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Original contribution

Solid pseudopapillary neoplasms of the pancreas do not express major pancreatic markers in pediatric patients☆

Julien Calvani MS[a], Pauline Lopez PhD[b], Sabine Sarnacki MD, PhD[c], Thierry Jo Molina MD, PhD[a], Laure Gibault MD, PhD[d], Monique Fabre MD[a], Raphael Scharfmann PhD[b], Carmen Capito MD, PhD[b,c,1], Louise Galmiche MD, PhD[a,*,1]

[a]*Department of Pathology, Hôpital Universitaire Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, and Université Paris Descartes, 75015 Paris, France*
[b]*INSERM U845, Research Center Growth and Signaling, Faculty of Medicine Cochin, Université Paris Descartes, 75014 Paris, France*
[c]*Department of Pediatric Surgery, Hôpital Universitaire Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, and Université Paris Descartes, 75015 Paris, France*
[d]*Department of Pathology, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, and Université Paris Descartes, 75015 Paris, France*

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Summary Solid pseudopapillary neoplasms (SPNs) of the pancreas are classified as "exocrine" pancreatic tumors by the World Health Organization. However, despite numerous studies using immunohistochemistry, electron microscopy, animal models, and molecular biology, the histogenesis of SPN remains unclear. At the same time, our knowledge of human pancreas development has significantly increased. It is now well known that the undifferentiated PDX1+ pancreatic progenitors proliferate and differentiate into endocrine, ductal, and acinar cells, thanks to the expression of numerous transcription factors, which can be used to better characterize pancreatic tumors. In a series of 14 pediatric SPN, we investigated the expression of 4 transcription factors associated with pancreatic development (PDX1, SOX9, PTF1A, and NKX2.2) to obtain new insights into the pathogenesis of SPN. In addition, we tested the expression of different markers of epithelial, endocrine, exocrine, and neural differentiation using both immunohistochemical and immunofluorescence analyses. All tumors displayed the typical histologic features of SPN, with both pseudopapillary and solid patterns. The immunoprofile was characterized by immunoreactivity for β-catenin (100%), progesterone receptor (100%), cyclin D1 (100%), synaptophysin (65%), and S100 (15%). In all cases, tumor cells were negative for the following markers: PDX1, SOX9, PTF1A, NKX2.2, chromogranin A, glucagon, insulin, somatostatin, ghrelin, pancreatic polypeptide, amylase, GFAP, calretinin, EPCAM, and estrogen receptor α. To conclude, SPNs do not express major transcription factors involved in pancreatic development and differentiation, which does not allow for precise pancreatic lineage of tumor cells. Thus, additional studies are still required to determine the origin of SPN.

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* Corresponding author at: Service D'anatomie et Cytologie Pathologiques, Hôpital Necker-Enfants Malades, 149 rue de Sèvres, 75015 Paris, France.
E-mail address: louise.galmiche-rolland@aphp.fr (L. Galmiche).

[1] These authors contributed equally to this work.

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1. Introduction

Solid pseudopapillary neoplasms (SPNs) of the pancreas account for up to 30% of pancreatic tumors in children. SPNs are classified as "exocrine" pancreatic tumors by the World Health Organization (WHO) [1]. However, despite numerous studies using immunohistochemistry, electron microscopy, animal models, and, more recently, molecular biology [2,3], the histogenesis of SPN remains unclear. At the same time, our knowledge of human pancreas development has significantly increased in recent years. It is now well known that the pancreas-committed endodermal region of the foregut first expresses the transcription factor PDX1 (pancreatic and duodenal homeobox 1) [4]. The undifferentiated PDX1+ pancreatic progenitors proliferate and differentiate into endocrine, ductal, and acinar cells, thanks to the expression of numerous transcription factors, summarized in Fig. 1 [5,6]. These transcription factors can be used to better characterize pancreatic tumors.

In a series of 14 pediatric SPN, we investigated the expression of 4 major pancreatic developmental transcription factors (PDX1, SOX9, PTF1A, and NKX2.2) to obtain new insights into the pathogenesis of these tumors. In addition, we tested the expression of different markers of epithelial, endocrine, exocrine, and neural differentiation using both immunohistochemical and immunofluorescence analyses to challenge the results obtained by other studies published thus far.

2. Materials and methods

Fourteen pediatric SPNs were sent to our department of pathology from 1995 to 2015. All these patients were previously used for a nationwide study by Irtan et al [7] in 2016. Histologic material was derived from surgical resection specimens or surgical biopsies. Each sample was fixed in 10% neutral-buffered formalin and paraffin embedded, except for one case (case 5 fixed in acidified formol alcohol). Sections (3-4 μm thick) were stained with hematoxylin eosin and safran.

Immunohistochemistry and immunofluorescence were performed on formalin-fixed and paraffin-embedded sections using a panel of antibodies (Table 1). Adequate positive and negative controls were run for all antibodies tested.

For immunohistochemical analyses, slides were labeled with antibodies to β-catenin, PS100, GFAP, calretinin, chromogranin A, synaptophysin, estrogen receptor α (ERα), progesterone receptor (PR), cyclin D1, and MIB-1 (Ki-67). Immunohistochemical analyses were realized with a Leica Bond automated immunohistochemistry slide processing platform (Bond Max, Leica, Germany) according to the manufacturer's instructions. Counterstaining was performed using hematoxylin.

For multiparametric immunofluorescence analyses, slides were labeled with antibodies to insulin, glucagon, pancreatic polypeptide, somatostatin, ghrelin, amylase, EPCAM, PDX1 [8], SOX9, NKX2.2, and PTF1A [9]. For pancreatic developmental transcription factors (PDX1, SOX9, NKX2.2, and PTF1A), nuclear staining was only considered.

Except for Ki-67, the immunostaining was scored on a sliding scale of 0 to 4+ according to the percentage of reactive cells (1+, 1%-25%; 2+, 26%-50%; 3+, 51%-75%; 4+, 76%-100%). Cases were considered positive for any marker if the percentage score was at least 1+. The Ki-67 score was defined as the percentage of total number of tumor cells with nuclear staining.

3. Results

3.1. Clinical and pathological findings

From 1995 to 2015, we took care of 14 pediatric patients for an SPN of the pancreas. The main clinical data are summarized in Table 2. There were 12 women and 2 men. The mean age at diagnosis was 12.4 years (range, 7.8-17.2 years). The mean size of the tumor was 74 mm (range, 25-210 mm). The distribution showed no preferential location within the pancreas (7 in the head and 7 in the tail). Tumor resection was performed in all cases by atypical resection (5 cases), distal pancreatectomy (4 cases), distal pancreatectomy with concomitant splenectomy (2 cases), and cephalic duodenopancreatectomy or Whipple procedure (3 cases). Three patients experienced recurrence (1 pancreatic, 1 widespread peritoneal dissemination, and 1 peritoneal involving the hepatic hilum) at a mean delay of 38 months. Two were reoperated with one success (pancreatic recurrence), and the third was considered unresectable (hepatic hilum involvement).

The adjacent pancreas had a completely normal aspect in all cases. All SPNs except one (tumor of case 13) were encapsulated. All tumors displayed the typical histologic features of SPN (Fig. 2). Microscopic examination showed both pseudopapillary and solid patterns. In both components, tumor cells were monomorphic, with an eosinophilic cytoplasm and round-to-oval nuclei. There were variable amounts of necrosis, sometimes mixed with cholesterol crystals and foamy macrophages. Necrosis sometimes produced pseudocysts. There was a vascular invasion in 1 case (case 4, recurrence) and a perineural invasion in 2 cases (cases 4 and 10, both recurrences). There was no peripancreatic tissue invasion. Surgical margins were microscopically positive (R1) in 3 cases (cases 4, 9, and 10), all of which experienced a recurrence. A rupture of the tumor was observed in 2 cases (cases 3 and 14).

3.2. Immunohistochemical and immunofluorescence findings

All cases showed an abnormal intense nuclear expression of β-catenin in tumor cells (Fig. 2). All cases were positive for PR (6 cases, 3+; 7 cases, 4+; PR staining not performed in 1 case). Synaptophysin was positive in 9 cases (64%; 3

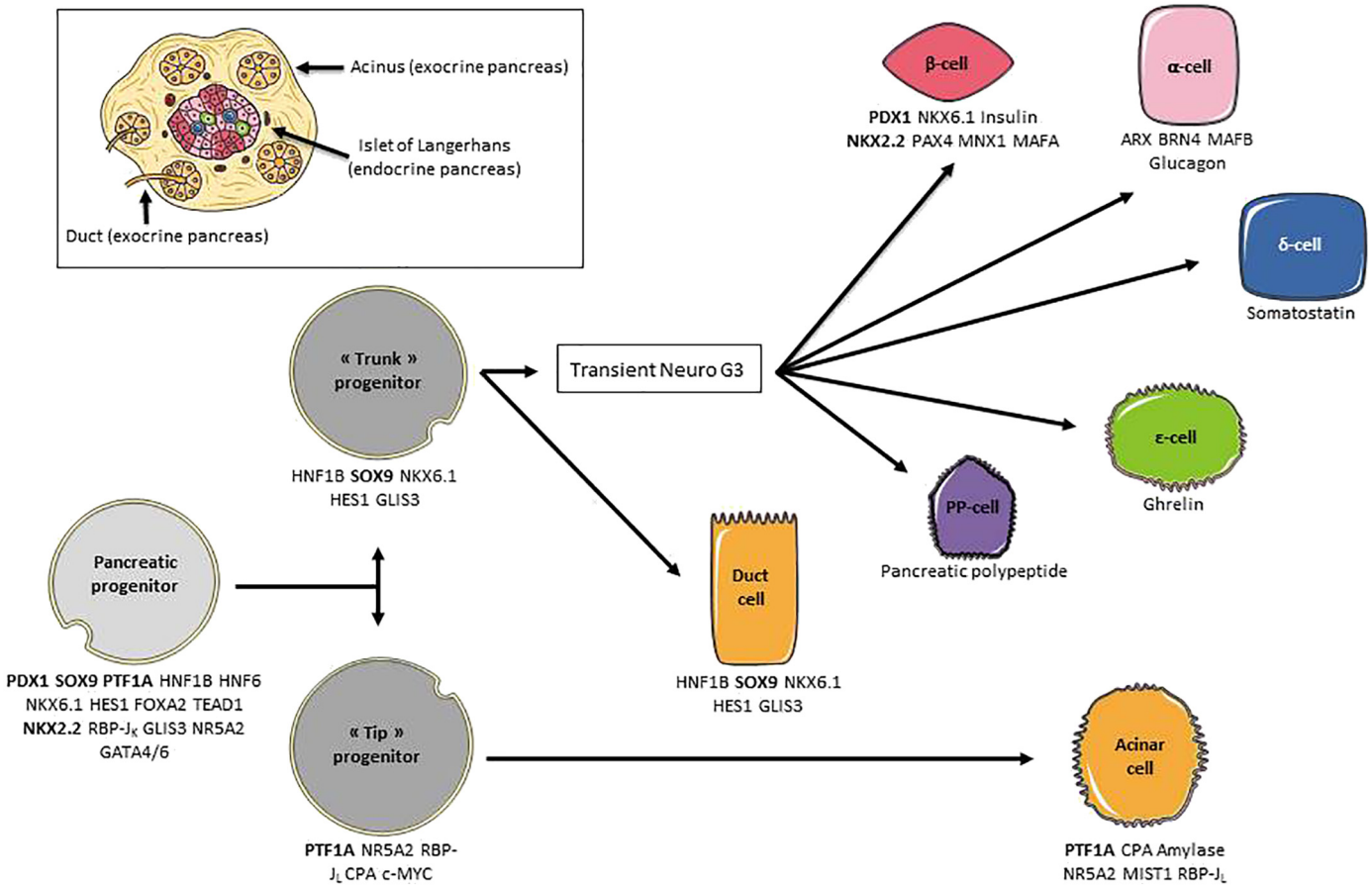

Fig. 1 Main transcription factors involved in pancreas development [5,6]. The undifferentiated PDX1+ pancreatic progenitors proliferate and differentiate into endocrine, ductal, and acinar cells, thanks to the expression of numerous transcription factors. Transcription factors in bold were used for this study.

Table 1 Antibodies

Antibodies	Clone	Company	Dilution
Antibodies for immunofluorescence			
Insulin	20056	Euromedex, Souffelweyerrsheim, France	1:1000
Glucagon	20076	Euromedex, Souffelweyerrsheim, France	1:1000
Pancreatic polypeptide	AB939	Chemicon International	1:1000
Somatostatin	A0566	Dako, Carpinteria, CA	1:500
Ghrelin	MAB 10404	Millipore, Billerica, MA	1:500
Amylase	A-8273	Sigma Aldrich, St. Louis, MO	1:300
EpCAM	VU1D9	Cell Signaling, Danvers, Mass	1:300
PDX1	–	INSERM U1016, Institut Cochin, Paris, France [8]	1:1000
SOX9	AB5535	Millipore, Billerica, MA	1:500
NKX2.2	74-5A5	Developmental Studies Hybridoma Bank	1:50
PTF1A	–	INSERM U671, IFR58, Institut Biomédical Des cordeliers, Paris, France [9]	1:1000
Antibodies for immunohistochemistry			
β-Catenin	ABC10-B016	AbCys Abcam, Cambridge, UK	1:300
Chromogranin A	M 0869	Dako, Carpinteria, CA	1:200
Synaptophysin	NCL-L-SYNAP-299	Novo, Leica Microsystems, Wetzlar, Germany	1:150
S100	Z0311	Dako, Carpinteria, CA	1:1000
GFAP	M0761	Dako, Carpinteria, CA	1:500
Calretinin	IS 627	Dako, Carpinteria, CA	1:50
ERα	SP1	Roche, France	–
PR	1E2	Roche, France	–
Cyclin D1	RM9104-S1	Thermo Scientific	1:20
MIB-1 (Ki-67)	M7240	Dako, Carpinteria, CA	1:100

cases, 1+; 1 case, 2+; 3 cases, 3+; 2 cases, 4+) and S100 in 2 cases (14%; score 1+ for the 2 cases). The proliferation index (MIB-1) was low in all cases, ranging from less than 5% to 10% of tumor cells. Diffuse and strong nuclear staining for cyclin D1 was noted in all cases, except for 1 tumor (case 5) in which the staining was focal and weak probably linked to alternative acidified formol alcohol fixative. In all cases, tumor cells were negative for PDX1, SOX9, PTF1A, NKX2.2, EPCAM (Fig. 3), insulin, glucagon, somatostatin, ghrelin, pancreatic polypeptide, amylase (Supplementary Fig. S1), chromogranin A, GFAP, calretinin, and ERα (ERα staining not performed in 1 case).

In the normal adjacent pancreas, all endocrine and exocrine cells had a membranous expression of β-catenin (Fig. 2) and EPCAM (Fig. 3). All acinar cells were positive for amylase and PTF1a (Fig. 3). All duct cells were positive for SOX9 (Fig. 3). All endocrine cells were positive for synaptophysin, chromogranin A, and PR. A few endocrine cells were positive for PDX1, NKX2.2 (Fig. 3), and ERα. The islets of Langerhans were positive for insulin, glucagon, ghrelin, somatostatin,

Table 2 Clinical data

Case	Sex	Age (y)	Location	Size (mm)	Surgery	Recurrence
1	M	12.9	Tail	55 × 30 × 60	Distal splenopancreatectomy	No
2	F	12.6	Head	25 × 30 × 30	Tumorectomy	No
3	F	10.5	Head	25	Tumorectomy	No
4	F	13.1	Head	120 × 60 × 60	Tumorectomy	Yes, hepatic hilum
5	F	13.1	Tail	110 × 110 × 60	Tumorectomy	No
6	M	11.3	Tail	70 × 50 × 60	Distal pancreatectomy	No
7	F	13.5	Head	100 × 80 × 60	Tumorectomy	No
8	F	13.1	Tail	100 × 70 × 60	Distal pancreatectomy	No
9	F	10.5	Tail	60 × 60 × 20	Distal pancreatectomy	Yes, pancreatic
10	F	9.4	Tail	70 × 50 × 60	Distal splenopancreatectomy	Yes, widespread peritoneal dissemination
11	F	16.6	Head	25	Cephalic duodenopancreatectomy	No
12	F	17.2	Head	35 × 35 × 8	Cephalic duodenopancreatectomy	No
13	F	7.8	Head	20 × 25 × 15	Cephalic duodenopancreatectomy	No
14	F	12.2	Tail	210 × 100 × 60	Distal pancreatectomy	No

Abbreviations: F, female; M, male.

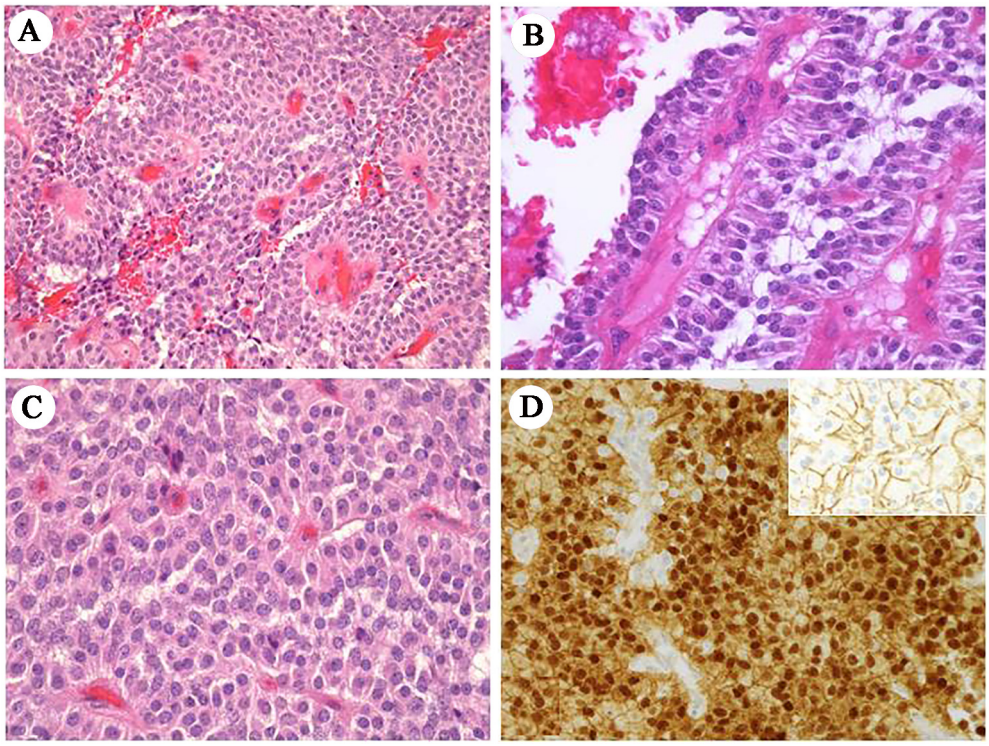

Fig. 2 Microscopic and immunohistochemical findings in SPNs of the pancreas. A and B, Pseudopapillary pattern: fibrovascular cores are surrounded by tumor cells arranged radially (hematoxylin and eosin, original magnifications ×100 [A] and ×200 [B]). C, Cells are monomorphic with eosinophilic cytoplasm and round-to-oval nuclei (hematoxylin and eosin, ×200). D, Nuclear positivity for β-catenin (×200). Note the membranous labeling of the normal pancreatic epithelial cells (inset).

and pancreatic polypeptide (Supplementary Fig. S1). A few nerves were positive for S100 and calretinin. No immunostaining was noted for GFAP.

There were no differences between men and women regarding histologic, immunohistochemical, and immunofluorescence features.

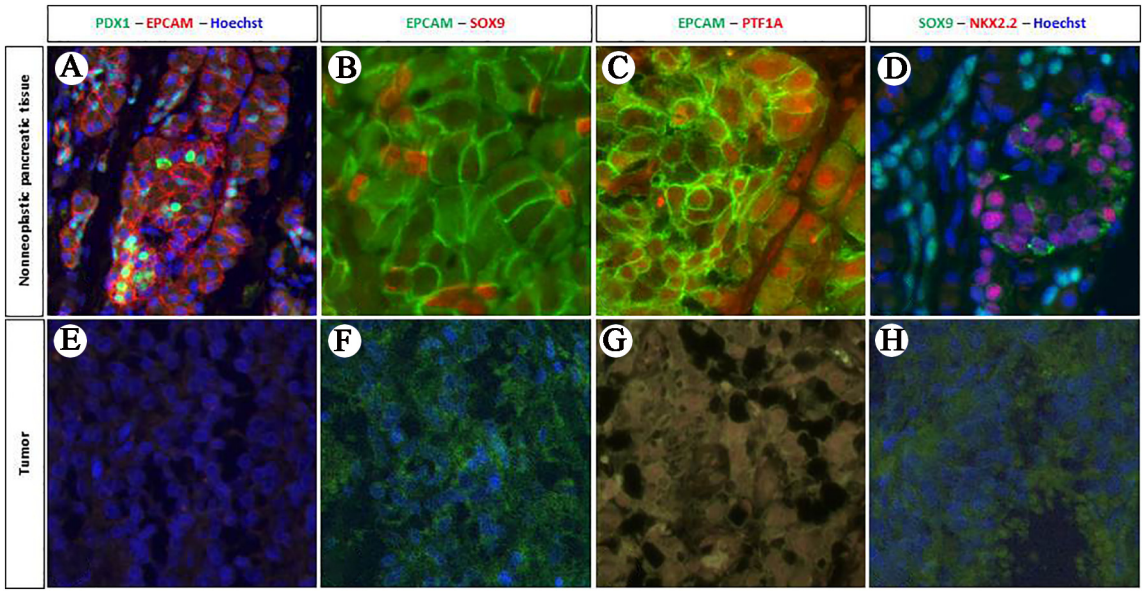

Fig. 3 Immunostaining for PDX1, SOX9, PTF1A, NKX2.2, and EPCAM in nonneoplastic pancreatic tissue (A–D) and SPN (E–H). PDX1 and NKX2.2 are expressed in normal endocrine cells in the islets of Langerhans (A and D), SOX9 in duct cells (B), and PTF1A in acinar cells (C). EPCAM is expressed on the membrane of all epithelial cells (A–C). SPN shows no immunoreactivity for PDX1, SOX9, PTF1A, NKX2.2, and EPCAM (E–F). Original magnifications, ×200 (A and E) and ×400 (B-D and F-H).

4. Discussion

Although SPNs arise mainly in the pancreas; no study has identified their nonneoplastic cell counterparts in the pancreas or has even proven their pancreatic origin. In this context, we examined the expression of 4 markers associated with pancreatic development: PDX1, SOX9, NKX2.2, and PTF1A. In our pediatric series, tumor cells did not express any of these markers, failing to precise pancreatic lineage of tumor cells. These markers have been considered previously as helpful to appreciate potential pancreatic lineage for some neoplasms: they are found to be expressed in pancreatic neuroendocrine neoplasms for PDX1 and NKX2.2 [10-12] and in pancreatic ductal adenocarcinomas for Sox9 [13].

Some authors have reported SPN morphologically and immunophenotypically similar to pancreatic SPN in other organs: ovary [14-19], testis [20], retroperitoneal space [15,21], mesocolon [22], and greater omentum [23]. None of the patients had a tumor in the pancreas. In ovarian [14] and testicular [20] SPN, a mutation in exon 3 of the *CTNNB1* (β-catenin) gene has also been reported. Interestingly, some authors suggested that SPN may derive from the genital ridges [24,25]. Indeed, genital ridges are very close to the pancreatic anlage during embryogenesis raising the possibility that cells from the primitive gonad may be incorporated into the embryonic pancreas.

In addition to PDX1, SOX9, NKX2.2, and PTF1A, we performed a large panel of immunohistochemical and immunofluorescence analyses. Our findings are consistent with the literature [1,26,27]: we found an immunoreactivity for β-catenin, cyclin D1, and PR in all cases; synaptophysin in 9 cases (64%); and S100 in 2 cases (14%), but no immunoreactivity for endocrine hormones, chromogranin A, exocrine enzymes, ERα, GFAP, calretinin, and EPCAM. EPCAM is a transmembrane glycoprotein previously demonstrated to mark fetal pancreatic epithelium [28] at early developmental stages with a sustained expression in adult human pancreas [29].

Over time, neuroendocrine, centroacinar/acinar [30,31], and ductal [32] origins have been postulated to explain the histogenesis of SPN. However, the SPN phenotype seems to differ too many from these lineages. (1) An expression of CD56 and synaptophysin is common in SPN, but a neuroendocrine origin remains unlikely considering the negativity for chromogranin A and endocrine hormones. (2) The markers α_1-antitrypsin, α_1-antichymotrypsin, CD10, cyclin D1, vimentin, NSE [31], and DOG1 [30] are expressed in SPN and in normal centroacinar cells of the pancreas. However, a recent study did not confirm the DOG1 immunoreactivity previously observed [33], and the weak/focal cytokeratin staining in SPN is not in favor of a centroacinar origin [26]. (3) Stains for acinar differentiation such as amylase, trypsin, and chymotrypsin are consistently negative [26]. (4) The marker galectin-3 was detected in a series of 5 cases of SPN and in normal ductal cells [32], but has yet to be confirmed by other studies. Other markers for ductal differentiation, such as B72.3, CA19.9 and carcinoembryonic antigen, are not found in SPN [26].

Molecular studies revealed new insights into the tumorigenesis of SPN but could not specify the exact origin of the tumor cells. SPNs are characterized by an important activation of the Wnt/β-catenin and Notch signaling pathways [2]. They present a decrease in endocrine and exocrine differentiations, attested by an important down-regulation of genes expressed in both the endocrine (glucagon, PPY2) and exocrine (PNLIPRP1, SERPINA3/SERPINA5, PTF1a) pancreas [2]. An up-regulation of different genes involved in neural crest specification and differentiation (SOX10, HAND2, EDN3, and the product of the class III β-tubulin gene) has been reported [2]. Some authors postulated a neural crest origin of SPN [2]. Lastly, Park et al [3] uncovered a down-regulation of micro-RNA families (miR-200 family and miR-192/215) related to an up-regulation of genes belonging to the epithelial-mesenchymal transition.

In conclusion, SPNs are uncommon low-grade malignant neoplasms with distinct clinicopathological features. In our pediatric series, SPN did not express major pancreatic developmental transcription factors (PDX1, SOX9, NKX2.2, and PTF1A), which does not allow for precise pancreatic lineage of tumor cells. Thus, additional studies are still required to determine the exact origin of SPN, which remains one of the most intriguing entities among pancreatic neoplasms.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2018.08.010.

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