

# Solid pseudopapillary neoplasm of the pancreas: cytomorphology, pitfalls, and literature review

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**Abstract:** Solid pseudopapillary neoplasm (SPN) of the pancreas is a rare pancreatic neoplasm. Clinically it has non-specific presentations like vague abdominal pain. Imaging studies usually shows a mass at the body or tail of the pancreas. It could be a solid or cystic mass. Distant metastasis is uncommon. Generally, it is considered a tumor with uncertain malignant potential. Overall prognosis is well. Activating somatic mutation of  $\beta$ -catenin gene (CTNNB1) is seen in nearly all cases with SPN. Radical resection is the management of choice and if SPN is unresectable, radiotherapy is the next treatment option. This neoplasm has a unique cytomorphology, immunohistochemistry and prognostically outcome compared with other pancreatic cystic neoplasm. Papillary fronds with fibrovascular core on a cytology smear, combined with a cell-block prepared specimen material that stains with  $\beta$ -catenin is diagnostic for this tumor. The proper cytological evaluation and diagnosis could enable appropriate surgical approach and further management. Since this neoplasm has a good prognosis, it is crucial to diagnose this rare tumor cytologically from other pancreatic tumors by its characteristic cytological features and plan appropriately for the surgical management to improve patient care. In this paper, we comprehensively review SPN and focus on cytomorphologic features, the importance of EUS-guided FNA cytology for diagnosis and management.

**Keywords:** Tumor; pancreas; solid pseudopapillary neoplasm (SPN); cytology;  $\beta$ -catenin

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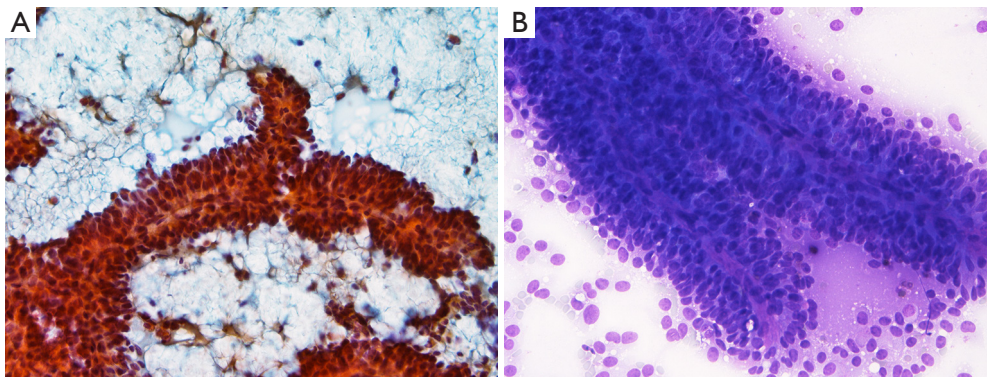
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## Introduction

SPN of the pancreas is considered a rare and uncommon neoplasm. First described in the literature by Frantz and then so-called Gruber-Frantz tumor (1). It is mostly seen in young females with a mean age of 25 to 30 years (2). High prevalence of SPN of the pancreas in women suggests a hormonal role in pathogenesis of this tumor (3). Cases occurred in men is very rare (<7% of cases) (4). It usually has no specific anatomical predilection. Unusual presentation like multicentricity or extra-pancreatic presentations were also described in the literature (5-8). The frequency of this tumor varies and ranges up to 2.7% of exocrine pancreatic

neoplasms (9). Literature review showed very few of these cases were diagnosed on cytologic specimens (10). Symptoms could range from abdominal discomfort, occasional mass or even incidental finding during imaging study. Uncommonly, local invasion and infiltration of the surrounding capsule may occur. Distant metastasis is very rare (11). As a general rule, SPN is considered a tumor with uncertain malignant potential. The treatment of choice is complete surgical excision and even in those with capsular invasion, is highly responsive to cure (12). There are few reports that some tumors may metastasize (13). The most common metastatic locations include adjacent structures or pleura. When metastasis is discovered, term “carcinoma”



**Figure 1** Diff-Quik and pap smear showing multi-layer lined delicate papillary fronds (40×). Diff-Quik smear stained with triaryl methane dye and Diff-Quik solutions I and II and Papanicolaou smear stained with Hematoxylin, orange G and eosin solutions.

is used instead of “neoplasm”. Even those that metastasize have excellent prognosis (14).

### Clinical presentation

Generally, abdominal pain, early satiety, nausea, vomiting or even incidental finding during imaging studies of abdomen for other reasons are the non-specific initial clinical presentations (15).

Typically, SPN patient presents as a young woman with few weeks of history of episodic epigastric and left upper quadrant vague abdominal pain. B symptoms like weight loss and fever are uncommon. Imaging studies of the abdomen mostly reveals a pancreatic mass at the body or tail of the pancreas.

### Histogenesis

It appears that the histogenesis of SPN is uncertain. Multiple proposed theories include originating from totipotent stem cells or primitive cells that could differentiate to both exocrine and endocrine cells or even deriving from small duct epithelium or acinar cells (16,17). In addition, presence of pre-melanosomes and melanosome granules suggested derivation from neural crest origin (18). More researches are required to better understand the histogenesis of this rare tumor.

### Cytomorphology

The aspirated material during EUS-FNA usually smeared onto glass slides, air-dried and then immediately stained

with hematoxylin for specimen adequacy and preliminary diagnosis. Other smears are fixed in 95% alcohol for PAP staining. The rest of the aspirated material is usually formalin fixed and paraffin embedded to make a cell block for ancillary studies. Fine needle aspiration of a SPN mass-lesion usually provides a highly cellular smear composed of monotonous population of cuboidal cells that are loosely cohesive or single isolated cells. The tumor cells may arrange as single or multiple layers around a fibrovascular core, but this type of appearance is uncommon in cytology smears. *Figure 1* shows an endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) biopsy from a patient with pre-operational suspicion of having SPN. The smears are highly cellular. Many single or small clusters of loosely cohesive monotonous tumor cells and few delicate papillary fronds with fibrovascular core lined by two to three layers of cuboidal cells identified. No significant atypia was noted. Tumor cells had round to oval nuclei with fine chromatin. Some tumor cells clearly had nuclear grooves. Tumor cell cytoplasm was mostly clear and poorly defined.

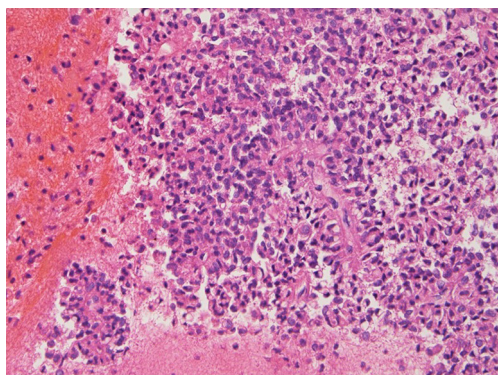
Naked capillaries could also be seen (19). The tumor cells have granular cytoplasm with indistinct cell borders. The nuclei are round-to-oval, having nuclear groove and indistinct nucleoli. The neoplastic cell lining may show some anisocytosis with round-to-oval nuclei and fine chromatin. The background of cytologic smear is usually bloody with amorphous myxoid material and necrotic debris (20). One study also pointed on cercariform cells as another cytologic feature that could be present in SPN cytology and help to distinguish it from pancreatic endocrine neoplasms and acinar cell carcinomas (21). *Figure 2* shows the cell block of an EUS-FNA biopsy of a SPN.

## Gross and histologic findings

SPN of the pancreas usually presents as a well-circumscribed mass that could have both solid and non-septated cystic components. Calcification and necrosis can sometimes present. Histologically the tumor is composed of solid and pseudopapillary components that are mixed together. A fibrovascular core is a prominent feature of the pseudopapillary component. The tumor cells are poorly cohesive, monomorphic cells with eosinophilic cytoplasm and nuclear grooves. Rare mitosis may be seen. Background stroma could have foam cells with cholesterol clefts (22).

## Immunohistochemistry

SPN is immunoreactive for  $\alpha$ 1-antitrypsin,  $\alpha$ 1-antichymotrypsin, PR, CD56, CD10 and CD117 (23,24). Cytokeratin can be positive but the stain is weak and

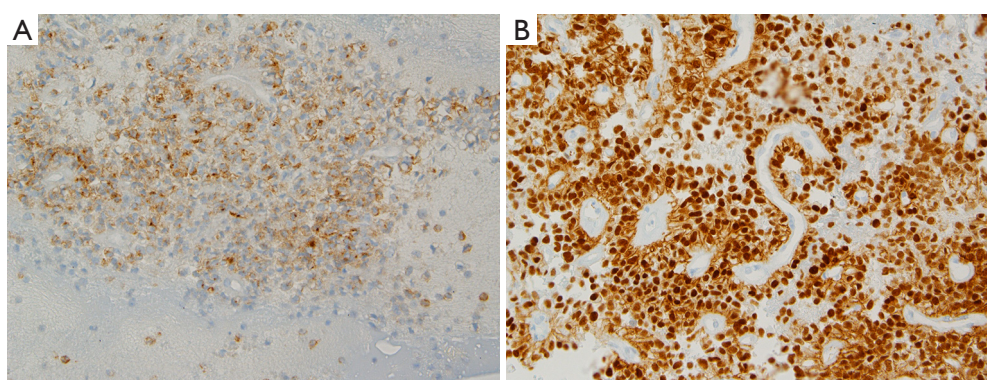


**Figure 2** Cell block showing multi-layer lined delicate papillary fronds with background necrotic debris (H&E staining; 40 $\times$ ).

focal. Nuclear staining for  $\beta$ -catenin is also a very useful marker. Sometimes the tumor cells may be focally immunoreactive with synaptophysin. *Figure 3* shows an immunohistochemical example of a SPN, in which the tumor cells are diffusely positive with CD10 and strong, diffuse nuclear staining with  $\beta$ -catenin.

## Molecular findings

Many studies have performed to detect molecular changes in SPN. It has been proven that variations in SMAD4, KRAS, TP53 and CDKN2A, which are common molecular changes in other pancreatic cancers, are not detected in SPN (25). On the other hand, it is confirmed that all the patients with SPN have activating somatic mutation of  $\beta$ -catenin gene (CTNNB1) which is located on chromosome 3p (26). Up to 70% of CTNNB1 mutations are detected on position 32 or 37 (27). In addition, it has been found that some proteins involving in Wnt signaling including DKK4 and some other proteins that function directly through binding with  $\beta$ -catenin protein like; NONO and FUS, are upregulated in SPN (28). Some studies also pointed out that there is a higher presence of single nucleotide polymorphism (SNPs) seen in those SPN patients who are older or having a larger tumor (>100 mm in diameter) or a metastasis (29). Inactivated mutations of epigenetic regulators (e.g., KDM6A, TET1, BAP1) with loss or reduction of their related proteins are also associated with SPN with metastatic lesions and appears to occur before metastasis happens (30). The importance of understanding these mutations is that they may be used as a treatment option in the future by increasing the BAP1 and KDM6A function to decrease the risk of metastasis.



**Figure 3** Tumor cells stained positive with CD10 and beta-catenin (40 $\times$ ).



## Differential diagnosis

The main differential diagnosis includes acinar cell carcinoma and pancreatic endocrine neoplasms. Papillary mucinous carcinoma and intraductal papillary mucinous tumor could rarely come into the differential diagnosis list. These tumors may share some cytological features that may overlap with SPN. On cytology specimen, pancreatic endocrine neoplasms have single or small clusters of monomorphic plasmacytoid cells with typical salt and pepper chromatin and may make rosettes but no papillary structures (31). On the other hand, acinar cell carcinoma cytology specimen is usually highly cellular with numerous isolated cells. The tumor cells have round-to-oval nucleus with smooth nuclear contours and prominent nucleolus. Tumor cells may have a granular cytoplasm.

Presence of thick mucus helps to differentiate intraductal papillary mucinous tumor from SPN. Also, columnar mucinous cells with architectural atypia are present. In papillary mucinous carcinoma tumor cells have cytoplasmic vacuoles with mucinous background (32,33).

## Current guidelines on the management of pancreatic cysts

The guideline for the management of pancreatic neoplastic cysts including SPN has recently been updated. A conservative approach is usually the management of choice for asymptomatic mucinous cystic neoplasm (MCN) and intraductal papillary mucous neoplasm (IPMN) that measure less than 40 mm with no enhancing nodule (34). IPMN with adjacent main pancreatic duct measured between 5 to 9.9 mm or the cyst measures more than 40 mm, is a relative indication of surgery. Because of high risk of malignancy, presence of an enhanced mural nodule of more than 5 mm or main pancreatic duct diameter of more than 10 mm, are absolute indications of surgery (34). Radical resection is also considered the management of choice for all SPN. And in cases of SPN with metastasis, recurrence or locally advanced cases, an aggressive surgical approach is warranted and makes a better long-term outcome (35,36). Neoadjuvant therapy is routinely recommended for IPMN or MCN-associated carcinoma but not for SPN but may be used as a palliative measurement in post-surgical recurrence patients (37). Some studies recommended that if the SPN is unresectable, it can be preoperatively treated with chemotherapy like with gemcitabine to decrease the size of the lesion before doing the surgery (38). In addition, SPN is

a radiosensitive tumor and radiotherapy can be considered as a treatment option in unresectable tumors (39).

American Society of Clinical Oncology recommends gene testing roles for those individuals who are susceptible for pancreatic cancers (e.g., with blood relative diagnosed with pancreatic cancer) (40). Even in individuals without a defined genetic mutation but having family risk criteria, surveillance is recommended and the consensus is around age 50 (41). The surveillance protocol could include imaging like EUS as the primary modality of choice (42).

## Conclusions

It is very important to distinguish SPN from other pancreatic mass tumors most specifically from its main differential diagnosis like acinar cell carcinoma and islet cell tumors. Appropriate surgical management and better prognosis differentiates this tumor from other pancreatic lesions. SPN can be diagnosed preoperatively with fine needle aspiration biopsy (43). This shows the significant role of cytology evaluation for definitive diagnosis and further management. Cytomorphology criteria including hypercellular smear, papillary fronds, fibrovascular core, monomorphic appearance of the lining tumor cells, nuclear grooves, occasional cercariform cells, and background foamy macrophages with necrotic debris are important diagnostic clue. Mitotic figures are usually uncommon in tumor cells. Amorphous myxoid material that appears red following Giemsa staining could be another hint for diagnosis (44). By immunohistochemistry the tumor cells are reactive to  $\alpha_1$ -antitrypsin, CD56 and CD10. Nuclear staining with  $\beta$ -catenin is very helpful to differentiate it from pancreatic neuroendocrine neoplasm. Progesterone receptors staining has also been described in the literature that could suggest a hormone-dependent role in SPN (44). Fine needle aspiration cytology is the most helpful and cost-effective approach for diagnosis and to plan for surgical management. The diagnostic accuracy of EUS-FNA is superior and more sensitive compared to imaging studies for making the diagnosis (94% compared to 69–83% respectively), especially for lesions less than 3 cm (45). A pre-operative accuracy is highly possible by EUS-guided FNA cytology. EUS-guided FNA can differentiate SPN from certain pancreatic neoplasms with similar imaging findings but with different clinical behavior, treatment and prognosis including acinar cell carcinoma and pancreatic neuroendocrine neoplasm.

In conclusion, EUS-FNA by providing high cellular

material and high sensitivity is the modality of choice for pre-operative diagnosis of SPN. We strongly believe and suggest to use this approach by reviewing cytomorphologic features in conjunction with clinic-radiologic findings to make the accurate diagnosis.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apc-20-42>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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