

## ORIGINAL ARTICLE

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# Nuclear Expression of E-Cadherin in Solid Pseudopapillary Tumors of the Pancreas

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### ABSTRACT

**Context** Solid pseudopapillary tumors of the pancreas are rare and have recently been shown to harbor mutations of the *beta-catenin* gene with resultant nuclear localization of beta-catenin protein to the nucleus. Moreover, there is a close relationship between beta-catenin and E-cadherin.

**Objective** To explore the protein expression of E-cadherin in a series of solid pseudopapillary tumors of the pancreas.

**Participants** Eighteen cases of solid pseudopapillary tumors of the pancreas.

**Design** The cases were studied using a tissue microarray that was constructed as follows: for each case, 4 to 14 cores measuring 1.0 mm each were drilled from the blocks. Tissue cores from normal pancreas were used as controls and for orientation purposes.

**Main outcome measures** The slides were stained with the following commercially available antibodies: CD10, CD56, vimentin, alpha-1-antitrypsin, alpha-1-antichymotrypsin, neuron-specific enolase, chromogranin, synaptophysin, beta-catenin and E-cadherin.

**Results** All the tumors were CD10, vimentin, alpha-1-antitrypsin and alpha-1-antichymo-

trypsin diffusely positive (50% or more of the tumor cells staining) and CD56 showed focal positivity in all cases with 5-10% of tumor cells displaying immunolabeling. All cases were negative for chromogranin and synaptophysin. All 18 cases displayed cytoplasmic and nuclear localization of beta-catenin protein. Similarly, E-cadherin protein was localized to the nucleus in all 18 cases, with loss of the characteristic membranous decoration of cells.

**Conclusion** This study is the first demonstration of aberrant nuclear localization of E-cadherin protein in solid pseudopapillary tumors of the pancreas. Whilst the exact mechanism is not known and nuclear E-cadherin is not related to tumor aggression, this staining pattern may be of diagnostic value in concert with beta-catenin staining.

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### INTRODUCTION

Decrease in or loss of E-cadherin is considered a molecular event signaling dysfunction of the cell-cell adhesion system, thereby triggering invasion and metastasis in many malignancies. In addition, alterations in the cadherin-catenin system may also be involved in tumorigenesis. E-cadherin and beta-catenin, components of the Wnt signal

transduction pathway, may serve as a common switch in central processes that regulate cellular differentiation and growth. Abnormalities of expression of beta-catenin protein and in the gene have been reported in solid pseudopapillary tumors (SPT) of the pancreas, and are considered a recurring, consistent finding associated with these lesions [1, 2]. SPT are rare neoplasms with a low malignant potential occurring most frequently in young women. Histologically, it is a solid and cystic tumor with a prominent vascular network and degenerative pseudopapillae [3]. Often times they may resemble endocrine tumors of the pancreas very closely because of the vascular network and relatively uniform cytological appearance. These tumors are composed of small uniform cells with nuclei that can show grooves and irregular contours.

The neoplastic cells in SPT are consistently vimentin, CD10 and CD56-positive and nuclear beta-catenin expression is also a well-recognized feature. Some cases express focal positivity for alpha-1-antitrypsin, alpha-1-antichymotrypsin, neuron-specific enolase and synaptophysin.

In view of the association between E-cadherin and beta-catenin, the purpose of this study was to examine expression of E-cadherin in a series of SPT using a tissue microarray and to

correlate immunoexpression with clinicopathological parameters.

## MATERIALS AND METHODS

Eighteen cases of SPT of the pancreas were utilized for tissue microarray analysis (TMA): 10 were retrieved from the archives of the Department of Pathology, University Health Network, Toronto, and 8 from the Department of Pathology, McMaster University, Hamilton.

### Tissue Microarray Analysis Construction

For each case, 4 to 14 cores measuring 1.0 mm each were drilled from the blocks. Tissue cores from normal pancreas were used as controls and for orientation purposes.

Size of tumor, necrosis, gross invasiveness/demarcation, lymphovascular invasion, lymph node involvement and liver metastasis were recorded. The mitotic count, expressed per 10 high powered fields (HPFs) was assessed.

### Immunohistochemistry

All the TMA blocks were stained with a panel of antibodies used in the routine work-up of SPTs, in addition to including beta-catenin

**Table 1.** Antibodies used.

Antibody	Source	Dilution	Retrieval method	Clone
CD10	Ventana, Tucson, AZ, USA	Prediluted	Heat <sup>a</sup>	56C6
Vimentin	American Research Products, Belmont, MA, USA	1/1,200	Protease	VIM3B4
alpha-1-antitrypsin	Ventana, Tucson, AZ, USA	Prediluted	Heat <sup>a</sup>	Polyclonal
alpha-1-antichymotrypsin	Dakocytomation, Glostrup, Denmark	Prediluted	Heat <sup>a</sup>	Polyclonal
CD56	Zymed, Carlsbad, CA, USA	1/100	Heat <sup>a</sup>	123C3
Neuron-specific enolase	Dakocytomation, Glostrup, Denmark	1/100	No retrieval	Polyclonal
Chromogranin	Ventana, Tucson, AZ, USA	Prediluted	No retrieval	Monoclonal
Synaptophysin	Dakocytomation, Glostrup, Denmark	1/100	No retrieval	Monoclonal
beta-catenin	BD-Transduction Laboratories, Franklin Lake, NJ, USA	1/3,000	Heat (Microwave)	14
E-cadherin	BD-Transduction Laboratories, Franklin Lake, NJ, USA	1/2,000	Heat (Microwave)	36

<sup>a</sup> BenchMark<sup>®</sup>, Ventana Medical System, Inc., Tucson, AZ, USA.

and E-cadherin which form the main thrust of this study (Table 1). Tissue sections were cut using sterile disposable microtome blades on a rotary microtome. They were floated on a water bath (50°C) and picked up on poly-L-lysine coated glass slides. The sections were baked on a hot plate at 60°C for 20 minutes. Deparaffinization was carried out in 2 changes of xylene for 5 minutes each. This was followed by rehydration in 2 changes of absolute ethanol for 3 minutes each and 2 changes of 95% ethanol for 3 minutes each before a stay of 5 minutes under running tap water. For the antibodies requiring microwave heat retrieval, the sections were processed to unmask antigens by conventional microwave heating in 0.01 M sodium citrate retrieval buffer (Table 1). The other heat retrieval method is indicated in Table 1.

Appropriate positive controls (cases known to be positive for all antibodies used in the study) were run in parallel. SPTs were regarded as positive for a particular antibody if the tumor cells displayed a similar staining pattern and intensity as the known positive control. Specifically, membranous immunoreactivity for E-cadherin/beta-catenin was considered normal; any reduction or loss of this pattern of immunoreactivity compared to normal tissue, together with nuclear and/or cytoplasmic staining was considered as abnormal immunoreexpression.

## ETHICS

Written informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the "World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18<sup>th</sup> WMA General Assembly, Helsinki, Finland, June 1964, as revised in Tokyo 2004, as reflected in a priori approval by the appropriate institutional review committee.

## STATISTICS

Means, ranges, and frequencies were evaluated as descriptive statistics. The Mann-Whitney U-test was applied to compare cases with and without metastases. Two-tailed P values less than 0.05 were considered significant. Data were analyzed by using the SPSS for Windows (version 13.0) package.

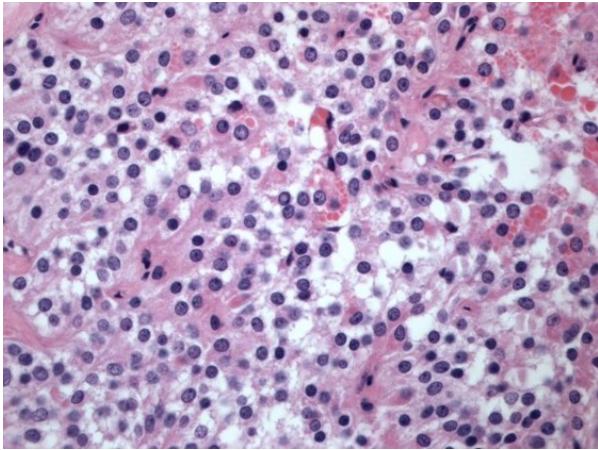
## RESULTS

Patient and tumor characteristics of the 18 cases of solid pseudopapillary tumor of the pancreas are shown in Table 2. Sixteen of the 18 cases were in female patients, 2 were males, ranging in age from 11 to 62 years (average: 38.0 years). Fifteen tumors arose in the tail/body of the pancreas, while 3 (16.7%)

**Table 2.** Patient and tumor characteristics of the 18 cases of solid pseudopapillary tumor of the pancreas.

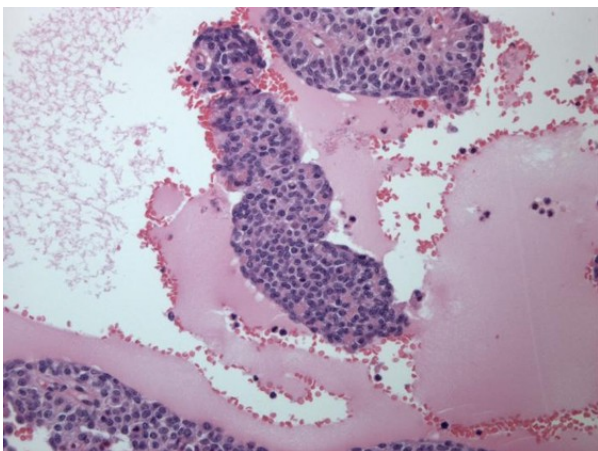
ID	Sex	Age (years)	Size (cm)	Location	Metastases
1	F	32	5.2	Head	Liver <sup>a</sup>
2	F	40	6.8	Tail	No
3	F	45	5.5	Body, tail	No
4	F	39	3.5	Head, body	No
5	F	24	4.5	Head	No
6	F	31	8.8	Tail	No
7	F	43	4.0	Tail	No
8	M	45	3.5	Tail	No
9	F	39	3.2	Tail	No
10	F	20	3.1	Body	Liver
11	F	43	13.0	Tail	Liver
12	F	39	6.3	Tail	No
13	F	11	8.0	Body, tail	No
14	F	61	9.0	Tail	Liver
15	M	62	17.0	Body, tail	No
16	F	40	4.5	Tail	No
17	F	52	2.0	Body	No
18	F	19	5.3	Body	No

<sup>a</sup> This patients had a liver recurrence one year later after the resection of the primary tumor.

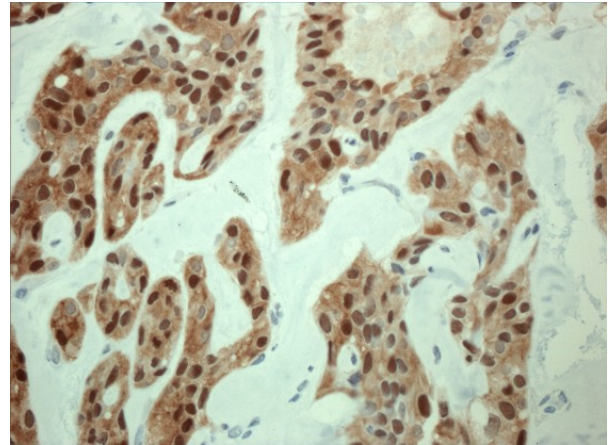


**Figure 1.** High power illustration of the cytology of a solid pseudopapillary tumor with clear cells, many of which contain indented and irregularly shaped nuclei (H&E x400).

were located in the head. The size of SPT ranged from 2 to 17 cm, with a mean size of 6.3 cm. Four cases (22.2%) had synchronous liver metastases; in addition one patient had a liver recurrence one year later after the resection of the primary tumor. All the tumors were macroscopically well circumscribed, but unencapsulated. On sectioning, they displayed solid areas with focally hemorrhagic and uni- or multilocular cystic spaces, filled with fluid ranging from straw- to red-colored. Histologically, all SPT studied showed a proliferation of uniform neoplastic cells arranged in sheets, nests and cords and characterized by eosinophilic and cytoplasmic vacuoles that sometimes indented grooved and vesicular nuclei (Figure 1). Nucleoli were



**Figure 2.** The typical appearance of pseudo-papillary structures where the cells have lost cohesion (H&E x200).



**Figure 3.** Intense nuclear labeling for beta-catenin (anti-beta-catenin x400).

inconspicuous. Periodic acid Schiff (PAS) and PAS following diastase digestion (PASD) positive hyaline globules were variably found in the cytoplasm and/or in the intercellular spaces. The mitotic activity was minimal and abnormal figures were not discerned. The average mitotic count was 1 mitotic figure per 10 HPF (range: 0-3) across all tumors. Degenerative changes were variably present and pseudo-papillae consisted of a fibrovascular core lined by poorly cohesive neoplastic cells (Figure 2). Cholesterol clefts, foamy macrophages and foreign body giant cells were seen. In areas of hemorrhage there was degeneration and deposition of hemosiderin. Although tumors are well demarcated from the surrounded pancreas, a true capsule was lacking and small projections of the tumor extended into the normal pancreatic parenchyma in a smooth, non-infiltrative manner. Lymphovascular or lymph node involvement was not seen in any case.

### Immunohistochemistry

Immunohistochemical results are shown in Table 3. All 18 cases contained 50% or more of tumor cells that were CD10 (cytoplasmic and often dot-like) (mean: 61.4%, range 50-75%), vimentin (mean: 63.2%, range 55-75%; 17 cases were available), alpha-1-antitrypsin (mean: 61.7%, range 55-70%) and alpha-1-antichymotrypsin (mean: 63.3%, range 55-80%) positive. At least focal positivity was

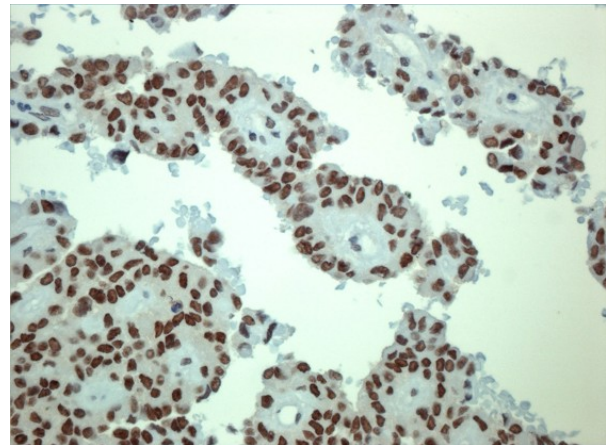


seen in all cases for CD56 and the range of immunopositivity was from 5 to 10% of tumor cells labeling (mean 7.8%). NSE staining was cytoplasmic (mean: 7.8%, range 5-15%). All cases were negative for chromogranin and synaptophysin.

All 18 cases displayed complete loss of membrane expression for beta-catenin; only cytoplasmic and nuclear localization of the protein was present in all tumor cells (Figure 3).

Similarly, E-cadherin protein was localized to the nucleus in all 18 cases, with loss of the characteristic membranous decoration of cells (Figure 4).

There was no significant differences in the immunohistochemical results between the 4 cases with metastases and those that were confined to the pancreas (CD10, P=0.128: mean 57.5%, range 55-60% vs. mean 62.6%, range 50-75%; vimentin, P=0.776: mean 61.7%, range 60-65%, n=3 vs. mean 63.6%, range 55-75%; alpha-1-antitrypsin, P=0.827: mean 61.3%, range 55-70% vs. mean 61.9%, range 55-70%; alpha-1-antichymotrypsin, P=0.661: mean 62.5%, range 55-80% vs. mean 63.6%, range 55-75%; neuron-specific



**Figure 4.** The tumour cells in solid pseudopapillary tumor show loss of membrane staining for E-cadherin; instead E-cadherin is now located in the nucleus (anti-E-cadherin x400).

enolase, P=0.633: mean 8.8%, range 5-15% vs. mean 7.5%, range 5-15%) a part from CD56 that was significantly (P=0.020) higher in metastases cases (mean 8.8%, range 5-10% vs. mean 5.7%, range 5-10%). The significance of CD56 staining lesions that metastasize is conjectural but may serve as a marker for lesions with metastatic potential. However, more cases need to be examined to validate this.

**Table 3.** Immunohistochemical results.

ID	CD10 (%)	Vimentin (%)	a1-AT (%)	a1-AC (%)	CD56 (%)	NSE (%)	beta-catenin	E-cadherin
1	60	60	55	55	10	5	Nc/Ct	Nc
2	60	60	56	70	5	5	Nc/Ct	Nc
3	60	60	60	55	5	10	Nc/Ct	Nc
4	75	60	60	70	5	5	Nc/Ct	Nc
5	60	55	65	75	5	10	Nc/Ct	Nc
6	75	60	55	60	10	5	Nc/Ct	Nc
7	60	60	55	60	5	5	Nc/Ct	Nc
8	60	70	60	55	5	10	Nc/Ct	Nc
9	75	70	60	75	5	10	Nc/Ct	Nc
10	60	65	60	80	10	15	Nc/Ct	Nc
11	55	60	60	55	5	5	Nc/Ct	Nc
12	55	60	55	75	5	5	Nc/Ct	Nc
13	50	75	70	65	5	15	Nc/Ct	Nc
14	55	-	70	60	10	10	Nc/Ct	Nc
15	66	60	65	55	5	10	Nc/Ct	Nc
16	60	60	70	60	5	5	Nc/Ct	Nc
17	60	70	70	60	10	5	Nc/Ct	Nc
18	60	70	65	55	5	5	Nc/Ct	Nc

a1-AT: alpha-1-antitrypsin

a1-AC: alpha-1-antichymotrypsin

NSE: neuron-specific enolase

Nc: nuclear

Ct: cytoplasmic

## DISCUSSION

SPT is a rare pancreatic tumor, constituting 1-2% of exocrine pancreatic tumors and about 5% of cystic pancreatic tumors, and its origin is still unresolved and controversial although a ductal origin has been favoured [3]. Although, it is a low-grade malignant tumor with a good prognosis after surgical excision, widespread liver metastases and vascular invasion have been reported [4], but invasion into surrounding organs such as the spleen and duodenum is rare [3].

Histologically, it is quite characteristic if not diagnostic, in most cases, however, there are variants such as the predominantly solid cases and even a clear cell variant that may cause mimicry of other tumours [5].

SPT is consistently immunoreactive for CD10, vimentin and CD56 and, frequently so for alpha-1-antitrypsin and alpha-1-antichymotrypsin. Sometimes immunoreactivity for synaptophysin is seen.

E-cadherin and beta-Catenin, two key components of the Wnt signal transduction pathway, are involved in cellular differentiation and growth [6]. The *E-cadherin* gene (*CDH 1*) is located at locus 16q22.1 and produces a 120 kDa protein. E-cadherin localizes to zonula adherens junctions that are adherens junctions typically seen in epithelial cells. Normal E-cadherin expression plays a key role in the maintenance of epithelial integrity and polarized function [7, 8]. Reduced E-cadherin expression was shown to promote epithelial cell invasiveness, dedifferentiation and metastases in various human carcinomas, supporting a role for this protein as an "invasion suppressor molecule" [9, 10, 11].

E-cadherin is a calcium-dependent transmembrane glycoprotein, involved in the cell-cell interaction and is localized to the basolateral surface of the epithelial cells. It has a cytoplasmic domain, a single-pass transmembrane domain and an extracellular domain that consists of five tandemly-repeated cadherin-motifs sub-domains with putative calcium binding sites. The

extracellular N-terminal end is essential for the homophilic calcium-dependent cell-cell adhesion [12]. Although cadherin binding is not a direct activator of Wnt-Wingless signal transduction, recently it has been demonstrated that classical cadherins do function as receptors in GTPase signaling [13, 14]. In particular, the small GTPases of the Rho family have been identified as part of a membrane-local signaling process that regulates cell actin dynamics, cell motility and adherens junction assembly in response to cadherin adhesion [15, 16]. It is thought that cadherin adhesion may influence the precise sites at the plasma membrane where Rho family signaling occurs. Thus, the loss of cadherin-mediated cell-cell adhesion is an important event that has many far-reaching consequences for the acquisition of the invasive phenotype and tumour progression.

The cytoplasmic domain of E-cadherin interacts with the catenin molecules that mediate its binding to the actin cytoskeleton. E-cadherin binds to either beta-catenin or gamma-catenin, but not to alpha-catenin [12]. Reduction in cell adhesion is considered a pivotal step in tumor metastasis and may be achieved by several mechanisms involving the E-cadherin-catenin complex, including the reduction or loss of E-cadherin expression, mutation or reduced transcription of the genes of the constituent molecules, redistribution of E-cadherin to different sites within the cell, shedding of E-cadherin, and competition for binding sites from other proteins [12].

beta-catenin is an integral component of the E-cadherin complexes at intercellular adherens junctions, and also recruits chromatin-remodeling complexes to activate transcription in the nucleus. The cytoplasmic tail of E-cadherin protein binds to beta-catenin that in turn complexes with alpha-catenin to form the E-cadherin-catenin unit.

The presence of some tumours with normal expression of beta-catenin but abnormalities of E-cadherin may suggest that E-cadherin dysregulation may also be independent of beta-catenin. Alterations of E-cadherin are more frequently seen than those of beta-

catenin in tumours in general, but there still appears to be a correlation between the two proteins.

Recently, nuclear beta-catenin has been found to be present in all reported cases of SPT [2] and has been associated with activating mutation, (34)Gly(GGA) to Arg(AGA), in exon 3 of the *beta-catenin* gene [2, 17].

All the tumors in our series showed cytoplasmic and nuclear immunoreactivity for beta-catenin. In addition, we found, and report for the first time, that SPT also displayed consistent nuclear localization of E-cadherin protein associated with a concomitant loss of membrane staining of E-cadherin. Built-in positive control of normal ducts and pancreatic parenchyma still showed prominent membrane decoration with E-cadherin.

Although E-cadherin does not contain any identifiable nuclear localization signal sequence, the cleaved or short fragment of E-cadherin can translocate to the nucleus.

The exact mechanism by which E-cadherin is over-expressed, stabilized or translocates to the nucleus is not clear. One possibility is that the cleaved E-cadherin, which normally is degraded by proteasome degradation, due to abnormality in the proteosomal pathway accumulates and subsequently translocates to the nucleus where it might participate in regulation of gene expression. Other studies suggest that E-cadherin modulates Wnt-dependent gene expression by regulating the availability of beta-catenin [18]. In malignant melanoma loss of E-cadherin leads to upregulation of NF-kappa beta activity [19]. E-cadherin dependent cell-cell adhesion has been shown to control the nuclear abundance of the nuclear transcription factors such as apolipoprotein A-IV [19]. Cell-matrix and cell-cell adhesion play a central role in the control of cell proliferation, differentiation, and gene expression and E-cadherin appears to play a key role in these processes in epithelial cells. Some studies suggest that loss of E-cadherin expression does not induce Wnt signaling, while in other studies a role of E-cadherin in modulation of Wnt-dependent

gene expression has been suggested [19, 20, 21].

In view of the close association between beta-catenin and E-cadherin, we speculate that the nuclear localization of E-cadherin is related to beta-catenin abnormalities in SPT. Given that *beta-catenin* gene abnormalities are common in SPT, it is possible that the E-cadherin-catenin unit is perturbed by such mutations leading to loss of E-cadherin function. Although E-cadherin has a role in both tumour and invasion suppression, its nuclear localization in SPT is not correlated with metastasis.

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**Keywords** Cadherins; Pancreas; Pancreatic Neoplasms

**Abbreviations** SPT: solid pseudopapillary tumor; TMA: tissue microarray analysis

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