Published in final edited form as:

Am J Surg Pathol. 2011 July ; 35(7): 981–988. doi:10.1097/PAS.0b013e31821a9a14.

Hyaline Globules in Neuroendocrine and Solid-Pseudopapillary Neoplasms of the Pancreas: A Clue to the Diagnosis

Zina Meriden, MD¹, Chanjuan Shi, MD PhD¹, Barish H. Edil, MD^{2,3}, Trevor Ellison, MD³, Christopher L. Wolfgang, MD PhD^{2,3}, Toby C. Cornish, MD PhD¹, Richard D. Schulick, MD^{2,3}, and Ralph H. Hruban, MD^{1,2}

¹Department of Pathology, The Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins Medical Institutions, Baltimore, MD 21231.

²Department of Oncology, The Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins Medical Institutions, Baltimore, MD 21231.

³Department of Surgery, The Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins Medical Institutions, Baltimore, MD 21231.

Abstract

Distinguishing between solid-pseudopapillary neoplasms (SPNs) and pancreatic neuroendocrine tumors (PanNETs) may pose a diagnostic dilemma. Both can demonstrate solid growth patterns, and both can be immunoreactive with neuroendocrine markers such as synaptophysin and CD56. One well-established feature of SPNs is the presence of hyaline globules, which in contrast has only rarely been reported in PanNETs. Clinicopathologic features of 361 cases originally classified as PanNETs were examined. Of these, 24 tumors (6.6%) had hyaline globules, raising the possibility of SPN. Immunohistochemistry for β -catenin was performed on these 24 neoplasms, and showed nuclear labeling in 6 cases. These 6 cases, which also demonstrated cytoplasmic CD10 staining, were reclassified as SPNs. The remaining 18 cases maintained their original diagnosis as PanNETs, and the hyaline globules in these cases were periodic acid-Schiff (PAS)-positive, diastase resistant and immunoreactive with alpha-1-antitrypsin. All 24 cases were histologically re-evaluated, and the pattern of invasion, presence of clear cells, and nuclear grooves were found to be helpful in distinguishing SPNs from PanNETs. We conclude that the presence of hyaline globules should raise SPNs in the differential diagnosis of a solid cellular neoplasm of the pancreas; however, these should not be used as the sole criterion in the diagnosis of SPNs, as hyaline globules may also be seen in 5% of PanNETs. Immunohistochemical and histologic features supporting the diagnosis of SPNs over PanNETs include CD10 and nuclear β -catenin labeling, an insidious pattern of invasion, clear cells, and nuclear grooves.

Keywords

pancreas; solid-pseudopapillary tumor; islet cell tumor; pancreatic neuroendocrine tumor; hyaline globules

Correspondence: Dr. Ralph H. Hruban Department of Pathology The Johns Hopkins Hospital Weinberg Building, Room 2242 401 N. Broadway Baltimore, MD 21231 rhruban@jhmi.edu Phone number: 410-955-9132 Fax number: 410-955-0115.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

INTRODUCTION

Differentiating between pancreatic neuroendocrine tumors (PanNETs) and solid-pseudopapillary tumors (SPNs) may be diagnostically challenging. Although SPN is classically described as a solid and cystic neoplasm consisting of poorly cohesive cells forming degenerative papillae, foamy histiocytes, and longitudinal nuclear grooves, SPNs may also exhibit a solid pattern of growth with uniform round-to-oval cells, mimicking PanNETs^{17,18,27,34}. Conversely, pseudopapillary areas may also be seen in PanNETs³⁴, and PanNETs may occasionally be cystic¹⁴. Additionally, neuroendocrine markers such as synaptophysin may be expressed focally in SPNs^{31,35,46}. Immunohistochemistry for β -catenin has proven useful, as there is nuclear labeling in SPNs and membranous labeling in PanNETs^{1,33,49}. Among the additional immunohistochemical markers which can assist in establishing the correct diagnosis are CD10, estrogen and progesterone receptors, and alpha-1-antitrypsin^{21,35,40}. Because the biological behavior, genetics, and therapeutic implications of PanNETs and SPNs can differ, it is imperative to make the correct diagnosis^{3,4,7-9,11-13,15,16,18-20,22,23,26,29,30,32,37-39,41,43,44,47,50-59}.

Hyaline globules are a feature which has classically been associated with SPNs^{2,25,28}. These globules are typically PAS-positive intracytoplasmic inclusions which are immunoreactive for alpha-1-antitrypsin. Eosinophilic globules are not specific to SPNs, but have also been reported in other pancreatic lesions, including intraductal oncocytic papillary neoplasms⁴⁸, hepatoid carcinoma³⁶, and clear cell ductal adenocarcinoma⁴². In contrast, eosinophilic globules have only rarely been described in PanNETs¹⁰.

We reviewed a large series of neoplasms originally diagnosed as PanNETs for hyaline globules. We show that eosinophilic globules may be seen not only in SPNs but also in PanNETs, and describe morphologic features which favor SPN in cases where the distinction between SPNs and PanNETs may be difficult.

MATERIALS AND METHODS

The surgical pathology and consultation files of the Johns Hopkins Hospital were searched for all cases from May 1984 to January 2010 originally diagnosed as pancreatic neuroendocrine tumors (PanNETs). A total of 361 cases were identified. All available pathology reports and slides were reviewed. This review yielded 24 neoplasms originally diagnosed as PanNETs which contained hyaline globules. Single immunolabeling was performed using the antibodies listed in Table 1. Immunohistochemical studies for synaptophysin and β -catenin were performed on all cases with hyaline globules, and immunolabeling for CD10 was performed as a confirmatory test in cases with nuclear β -catenin labeling. PAS, PAS with diastase, and immunohistochemistry with alpha-1-antitrypsin and trypsin were performed on all cases with hyaline globules to further characterize these globules. Because these globules were focal, they were not present on levels immunolabeled with alpha-1-antitrypsin in three cases, those immunolabeled with trypsin in two cases, and those stained with PAS and PAS with diastase in two cases. Immunohistochemistry for Ki-67 and CK19 was also performed.

The Ki-67 labeling index was measured manually using custom software written in ImageJ (Wayne Rasband, NIH, Bethesda, MD) to assist in performing the nuclear counts. Five images were acquired per case at a total magnification of 400x using a Q-Color3 digital camera (Olympus, Center Valley, PA) on an Olympus B-50 microscope (Center Valley, PA). Fields were selected that represented the highest density of Ki-67 positive cells.

Using an ImageJ macro, each image was presented to the user, who then labeled each Ki-67 positive nucleus with a color marker by clicking on it with the mouse. Each Ki-67 negative

nucleus was labeled using a marker of a different color. Non-neoplastic nuclei in the image were not labeled. The positive and negative markers in each image were automatically counted and a labeling index was calculated: % Ki-67 = (positive nuclei / (positive nuclei + negative nuclei)). On this basis, tumors were then classified as grade 1 (Ki-67 index: $\leq 2\%$), grade 2 (Ki-67 index: 3-20%), and grade 3 (Ki-67 index: $> 20\%$)^{3,43}.

Categorical data were compared using Chi square (or Fisher's exact test). Continuous variables, reported as means with standard deviations (SD), were compared using a student t-test. Statistical analyses were performed using the software programs PRISM (GraphPad, San Diego) and Microsoft Excel (Redmond, WA). A *P* value of < 0.05 was considered statistically significant.

RESULTS

Three hundred sixty-one pancreatic neoplasms originally classified as PanNETs were reviewed. Of these, 24 were noted to have hyaline globules. Due to the known association between hyaline globules and SPNs, immunolabeling with synaptophysin and β -catenin was performed to confirm whether all 24 cases were truly PanNETs or in fact solid SPNs misclassified as PanNETs (Figure 1, Table 2). In 18 of the 24 cases, nuclear labeling for β -catenin was absent (not shown), and synaptophysin was positive (diffusely in 17 cases, focally in 1 case), confirming these neoplasms as true PanNETs (Figure 1A and B). In 6 of the 24 cases, there was nuclear labeling for β -catenin and cytoplasmic CD10 positivity (not shown), and these neoplasms were re-classified as SPNs (Figure 1C and D). Synaptophysin immunoreactivity was present in 5 of 6 SPNs and was typically focal (not shown). Therefore, a total of 18 (5%) of 355 histologically confirmed PanNETs in this series contained hyaline globules.

The mean age in years ($\pm$ SD) for the total number of cases with hyaline globules ($n=24$), as well as the confirmed PanNETs ($n=18$) and reclassified SPNs ($n=6$) was 54.1 (± 13.4), 56 (± 12.4), and 48.3 (± 14.7), respectively (PanNETs vs. SPNs, $P = 0.2312$). There was no difference in patient gender (PanNETs: 55.6% male vs. SPNs: 50% male, $P = 1.000$). In 5 (27.8%) of the 18 confirmed PanNETs, the neoplasm was clinically functioning. Three of these were insulin secreting, while two were glucagon secreting. Two (11.1%) of the 18 confirmed PanNETs arose in patients with multiple endocrine neoplasia 1 (MEN 1).

The mean tumor size in cm ($\pm$ SD) for confirmed PanNETs was 4.7 (± 2.9). For the reclassified SPNs, it was 6.3 (± 6.0) (PanNETs vs. SPNs, $P = 0.3720$). The body and tail were most frequently involved in confirmed PanNETs (72.1%), while the body and head were the most common sites of the reclassified SPNs (33.3% each). Tumors were predominantly unifocal (88.9% PanNETs vs. 100% SPNs, $P = 1.000$). Both the confirmed PanNETs and reclassified SPNs were most frequently solid (72.2% and 50%, respectively), though they occasionally showed pure cystic or a combination of solid and cystic growth. A statistical comparison of the location distribution, focality, and type of growth in PanNETs vs. SPNs was precluded due to the small sample size.

The hyaline globules in the 24 cases ranged dramatically in size, and were both intracytoplasmic and extracellular (Figure 1). They did not show any unique distribution within the tumor. In both PanNETs and SPNs, they were frequently focal, and therefore no significant differences in their prevalence in PanNETs vs. SPNs were readily recognized. In all tested cases, they were PAS-positive (Figure 2A, Table 2), diastase resistant. Hyaline globules in 12 (80%) of the 15 tested confirmed PanNETs, as well as 6 (100%) of the 6 tested reclassified SPNs had globules immunoreactive with alpha-1-antitrypsin (Figure 2B, Table 2). In one PanNET, the globules were positive for trypsin (not shown).

The 24 cases with hyaline globules were histologically re-evaluated to assess whether any features aside from CD10 and nuclear β -catenin labeling could help distinguish PanNETs with hyaline globules from SPNs. All 24 cases were histologically examined for the pattern of invasion, and presence or absence of the following features: microcystic change, hemorrhage, cholesterol clefts, clear cells, foam cells, nuclear grooves, and foci of discohesion within the tumor (Figure 3, Table 2). Clear cells, characterized by clear cytoplasm and an eccentric nucleus, were one feature more commonly seen in SPNs (Figure 3A, 100% SPNs vs. 27.8% PanNETs, $P = 0.0034$). An additional feature frequently observed in SPNs was an insidious pattern of invasion (Figure 3B). In this pattern, the neoplastic cells subtly penetrate around and entrap normal pancreatic elements. Insidious invasion was noted in 83.3% of the SPNs and in only 11.1% of the PanNETs ($P = 0.0027$). Although rare and focal, longitudinal nuclear grooves were more often present in SPNs than PanNETs, while the nuclei of PanNETs more commonly were round with speckled chromatin and lacked grooves (Figure 3C and D, 50% SPNs vs. 0% PanNETs, $P = 0.0099$). Foci of discohesive, single cells were only rarely present in either neoplasm (Figure 3E), but surprisingly were not statistically more frequent in SPNs (33.3% SPNs vs. 5.6% PanNETs, $P = 0.1433$). Other features such as foam cells (Figure 3F), hyalinization (Figure 3G), cholesterol clefting (Figure 3H), microcystic change (not shown), and hemorrhage (not shown) were compared, but showed no statistically significant differences between SPNs and PanNETs (Table 2). Of the 6 SPNs, 4 were purely solid, with no pseudopapillary or pseudoglandular features, while 2 were predominantly solid with only a small focus of discohesion imparting a pseudopapillary appearance.

The PanNETs were assigned a WHO grade of 1, 2, or 3 on the basis of the Ki-67 immunolabeling index^{3,43}. The Ki-67 labeling indices of the SPNs were similarly grouped for the purposes of comparison. Fifty percent of confirmed PanNETs vs. 66.7% of reclassified SPNs were grade 1, 50% of PanNETs vs. 33.3% of SPNs were grade 2, and 0% of either PanNETs or SPNs were grade 3. Using American Joint Committee on Cancer (AJCC) staging criteria⁶, the primary tumor in cases of confirmed PanNETs was T1 in 22.2%, T2 in 33.3%, and T3 in 44.5% of cases. In cases of reclassified SPNs, the primary tumor was T2 in 100% of cases. Five (27.8%) of 18 PanNETs showed nodal metastases at the time of diagnosis, while 3 (16.7%) of 18 PanNETs had distant metastases. In contrast, none of the SPNs demonstrated nodal or distant metastases at the time of initial diagnosis. A statistical comparison of these parameters in PanNETs vs. SPNs could not be performed due to the small sample size.

The mean follow-up time in years ($\pm$ SD) for the confirmed PanNETs was 5.7 ($\pm$ 5). For the re-classified SPNs, it was 10.2 ($\pm$ 3.3) (SPNs vs. PanNETs, $P = 0.0532$). Fifteen (83.3%) of 18 confirmed PanNETs and 5 (83.3%) of 6 reclassified SPNs were alive with disease over the duration of the follow-up period (SPNs vs. PanNETs, $P = 1.000$). Eight (44.4%) of the 18 PanNETs, and 0 (0%) of the 6 SPNs immunolabeled with CK19 (PanNETs vs. SPNs, $P = 0.0664$). Only patients in the PanNET group developed metastases subsequent to the time of initial diagnosis. One (5.6%) of the 18 PanNETs metastasized to lymph nodes, and 3 (16.7%) had a metastasis to the liver. The mean time ($\pm$ SD) in years from the initial diagnosis to the metastasis was 3.2 ($\pm$ 2.4).

DISCUSSION

In summary, we identified hyaline globules in 6.6% of 361 neoplasms originally diagnosed as pancreatic neuroendocrine tumors (PanNETs). Although 6 of these cases with hyaline globules were shown to be misdiagnosed solid-pseudopapillary neoplasms (SPNs), the majority were confirmed to be PanNETs with hyaline globules. Thus, although hyaline

globules should raise the possibility of SPNs, hyaline globules may also be found in 5% of PanNETs.

There can be considerable morphologic overlap between SPNs and PanNETs^{17,18,27,34,34}. Importantly, we found that several histologic features, in addition to the hyaline globules, can facilitate the distinction between PanNETs and SPNs. An insidious pattern of invasion, clear cells, and nuclear grooves are features which, in addition to immunolabeling with β -catenin, favor SPN. Features such as foam cells, hyalinization, cholesterol clefting, microcystic change, hemorrhage, and foci of discohesion were no different in PanNETs vs. SPNs. Relying on pseudopapillary or pseudoglandular features to make the distinction between PanNETs and SPNs was of limited utility: 4 of 6 SPNs were solid with no such features, and 2 of 6 SPNs were predominantly solid with only a small discohesive focus conferring a pseudopapillary appearance.

When confronted with the diagnostic dilemma of PanNET vs. SPN, a number of immunomarkers can help establish the correct diagnosis³. Notohara et. al³⁵ have reported that CD10, CD56, vimentin, synaptophysin, chromogranin, and pancytokeratin are useful in distinguishing between SPNs and PanNETs. In the current study, we advocate a panel of immunomarkers to include synaptophysin, β -catenin, and (if the β -catenin is nuclear) CD10 to make the distinction between PanNETs and SPNs, whether hyaline globules are present or not. Trypsin and chymotrypsin can be included in the panel since acinar cell carcinomas are also solid cellular neoplasms and should be in the differential diagnosis. All 18 PanNETs strongly expressed synaptophysin (diffusely in 17 tumors and focally in 1 tumor). Although 5 of the 6 SPNs were immunoreactive for synaptophysin, such labeling was typically only focal. In contrast, all 18 PanNETs had a membranous pattern of labeling for β -catenin, while all 6 SPNs had abnormal nuclear β -catenin immunolabeling and cytoplasmic CD10 staining.

Among 361 tumors originally classified as PanNETs, 18 were true PanNETs with hyaline globules. This corresponds to an incidence of hyaline globules in PanNETs of nearly 5%. The hyaline globules in PanNETs are PAS-positive/diastase resistant, and are most frequently immunoreactive with alpha-1-antitrypsin. Garg et al. previously reported a case of a PanNET with PAS-positive hyaline globules¹⁰. This case was of ectopic ACTH syndrome in a 12-year-old boy with a pancreatic neuroendocrine tumor consisting of monomorphic cells and delicate vessels. In the current study, only 5 (27.8%) of the PanNETs were clinically functional, three of which were insulinomas, two of which were glucagonomas, and none of which were ACTH-secreting. The PanNETs with hyaline globules in our series were often large, a number of which had nodal and distant metastases at the time of initial diagnosis, as well as subsequent metastases.

Six of the 24 cases originally diagnosed as PanNETs were in fact SPNs with hyaline globules. Such globules have long been associated with SPNs, and their presence in a solid cellular neoplasm of the pancreas should raise the possibility of an SPNs in the differential diagnosis^{2,25,28}. As with those in PanNETs, hyaline globules in SPNs were PAS-positive/diastase resistant, and were also immunoreactive with alpha-1-antitrypsin. Unlike PanNETs, however, SPNs typically showed more focal synaptophysin positivity as has been previously documented^{31,35,46}, as well as immunoreactivity with β -catenin (nuclear) and CD10^{1,33,35,49}.

The clinical importance of correctly distinguishing between SPNs and PanNETs is growing, from the standpoints of therapeutics, genetics, and outcome. SPNs are treated surgically; historically, chemoradiation has not played a beneficial role^{24,29,58}. PanNETs, too, may be surgically resected, and a number of studies have shown that they are also amenable to both chemotherapy and radiation^{4,26,30,41,47,51,53,54,57}. Among the non-surgical approaches to the

treatment of PanNETs are peptide receptor radionuclide therapy (PRRT), chemotherapy, somatostatin analogs, and interferon⁸. A recent study showed that PanNETs harbor frequent alterations in several genes, including those involved in the mammalian target of rapamycin (mTOR) pathway¹⁵. Specific targeted therapies, such as Everolimus, have been shown to be effective in some patients with PanNETs, and these therapies are likely to be effective only in neoplasms, such as PanNETs, in which the mTOR pathway has been activated^{8,13,32,56,59}. Although a few studies have suggested that a proportion of SPNs behave in an aggressive fashion^{22,23,29,39,44,50,52}, several studies have demonstrated that they have an excellent prognosis^{11,16,18,37}. PanNETs can also exhibit a spectrum of behaviors^{5,7,9,9,12,19,20,38,43,45,55}, and their malignant potential may not be readily ascertained histologically.

In conclusion, the morphologic features of SPNs and PanNETs overlap. Small SPNs with minimal degenerative changes are particularly hard to recognize. In these cases, hyaline globules should raise SPNs in the differential diagnosis, and the diagnosis can be established with immunolabeling for β -catenin and CD10. Additionally, the presence of hyaline globules should not be used as a sole diagnostic criterion for SPNs, as 5% of PanNETs contain hyaline globules. Features supporting the diagnosis of SPN include nuclear β -catenin labeling and CD10 expression, an insidious pattern of invasion, clear cells, and nuclear grooves.

Acknowledgments

This work was funded by a GI SPORE grant (NIH grant P50-CA62924).

REFERENCES

1. Abraham SC, Klimstra DS, Wilentz RE, et al. 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. [PubMed: 11943721]
2. Bhanot P, Nealon WH, Walser EM, et al. Clinical, imaging, and cytopathological features of solid pseudopapillary tumor of the pancreas: a clinicopathologic study of three cases and review of the literature. *Diagn Cytopathol.* 2005; 33:421–428. [PubMed: 16389690]
3. Bosman, F.; Carneiro, F.; Hruban, R., et al. WHO Classification of Tumours of the Digestive System. IARC; Lyon: 2010.
4. Contessa JN, Griffith KA, Wolff E, et al. Radiotherapy for pancreatic neuroendocrine tumors. *Int J Radiat Oncol Biol Phys.* 2009; 75:1196–1200. [PubMed: 19327905]
5. Deshpande V, Fernandez-del CC, Muzikansky A, et al. Cytokeratin 19 is a powerful predictor of survival in pancreatic endocrine tumors. *Am J Surg Pathol.* 2004; 28:1145–1153. [PubMed: 15316313]
6. Edge, SB.; Byrd, DR.; Compton, CC., et al. AJCC Cancer Staging Manual. 7th ed. Springer; New York, NY: 2010.
7. Ekeblad S, Skogseid B, Dunder K, et al. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. *Clin Cancer Res.* 2008; 14:7798–7803. [PubMed: 19047107]
8. Fazio N, Cinieri S, Lorizzo K, et al. Biological targeted therapies in patients with advanced enteropancreatic neuroendocrine carcinomas. *Cancer Treat Rev.* 2010; 36(Suppl 3):S87–S94. [PubMed: 21129617]
9. Fischer L, Kleeff J, Esposito I, et al. Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas. *Br J Surg.* 2008; 95:627–635. [PubMed: 18306152]
10. Garg SK, Vashist R, Pathak IC, et al. Ectopic ACTH syndrome due to islet cell carcinoma in a 12 year old child. *Indian J Pediatr.* 1988; 55:155–160. [PubMed: 2837439]

11. Goh BK, Tan YM, Cheow PC, et al. Solid pseudopapillary neoplasms of the pancreas: an updated experience. *J Surg Oncol.* 2007; 95:640–644. [PubMed: 17477365]
12. Hochwald SN, Zee S, Conlon KC, et al. Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. *J Clin Oncol.* 2002; 20:2633–2642. [PubMed: 12039924]
13. Horsch D, Tielke S, Schrader J. Expression and activation of mTOR in neuroendocrine tumors. Effects of mTOR inhibition by RAD001 upon growth, cell cycle regulation and signalling in neuroendocrine cell lines. *J Clin Oncol.* 2007; 25(18S):10570.
14. Iacono C, Serio G, Fugazzola C, et al. Cystic islet cell tumors of the pancreas. A clinico-pathological report of two nonfunctioning cases and review of the literature. *Int J Pancreatol.* 1992; 11:199–208. [PubMed: 1325529]
15. Jiao Y, Shi C, Edil BH, et al. DAXX/ATRX, MEN1 and mTOR Pathway Genes are Frequently Altered in Pancreatic Neuroendocrine Tumors. *Science Express.* 2011 (In press).
16. Kaufman SL, Reddick RL, Stiegel M, et al. Papillary cystic neoplasm of the pancreas: a curable pancreatic tumor. *World J Surg.* 1986; 10:851–859. [PubMed: 3022489]
17. Klimstra DS. Noductal neoplasms of the pancreas. *Mod Pathol.* 2007; 20(Suppl 1):S94–112. [PubMed: 17486055]
18. Klimstra DS, Wenig BM, Heffess CS. Solid-pseudopapillary tumor of the pancreas: a typically cystic carcinoma of low malignant potential. *Semin Diagn Pathol.* 2000; 17:66–80. [PubMed: 10721808]
19. La Rosa, Klersy C, Uccella S, et al. Improved histologic and clinicopathologic criteria for prognostic evaluation of pancreatic endocrine tumors. *Hum Pathol.* 2009; 40:30–40. [PubMed: 18715612]
20. La Rosa, Sessa F, Capella C, et al. Prognostic criteria in nonfunctioning pancreatic endocrine tumours. *Virchows Arch.* 1996; 429:323–333. [PubMed: 8982376]
21. Ladanyi M, Mulay S, Arseneau J, et al. Estrogen and progesterone receptor determination in the papillary cystic neoplasm of the pancreas. With immunohistochemical and ultrastructural observations. *Cancer.* 1987; 60:1604–1611. [PubMed: 3304615]
22. Lai HW, Su CH, Li AF, et al. Malignant solid and pseudopapillary tumor of the pancreas--clinicohistological, immunohistochemical, and flow cytometric evaluation. *Hepatogastroenterology.* 2006; 53:291–295. [PubMed: 16608042]
23. Lam KY, Lo CY, Fan ST. Pancreatic solid-cystic-papillary tumor: clinicopathologic features in eight patients from Hong Kong and review of the literature. *World J Surg.* 1999; 23:1045–1050. [PubMed: 10512945]
24. Lee SE, Jang JY, Lee KU, et al. Clinical comparison of distal pancreatectomy with or without splenectomy. *J Korean Med Sci.* 2008; 23:1011–1014. [PubMed: 19119445]
25. Lieber MR, Lack EE, Roberts JR Jr. et al. Solid and papillary epithelial neoplasm of the pancreas. An ultrastructural and immunocytochemical study of six cases. *Am J Surg Pathol.* 1987; 11:85–93. [PubMed: 3812876]
26. Lillemoe KD, Kaushal S, Cameron JL, et al. Distal pancreatectomy: indications and outcomes in 235 patients. *Ann Surg.* 1999; 229:693–698. [PubMed: 10235528]
27. Liu BA, Li ZM, Su ZS, et al. Pathological differential diagnosis of solid-pseudopapillary neoplasm and endocrine tumors of the pancreas. *World J Gastroenterol.* 2010; 16:1025–1030. [PubMed: 20180245]
28. Liu X, Rauch TM, Siegal GP, et al. Solid-pseudopapillary neoplasm of the pancreas: Three cases with a literature review. *Appl Immunohistochem Mol Morphol.* 2006; 14:445–453. [PubMed: 17122644]
29. Martin RC, Klimstra DS, Brennan MF, et al. Solid-pseudopapillary tumor of the pancreas: a surgical enigma? *Ann Surg Oncol.* 2002; 9:35–40. [PubMed: 11833495]
30. Menegaux F, Schmitt G, Mercadier M, et al. Pancreatic insulinomas. *Am J Surg.* 1993; 165:243–248. [PubMed: 8427405]
31. Miettinen M, Partanen S, Fraki O, et al. Papillary cystic tumor of the pancreas. An analysis of cellular differentiation by electron microscopy and immunohistochemistry. *Am J Surg Pathol.* 1987; 11:855–865. [PubMed: 3674283]

32. Missiaglia E, Dalai I, Barbi S, et al. Pancreatic endocrine tumors: expression profiling evidences a role for AKT-mTOR pathway. *J Clin Oncol.* 2010; 28:245–255. [PubMed: 19917848]
33. Nishimori I, Kohsaki T, Tochika N, et al. Non-cystic solid-pseudopapillary tumor of the pancreas showing nuclear accumulation and activating gene mutation of beta-catenin. *Pathol Int.* 2006; 56:707–711. [PubMed: 17040296]
34. Notohara K, Wani Y, Fujisawa M. Solid pseudopapillary neoplasm: pathological diagnosis and distinction from other solid cellular tumours of the pancreas. *Diagnostic Histopathology.* 2008; 14:266–274.
35. Notohara K, Hamazaki S, Tsukayama C, et al. Solid-pseudopapillary tumor of the pancreas: immunohistochemical localization of neuroendocrine markers and CD10. *Am J Surg Pathol.* 2000; 24:1361–1371. [PubMed: 11023097]
36. Paner GP, Thompson KS, Reyes CV. Hepatoid carcinoma of the pancreas. *Cancer.* 2000; 88:1582–1589. [PubMed: 10738216]
37. 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. [PubMed: 15922212]
38. Pape UF, Jann H, Muller-Nordhorn J, et al. Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors. *Cancer.* 2008; 113:256–265. [PubMed: 18506737]
39. Pasquiou C, Scoazec JY, Gentil-Perret A, et al. Solid pseudopapillary tumors of the pancreas. Pathology report of 13 cases. *Gastroenterol Clin Biol.* 1999; 23:207–214. [PubMed: 10353015]
40. Pettinato G, Manivel JC, Ravetto C, et al. Papillary cystic tumor of the pancreas. A clinicopathologic study of 20 cases with cytologic, immunohistochemical, ultrastructural, and flow cytometric observations, and a review of the literature. *Am J Clin Pathol.* 1992; 98:478–488. [PubMed: 1283055]
41. Phan GQ, Yeo CJ, Cameron JL, et al. Pancreaticoduodenectomy for selected periampullary neuroendocrine tumors: fifty patients. *Surgery.* 1997; 122:989–996. [PubMed: 9426411]
42. Ray S, Lu Z, Rajendiran S. Clear cell ductal adenocarcinoma of pancreas: a case report and review of the literature. *Arch Pathol Lab Med.* 2004; 128:693–696. [PubMed: 15163226]
43. Rindi G, Kloppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch.* 2006; 449:395–401. [PubMed: 16967267]
44. Salla C, Chatzipantelis P, Konstantinou P, et al. Endoscopic ultrasound-guided fine-needle aspiration cytology diagnosis of solid pseudopapillary tumor of the pancreas: a case report and literature review. *World J Gastroenterol.* 2007; 13:5158–5163. [PubMed: 17876886]
45. Schmitt AM, Anlauf M, Rousson V, et al. WHO 2004 criteria and CK19 are reliable prognostic markers in pancreatic endocrine tumors. *Am J Surg Pathol.* 2007; 31:1677–1682. [PubMed: 18059224]
46. Stommer P, Kraus J, Stolte M, et al. Solid and cystic pancreatic tumors. Clinical, histochemical, and electron microscopic features in ten cases. *Cancer.* 1991; 67:1635–1641. [PubMed: 1900454]
47. Strosberg J, Hoffs S, Gardner N, et al. Effective treatment of locally advanced endocrine tumors of the pancreas with chemoradiotherapy. *Neuroendocrinology.* 2007; 85:216–220. [PubMed: 17541257]
48. Tajiri T, Inagaki T, Ohike N, et al. Intraductal oncocytic papillary carcinoma of the pancreas showing numerous hyaline globules in the lumen. *Pathol Int.* 2010; 60:48–54. [PubMed: 20055952]
49. Tanaka Y, Notohara K, Kato K, et al. Usefulness of beta-catenin immunostaining for the differential diagnosis of solid-pseudopapillary neoplasm of the pancreas. *Am J Surg Pathol.* 2002; 26:818–820. [PubMed: 12023593]
50. Tang LH, Aydin H, Brennan MF, et al. Clinically aggressive solid pseudopapillary tumors of the pancreas: a report of two cases with components of undifferentiated carcinoma and a comparative clinicopathologic analysis of 34 conventional cases. *Am J Surg Pathol.* 2005; 29:512–519. [PubMed: 15767807]
51. Tennvall J, Ljungberg O, Ahren B, et al. Radiotherapy for unresectable endocrine pancreatic carcinomas. *Eur J Surg Oncol.* 1992; 18:73–76. [PubMed: 1310647]

52. Tipton SG, Smyrk TC, Sarr MG, et al. Malignant potential of solid pseudopapillary neoplasm of the pancreas. *Br J Surg*. 2006; 93:733–737. [PubMed: 16609955]
53. Torrisi JR, Treat J, Zeman R, et al. Radiotherapy in the management of pancreatic islet cell tumors. *Cancer*. 1987; 60:1226–1231. [PubMed: 3040209]
54. Udelsman R, Yeo CJ, Hruban RH, et al. Pancreaticoduodenectomy for selected pancreatic endocrine tumors. *Surg Gynecol Obstet*. 1993; 177:269–278. [PubMed: 8102815]
55. Venkatesh S, Ordonez NG, Ajani J, et al. Islet cell carcinoma of the pancreas. A study of 98 patients. *Cancer*. 1990; 65:354–357. [PubMed: 2153046]
56. Yao JC, Shah MH, Ito T, et al. A randomized, double-blind, placebo-controlled, multicenter phase III trial of everolimus in patients with advanced pancreatic neuroendocrine tumors (pNET) (RADIANT-3). *Ann Oncol*. 2010; 21
57. Yeo, CJ. Neoplasms of the endocrine pancreas. In: Greenfield, LJ.; Mulholland, MW.; Oldham, KT., editors. *Surgery: Scientific Principles and Practice*. Lippincott; Philadelphia, PA: 2001. p. 899-913.
58. Zhang H, Liang TB, Wang WL, et al. Diagnosis and treatment of solid-pseudopapillary tumor of the pancreas. *Hepatobiliary Pancreat Dis Int*. 2006; 5:454–458.
59. Zitzmann K, De Toni EN, Brand S, et al. The novel mTOR inhibitor RAD001 (everolimus) induces antiproliferative effects in human pancreatic neuroendocrine tumor cells. *Neuroendocrinology*. 2007; 85:54–60. [PubMed: 17310129]

Figure 1.

This pancreatic neuroendocrine tumor (PanNET) demonstrates abundant hyaline globules of varying size (A). The neoplastic cells are strongly immunoreactive with antibodies to synaptophysin (B). Solid-pseudopapillary neoplasm (SPN) displays characteristic hyaline globules (C) as well, but in contrast to PanNET, shows nuclear labeling with β -catenin (D).

Figure 2. The hyaline globules of pancreatic neuroendocrine tumor (PanNET) are PAS-positive (A). In most cases, these hyaline globules immunolabel with alpha-1-antitrypsin (B).

Figure 3.

Comparison of the microscopic features of pancreatic neuroendocrine tumor (PanNET) and solid-pseudopapillary neoplasm (SPN) reveals similarities and differences between the two lesions. Three morphologic features can distinguish PanNET from SPN. Clear cells, with abundant clear cytoplasm and an eccentric nucleus, are more commonly seen in SPN (A). Cases of SPN frequently display an insidious pattern of invasion, typified by a sinuous and winding arrangement of neoplastic cells around normal pancreatic tissue (B). Rare foci of nuclear grooves are seen in SPN (C), in contrast to the round nuclei with salt and pepper chromatin of PanNET (D). Foci of discohesion with single cells (E), foam cells (F), hyalinization (G), microcystic change (not shown), and hemorrhage (not shown) are present in both neoplasms. Cholesterol clefts are observed in 1 case of SPN (H).

Table 1

Antibodies used for immunostaining.

Antibody	Source	Dilution	Detection system	Stainer
Alpha-1-antitrypsin	Dako (Carpinteria, CA)	1:20,000	Polymer-based	Dako PlusLink
β -catenin	BD Transduction (Franklin Lakes, NJ)	1:2,000	Polymer-based	Leica Bond Max
CK19	Dako (Carpinteria, CA)	Predilute	Avidin-biotin	Ventana Benchmark XT
Ki-67	Ventana (Tucson, AZ)	Predilute	Avidin-biotin	Ventana Benchmark XT
Synaptophysin	Leica Microsystems (Bannockburn, IL)	1:400	Polymer-based	Leica Bond Max
Trypsin	BioDesign (Saco, ME)	1:3,000	Polymer based	Leica Bond Max

Table 2

Microscopic features.

	All cases with HG	PanNETs	SPNs	
	N (%)	N (%)	N (%)	<i>P value</i> [†]
Total number of cases	24 (100)	18 (100)	6 (100)	
Immunohistochemical tumor profile				
Synaptophysin	23 (95.8)	18 (100)	5 (83.3)	0.2500
β-catenin (nuclear)	6 (25)	0 (0)	6 (100)	< 0.0001
CD10 [‡]	6 (100)	NT	6 (100)	CBD
Characterization of globules*				
PAS	22/22 (100)	16/16 (100)	6/6 (100)	CBD
PASD	22/22 (100)	16/16 (100)	6/6 (100)	CBD
AAT-1	19/21 (90.5)	12/15 (80)	6/6 (100)	0.5263
Trypsin	1/22 (4.5)	1/16 (6.3)	0/6 (0)	1.0000
Hemorrhage	18 (75)	13 (72.2)	5 (83.3)	1.0000
Microcystic change	18 (75)	12 (66.7)	6 (100)	0.2770
Focal discohesion	3 (12.5)	1 (5.6)	2 (33.3)	0.1433
Hyalinization	10 (41.7)	7 (38.9)	3 (50)	0.6653
Insidious invasion	7 (29.2)	2 (11.1)	5 (83.3)	0.0027
Foam cells	4 (16.7)	3 (16.7)	1 (16.7)	1.0000
Clear cells	11 (45.8)	5 (27.8)	6 (100)	0.0034
Nuclear grooves	3 (12.5)	0 (0)	3 (50)	0.0099
Cholesterol clefts	1 (4.2)	0 (0)	1 (16.7)	0.2500

AAT-1: alpha-1-antitrypsin, CBD: cannot be determined, HG: hyaline globules, NT: not tested, PASD: PAS with diastase, PanNETs: pancreatic neuroendocrine tumors, SPNs: solid-pseudopapillary neoplasms

[†] P value has been calculated between PanNETs and SPNs

[‡] CD10 was only performed as a confirmatory test when nuclear immunolabeling for β-catenin was present

* In some cases, HG were focal and were not present on levels immunolabeled with AAT-1 (n=3) or trypsin (n=2), or those stained with PAS or PASD (n=2)