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Solid Pseudopapillary Neoplasm of the Pancreas: Analysis of Seven Cases

Audrius Šileikis[a] Vitalija Nutautienė[a] Dmitrij Šeinin[b] Kęstutis Strupas[a]

[a]Center of Abdominal Surgery, Vilnius University,
[b]National Center of Pathology, Vilnius, Lithuania

Keywords
Solid pseudopapillary neoplasm · Pancreas · Surgical treatment

Summary
Background: The purpose of this study was to describe as well as compare our surgical treatment experiences of solid pseudopapillary neoplasms (SPN) of the pancreas and to provide a review of the literature. **Methods:** A retrospective analysis of data from Vilnius University Hospital Santariskiu Klinikos (VUH SK) and of the literature, which was researched using Karger Publishers, Springer Science, BioMed Central, and disserCat databases, was conducted. **Results:** From 2001 to 2012, seven cases were identified with pathologically confirmed SPN diagnosis. A precise preoperative diagnosis was made by computertomography and magnetic resonance imaging. The median diameter of the tumors was 6.36 cm (range 1.5–12 cm). Surgical treatment was undertaken for all patients. Results of the immunohistochemical analysis confirmed a nuclear accumulation of β-catenin. The Ki-67 level was 1–2% in all of the cases. According to our collected data, all types of histological analysis revealed decent prognostic behavior with low mitotic activity (1–2 mitoses per 50 high power fields). Besides, angioinvasion, perineural invasion, and outside capsule invasion were not detected. **Conclusions:** There was no correlation between more aggressive types of SPN and tumor size, localization, age, and gender.

Schlüsselwörter
Solider pseudopapillärer Tumor · Pankreas · Chirurgische Behandlung

Zusammenfassung
Hintergrund: Ziel dieser Studie war es, unsere chirurgischen Behandlungserfahrungen bei soliden pseudopapillären Neoplasien (SPN) der Bauchspeicheldrüse zu beschreiben und zu vergleichen sowie einen Überblick über die Literatur zu geben. **Methoden:** Eine retrospektive Analyse anhand der Daten des Vilnius University Hospital Santariskiu Klinikos (VUH SK) und der Literatur anhand der Datenbanken des Karger Verlags, von Springer Science, von BioMed Central und von disserCat wurde durchgeführt. **Ergebnisse:** Für den Zeitraum von 2001 bis 2012 wurden sieben Fälle mit pathologisch bestätigter Diagnose von SPN identifiziert. Eine genaue präoperative Diagnose wurde mittels Computertomographie und Magnetresonanztomographie vorgenommen. Der mediane Durchmesser der Tumoren betrug 6,36 cm (Bereich 1,5–12 cm). Bei allen Patienten wurde ein chirurgischer Eingriff durchgeführt. Die Ergebnisse der immunhistochemischen Analyse bestätigten eine Kernakkumulation von β-Catenin. In allen Fällen betrug der Ki-67-Wert 1–2%. Gemäß unserer gesammelten Daten zeigten alle Varianten der histologischen Analyse ein annehmbares prognostisches Verhalten mit niedriger mitotischer Aktivität (1–2 Mitosen auf 50 Hauptgesichtsfelder). Angioinvasion, perineurale Invasion und Kapselinvasion wurden nicht festgestellt. **Schlussfolgerungen:** Es bestand kein Zusammenhang zwischen aggressiven Arten von SPN sowie Tumorgröße, Lokalisation, Alter und Geschlecht.

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Dr. Vitalija Nutautienė
Center of Abdominal Surgery, Vilnius University
Santariškių str. 2, Vilnius, LT-08661, Lithuania
vaisvita2000@gmail.com

Introduction

Solid pseudopapillary neoplasm (SPN) of the pancreas, which was first reported on by Frantz in 1959 [1], is a rare epithelial tumor composed of monomorphous cells forming solid and pseudopapillary structures, frequently with hemorrhagic cystic changes with low malignant potential [2]. Criteria that could distinguish potentially malignant tumors, classified as a solid pseudopapillary carcinoma, include the following: i) perineural invasion, ii) angioinvasion, iii) deep invasion into the surrounding tissues, and iv) distant metastases [3]. SPN represents 1–3% of all pancreatic tumors and 10–15% of cystic tumors of the pancreas [4–6]. SPN predominantly affects females during their reproductive phase and exhibits relatively indolent biological behavior with a favorable prognosis [6, 7]. A metastatic disease is uncommon and only occurs in about 15–20% of the patients. The overall mortality due to this type of tumor is estimated to be approximately 2%; the recurrence rate after surgery is estimated to encompass 10–15% of the patients [8]. There are limited reports on this neoplasm as it is rare; according to the literature review by Lin et al. from 2010 [9], 1,014 SPN patients were described. Preoperative diagnosis of SPN provides important management information for clinicians as its indolent clinical behavior compares favorably with other more aggressive pancreatic neoplasms.

Patients and Methods

A retrospective analysis of medical documentation data of the patients who underwent surgery for SPN between 2001 and 2012 was undertaken at Vilnius University Hospital Santariskiu Klinikos (VUH SK). Other scientific sources, i.e. Karger Publishers, Springer Science, BioMed Central, and disserCat databases, were searched and consulted.

Results

From 2001 to 2012, SPNs amounted to 0.5% of all performed pancreatic operations for pancreatic and periampullar tumors at VUH SK. 7 patients with pathologically confirmed SPN diagnosis were identified (table 1). The group of SPN patients included 6 (85.7%) females and 1 (14.3%) male, with an average age of 30.9 years (range 8–60 years). All patients underwent testing of tumor markers (CA 19-9, CEA), whereas normal levels were detected. Correct SPN diagnosis was made before the surgery in all cases: Diagnoses of 6 patients were revealed by computed tomography (CT) (fig. 1a, b), and the doubtful diagnosis of 1 patient was specified after magnetic resonance imaging (MRI) (fig. 1c). The clinical data of our group revealed that 14.3% of SPNs were located in the head, 28.6% in the body, 28.6% in the body and tail, and 28.6% in the tail of the pancreas. Median diameter of the tumors was 6.36 cm (range 1.5–12 cm). 5 patients with a tumor diameter >6 cm were identified. Pancreas resection and extirpation were performed for 5 and for 2 patients, respectively. A more aggressive surgery type with selective lymphadenectomy was applied to 4 patients. Lymph node enlargements were confirmed to be benign. Distal metastases were not detected. Results of immunohistochemical analysis revealed a nuclear accumulation of β-catenin. The Ki-67 level was 1–2% in all of the cases. There was no correlation between more aggressive types of SPN and a larger tumor size. According to clinical data of the patients, all types of pathohistochemical analyses revealed a decent prognostic behavior with low mitotic rate. A yearly follow-up was performed for the years 1–11. No recurrence of the disease was identified.

Discussion

SPNs are characterized by mutations in exon 3 of CTNNB1 [10] that predispose cells to the dysregulation and redistribution of β-catenin, which is an integral component of the E-cadherin complexes at the intercellular adherence junctions [11]. The protein also plays a key role in the Wnt signaling pathway as a transcriptional activator in conjunction with T-cell factor/lymphoid enhancer factor, with the transcription factors inducing the target gene expression that is required for cell proliferation and differentiation [12]. Mutations in the β-catenin gene which impaired adhesion may be one of the factors accounting for the pseudopapillary appearance [10]. Wnt/β-catenin, hedgehog, and androgen receptor signaling pathway activation as well as genes involved in epithelial mesenchymal transition are closely associated with lesser epithelial cell differentiation than other common pancreatic tumors, therefore suggesting that it might be a hormone-dependent tumor [13].

SPN arises from primitive pancreatic cells (e.g. acinar cells, ductal epithelial cells, or endocrine cells) or from cell lines of the female genital bud [8].

In general, SPN occurs predominantly in young women (86.5%) and is rare in men (13.5%). Men are on average 5 years older, have a twice as high incidence of metastases (women: 4.3%; men: 10.2%) and invasive malignancy (women: 12.4%; men: 24.4%), and show a threefold higher death rate (women: 3.6%; men: 11.4%) [9]. Approximately 20–25% of the cases are determined in pediatric patients. SPNs usually form large masses, with a mean diameter of 6 cm and range of 0.5–34.5 cm [7], and are mostly distributed in the pancreatic head (39.8%), tail (24.1%), and body and tail (19.5%) [14]. The clinical presentation of SPN is non-specific. Most of the patients present with non-specific symptoms including abdominal discomfort, mild abdominal pain, or palpable abdominal mass. Due to its slow growth, SPN often remains asymptomatic until the tumor enlarges considerably; accordingly, the majority of SPNs is detected incidentally during diagnostic imaging for unrelated diseases [15].

Concerning diagnostics, routine laboratory parameters and tumor markers are of no help. CT/MRI scans typically show a

Table 1. Pathologically confirmed SPN patient data of VUH SK

Parameters	P1	P2	P3	P4	P5	P6	P7
Age, years	17	8	37	28	25	60	41
Gender	female	male	female	female	female	female	female
Localization of pancreatic tumor	head	body	body and tail	body and tail	body	tail	tail
Tumor size, cm	8 × 8 × 7	2 × 2 × 2	6 × 5 × 4	6 × 4.5 × 2.7	1.5 × 1.5 × 1.5	12 × 12 × 12	8 × 9 × 8
Tumor tissue characteristics	solid cystic	solid	solid	solid	solid	cystic	cystic
Surgery type	extirpation	segmental resection	extirpation	left hemipancreatectomy	segmental resection	distal resection	distal resection
Lymph nodes	6	1	–	12	1	5	3
Mitotic activity index	1 per 50 HPF	2 per 50 HPF	1 per 50 HPF	1 per 50 HPF	2 per 50 HPF	1 per 50 HPF	2 per 50 HPF
Ki-67	1–2%	2%	1%	1%	1%	1%	1%

HPF = High power fields.

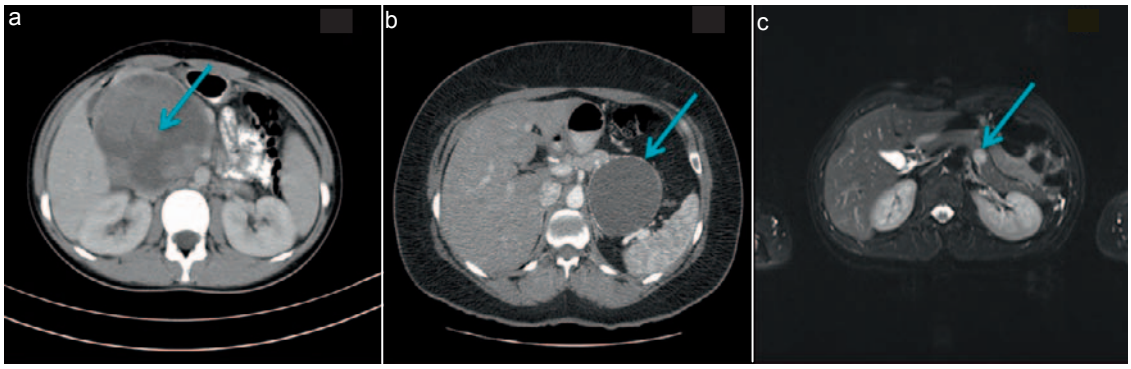

Fig. 1. a CT scan reveals encapsulated, round, non-homogenic mass of pancreatic head. **b** CT scan reveals SPN with peripheral calcifications of the capsule. **c** MRT imaging in T2 sequence reveals round, well-defined peripheral capsule of SPN in the body of the pancreas.

large, well-circumscribed (97%), heterogeneous mass with varying solid and cystic components, generally demarcated by enhancing capsule (77%). These tumors tend to be predominantly round or oval (66%), demonstrate well-defined, often contained, either peripheral or central calcifications (47%), and overwhelmingly show no evidence of biliary dilatation, pancreatic ductal dilatation, or pancreatic parenchymal atrophy. Despite the large size of these tumors, vascular encasement or occlusion is quite rare (13%), although the large size of the masses sometimes leads to considerable displacement of the adjacent vasculature. MRI is superior to CT in distinguishing certain tissue characteristics, such as hemorrhage, cystic degeneration, or the presence of a capsule, and may enable correct diagnosis [16]. CT scans might help to diagnose SPNs accurately in 80% of the cases [17]. In 2012, Yin et al. [18] described some characteristic features based on CT and/or MRI which can differentiate between benign and malignant SPNs. Focal discontinuity of the capsule, large tumor size (>6.0 cm), and pancreatic tail location may suggest malignancy of SPN. In contrast, tumors with amorphous or scattered calcifications and all near-solid tumors may be indicative of benignancy.

An accurate preoperative diagnosis would be helpful in surgical planning. In uncertain cases, the diagnosis can be confirmed by endoscopic ultrasound scan with fine-needle aspiration (FNA) biopsy or percutaneous core needle biopsy with ultrasound or CT guidance.

The classic morphologic findings on FNA include branching papillary-like fronds composed of central fibrovascular cores with attached small uniform tumor cells. The neoplastic cells also present as small aggregates, rosettes, and numerous single cells, which may be plasmacytoid. The cytoplasm is pale, ill-defined, and variable in amount. Occasionally cytoplasmic vacuoles might be found. The nuclei are round to oval with fine, evenly dispersed chromatin and nuclear grooves. Positive immunocytochemistry for β-catenin (nuclear staining), CD10, vimentin, CD56, and α1-antitrypsin led to the correct diagnosis of SPN.

Clear-cut criteria of malignancy have not been established. Features that may indicate an aggressive clinical behavior are venous invasion, diffuse infiltrative growth pattern, extensive tumor necrosis, significant nuclear atypia, high mitotic count, nuclear pleomorphism, DNA aneuploidy, double loss of X chromosomes, trisomy of chromosome 3, and unbalanced translocation between chromosomes 13 and 17 [20, 21].

Unlike most other pancreatic tumors, malignant behavior of SPN is observed in about 10–15% of the cases. Metastases

were described in regional lymph nodes, liver, and peritoneum/omentum [7]. Given their low malignant potential and the excellent overall prognosis, surgical resection has been the standard of care in the management of SPN. SPN can be treated by complete tumor resection with limited resection or a minimally invasive approach, when applicable. The combination of surgical resection and chemotherapy by paclitaxel may therefore prolong survival, even in malignant cases [22]. Tumor enucleation and incomplete excision should be avoided due to the risk of a higher recurrence rate [23]. Despite this fact, there was no recurrence determined for the patients treated with extirpation at VUH SK. Extensive lymphatic dissection or resection of adjacent structures is not suggested since lymph node metastases are found in <2% [24, 25]. In our cases, all histologically examined lymph nodes were negative for metastatic disease. Tumor size should not be regarded as a predictor of unresectability because lesions as large as 30 cm may be resected without problems [26]. Unlike other pancreatic tumors, the stage of the disease does not play any role in the treatment of SPN [24]. If veins are infiltrated, vascular en bloc resection and reconstruction with vein grafts has been proposed, and the results were encouraging [24]. Neoadjuvant chemotherapy or radiotherapy is not indicated for treatment [27, 28]. The overall 5-year survival rate approaches 97% in patients undergoing surgical resection [24, 29].

Conclusion

SPN is a rare pancreatic neoplasm of unclear histogenesis that typically affects young females without significant symptoms. Appearance on imaging is fairly characteristic and may suggest diagnosis. In uncertain cases, preoperative diagnosis should be accomplished by FNA biopsy in order to avoid not indicated preoperative chemotherapy or radiotherapy. Complete surgical resection of the tumor is the only effective treatment option.

Disclosure Statement

The authors did not provide a conflict of interest statement.

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