respectively). It is still unknown whether SPN or IPMN neoplasms occur independently or are in some way linked. From the comparison of the 2 cases, it appears that the β -catenin gene abnormalities play a role exclusively in the development of SPN, whereas a different molecular pathogenesis has to be considered for the IPMN counterpart.

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REFERENCES

- 1 Abraham SC, Klimstra DS, Wilentz RE, Yeo CJ, Conlon K, Brennan M, Cameron JL, Wu TT, Hruban RH. Solid-pseudopapillary tumors of the pancreas are genetically distinct from pancreatic ductal adenocarcinomas and almost always harbor beta-catenin mutations. *Am J Pathol* 2002; **160**: 1361-1369 [PMID: 11943721 DOI: 10.1016/S0002-9440(10)62563-1]
- 2 Notohara K, Hamazaki S, Tsukayama C, Nakamoto S, Kawabata K, Mizobuchi K, Sakamoto K, Okada S. Solid-pseudopapillary tumor of the pancreas: immunohistochemical localization of neuroendocrine markers and CD10. *Am J Surg Pathol* 2000; **24**: 1361-1371 [PMID: 11023097 DOI: 10.1097/00000478-200010000-00005]
- 3 Zamboni G, Bonetti F, Scarpa A, Pelosi G, Doglioni C, Iannucci A, Castelli P, Balercia G, Aldovini D, Bellomi A. Expression of progesterone receptors in solid-cystic tumour of the pancreas: a clinicopathological and immunohistochemical study of ten cases. *Virchows Arch A Pathol Anat Histopathol* 1993; **423**: 425-431 [PMID: 8291215 DOI: 10.1007/BF01606531]
- 4 Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. 4th ed. Lyon: International Agency for Research on Cancer, 2010
- 5 Furukawa T, Klöppel G, Volkan Adsay N, Albores-Saavedra J, Fukushima N, Horii A, Hruban RH, Kato Y, Klimstra DS, Longnecker DS, Lüttges J, Offerhaus GJ, Shimizu M, Sunamura M, Suriawinata A, Takaori K, Yonezawa S. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. *Virchows Arch* 2005; **447**: 794-799 [PMID: 16088402 DOI: 10.1007/s00428-005-0039-7]
- 6 Chahal P, Saad AJ, Jeyarajah RD. An unusual case of a co-existent serous cystadenoma and intraductal papillary mucinous neoplasm of pancreas. *EUS to the rescue! JOP* 2011; **12**: 244-246 [PMID: 21546700]
- 7 Larghi A, Stobinski M, Galasso D, Lecca PG, Costamagna G. Concomitant intraductal papillary mucinous neoplasm and pancreatic endocrine tumour: Report of two cases and review of the literature. *Dig Liver Dis* 2009; **41**: 759-761 [PMID: 19223252 DOI: 10.1016/j.dld.2009.01.005]
- 8 Yamaguchi K, Kanemitsu S, Hatori T, Maguchi H, Shimizu Y, Tada M, Nakagohri T, Hanada K, Osanai M, Noda Y, Nakaizumi A, Furukawa T, Ban S, Nobukawa B, Kato Y, Tanaka M. Pancreatic ductal adenocarcinoma derived from IPMN and pancreatic ductal adenocarcinoma concomitant with IPMN. *Pancreas* 2011; **40**: 571-580 [PMID: 21499212 DOI: 10.1097/MPA.0b013e318215010c]
- 9 Ishida M, Shiomi H, Naka S, Tani T, Okabe H. Concomitant intraductal papillary mucinous neoplasm and neuroendocrine tumor of the pancreas. *Oncol Lett* 2013; **5**: 63-67 [PMID: 23255895 DOI: 10.3892/ol.2012.952]
- 10 Imamura N, Chijiwa K, Ohuchida J, Hiyoshi M, Takahashi N, Yorita K, Kataoka H. Synchronous solid pseudopapillary neoplasm and intraductal papillary mucinous neoplasm of the pancreas: report of a case. *Surg Today* 2011; **41**: 865-871 [PMID: 21626339 DOI: 10.1007/s00595-010-4361-6]
- 11 Papavramidis T, Papavramidis S. Solid pseudopapillary tumors of the pancreas: review of 718 patients reported in English literature. *J Am Coll Surg* 2005; **200**: 965-972 [PMID: 15922212 DOI: 10.1016/j.jamcollsurg.2005.02.011]
- 12 Takahashi Y, Hiraoka N, Onozato K, Shibata T, Kosuge T, Nimura Y, Kanai Y, Hirohashi S. Solid-pseudopapillary neoplasms of the pancreas in men and women: do they differ? *Virchows Arch* 2006; **448**: 561-569 [PMID: 16523258 DOI: 10.1007/s00428-006-0174-9]
- 13 Tien YW, Ser KH, Hu RH, Lee CY, Jeng YM, Lee PH. Solid pseudopapillary neoplasms of the pancreas: is there a pathologic basis for the observed gender differences in incidence? *Surgery* 2005; **137**: 591-596 [PMID: 15933625 DOI: 10.1016/j.surg.2005.01.015]
- 14 Machado MC, Machado MA, Bacchella T, Jukemura J, Almeida JL, Cunha JE. Solid pseudopapillary neoplasm of the pancreas: distinct patterns of onset, diagnosis, and prognosis for male versus female patients. *Surgery* 2008; **143**: 29-34 [PMID: 18154930 DOI: 10.1016/j.surg.2007.07.030]
- 15 Lin MY, Stabile BE. Solid pseudopapillary neoplasm of

the pancreas: a rare and atypically aggressive disease among male patients. *Am Surg* 2010; **76**: 1075-1078 [PMID: 21105613]

- 16 **Chetty R**, Salahshor S, Bapat B, Berk T, Croitoru M, Gallinger S. Intraductal papillary mucinous neoplasm of the pancreas in a patient with attenuated familial adenomatous polyposis. *J Clin Pathol* 2005; **58**: 97-101 [PMID: 15623495]

DOI: 10.1136/jcp.2004.020925]

- 17 **Chetty R**, Serra S, Salahshor S, Alsaad K, Shih W, Blaszyk H, Woodgett JR, Tsao MS. Expression of Wnt-signaling pathway proteins in intraductal papillary mucinous neoplasms of the pancreas: a tissue microarray analysis. *Hum Pathol* 2006; **37**: 212-217 [PMID: 16426922 DOI: 10.1016/j.humpath.2005.11.002]

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