Expression of Wnt target genes in solid pseudopapillary tumor of the pancreas

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Expression of Wnt target genes in solid pseudopapillary tumor of the pancreas

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David said to Goliath, “I come to you in the name of the Lord.”

– 1 Samuel 17:45

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< ABSTRACT>

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Solid pseudopapillary tumor (SPT) of the pancreas is very rare, which has indolent behavior, favorable prognosis, and predilection for young women. However, the clinical course after complete tumor resection is known to be unpredictable. This study was performed to analyze the expression of Wnt target genes (MMP-7, cyclin-D1, c-myc) and Ki-67 in resected SPTs of the pancreas by immunohistochemistry and to determine clinicopathologic characteristics of SPT of the pancreas according to their expression. In twelve resected SPTs, immunohistochemistry was performed to detect Wnt target genes and Ki-67. All SPTs of the pancreas showed cytoplasmic/nuclear accumulation of β-catenin, frequent expression of cyclin-D1 and low proliferation index. However, the expression of MMP-7 and c-myc was unevenly expressed. Tumor size was closely related to microscopic feature of malignant potential and apparently have inverse relationship with expression of cyclin-D1 and Ki-67 ($p<0.05$). Very low proliferative index and associated MMP-7 expression may cause clinical unpredictable

course in this tumor. Subtle changes in the intracellular environment, not pathologic (morphologic) changes, may elucidate the unpredictable clinical course of SPT of the pancreas in near future.

Key words: solid pseudopapillary tumor, Wnt, β-catenin, MMP-7, cyclin-D1, c-myc, Ki-67, immunohistochemistry

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I. INTRODUCTION

Solid pseudopapillary tumor (SPT) of the pancreas is a very uncommon pathologic condition that accounts for just 0.17% to 2.7% of all pancreatic neoplasms[1-4]. Increasing numbers of case reports and literatures about SPT of the pancreas have been published recently. This may be the result of greater awareness of this unfamiliar disease entity, as well as a better understanding of this pathologic condition since this tumor was included in the World Health Organization's classification of pancreatic neoplasms in 1996[5,6]. We also have serially published clinical reports that include long-term follow-up after surgical resection in order to more precisely understand this tumor[7-9].

SPT of the pancreas is well known for its indolent behavior, favorable prognosis, and predilection for young women. Despite large tumor size at the time of diagnosis, surgical resection is usually curative[3, 10]. However, there are several issues that remain

to be solved. First, the pathogenesis of the tumor is unclear. Acinar[11], centriacinar[12], ductal[11], endocrine[13,14], multipoint primordial cells[15,16] and neurocrest origins[17] have been proposed, but the exact histogenesis of this tumor has yet to be determined. Second, the clinical course after complete tumor removal is unpredictable. No reliable pathologic factors that are predictive of prognosis have been identified[5, 18, 19]. It has been suggested that pathologic features like perineural and vascular invasion, a high degree of cellular pleomorphism, an elevated mitotic rate, lymph node metastasis, and pancreatic parenchyma and capsular invasion are associated with metastasis and recurrence (malignancy)[1,7,20-22]. However, these findings are known to be relatively nonspecific; in the absence of the aforementioned features, recurrence and metastasis cannot be completely excluded[19]. To complicate matters further, long-term survival has been observed with recurrence and metastasis[23, 24]. In our previous report[7], survival and prognosis of SPT of the pancreas with malignant potential were not different from SPT without malignant potential. This means that pathologic changes that suggest malignant potential may fail to discriminate between the prognosis of benign and malignant clinical evolution postoperatively. This unpredictable clinical feature of SPT of the pancreas is very important to surgeons who administer proper surgical management and regular follow-up thereafter.

It is necessary to understand the reasons for unpredictable clinical behavior of SPT of the pancreas, and, if possible, to select the

patients who need more careful follow-up with regard to recurrence and metastasis postoperatively.

Recently, Wnt signal expression, mostly associated with β-catenin mutations, has been suggested to play a major role in the tumorigenesis of SPTs[25, 26]. Therefore, this study was performed to analyze the expression of Wnt signal target genes (MMP-7, cyclin-D1, c-myc) and Ki-67 in resected SPTs of the pancreas by immunohistochemistry and to correlate clinicopathologic features with their genes expressions.

II. MATERIALS AND METHODS

From January 1995 to December 2005, 23 patients underwent pancreatic resections for SPT of the pancreas in the Department of Surgery, Yonsei University Health System, Seoul, Korea. Clinical information was obtained from our institutional SPT database. There were 18 female and five male patients with a median age of 32 years (range 17-59 years). Among 23 formalin-fixed, paraffin-embedded tissues, only 21 tissue blocks were available for this study. Six cases were SPT with malignant potential (group Tmp) as defined in our previous reports[7], and the other 15 were SPT without microscopic changes suggesting malignant potential (group T). All six tissue blocks of patients in group Tmp were studied, along with six randomly selected tissue blocks from group T. The formalin-fixed and paraffin-embedded tissue was studied in routine diagnosis with hematoxylin and eosin. Immunohistochemistry was performed using various detection and antigen retrieval methods in order to detect MMP-7, cyclin-D1, c-myc, and Ki-67 (Table 1). To evaluate the immunohistochemical results of MMP-7, cyclin-D1, and c-myc, the amount of reactive cells and intensity of the reactions were taken into account (-; negative, +/-; weak, +; strong). The following scoring system was used for Ki-67 evaluation: 0%, 1-2%, 2-5%, and 5-10%. Results of immunohistochemical staining and clinicopathologic variables were correlated. The chi-squared test (Fisher's exact test, linear by

linear association) was used to analyze the relationship between tumor groups (Tmp /T), tumor size, MMP-7, cyclin-D1, c-myc, and Ki-67. A P value of <0.05 was considered statistically significant. Statistical analyses were performed with SPSS version 10.0 (Chicago, USA)

Table 1. List of antisera

Antibody	Origin & Catalogue number	Source	Dilution factor	Antigen retrieval method
ß-catenin	Lab Vision, RB9035	Rabbit	1:500	HIER, Citrate buffer (pH 6.0)
Cyclin-D1	Lab Vision, RB9104	Rabbit, monoclonal	1:50	HIER, Tris buffer (pH 9.0)
c-myc	SantaCruz, sc764	Rabbit, polyclonal	1:200	No treatment
MMP-7	Calbiochem, IM71T	Mouse, monoclonal	1:400	No treatment
Ki-67	DAKO, M7240	Mouse, monoclonal	1:100	HIER, Tris buffer (pH 9.0)

HIER; heat induced epitope retrieval

III. RESULTS

1. Clinical characteristics of patients with SPT of the pancreas

Twelve patients and their tissue samples were included in this study. There were three male patients and nine female patients with a median age of 33.5 years (range 17-57). Eight patients had tumors that were found in the body and tail of the pancreas. Therefore, distal pancreatectomy with or without splenectomy was the most common surgical procedure (6 out of 12 patients). One patient had simultaneous hepatic metastasis, which required a concomitant resection of segment 6 of the liver (S6). Microscopic resection-margin positive status was reported in three patients; however, no additional treatments were given. The median follow-up period for all twelve patients was 41.5 months (range 24-157). No patients showed evidence of tumor recurrence. Clinical information, such as symptoms, tumor size, microscopic features suggesting malignant potential, margin status, and follow-up period, are described in Table 2.

Table 2. Patient characteristics and clinical information

No.	Gender	Age (yr)	Symptom	Size (cm)	Location	Op.	Malignant Potential	Margin	Follow up (Month)	Current Status
1	F	28	back pain	4.7	tail	DP S6	peripancreatic tissue invasion & liver metastasis	-	38	DF
2	F	43	indigestion	6	head	PPPD	peripancreatic tissue invasion & perineural invasion	+	42	DF
3	F	42	No	10	tail	DP	focal pericapsular extension	-	41	DF
4	M	57	No	6	head	PPPD	capsular invasion	-	39	DF
5	M	39	No	10	tail	DP	parenchymal focal invasion	+	137	DF
6	F	17	abdominal discomfort	6	head	En	peripancreatic tissue invasion	-	157	DF
7	F	19	abdominal discomfort	5	tail	DP		-	94	DF
8	F	30	No	3	body	En		-	49	DF
9	M	41	No	2.5	tail	DP		-	43	DF
10	F	25	No	4	tail	DP		-	26	DF
11	F	19	abdominal discomfort	3.5	body	MP		+	25	DF
12	F	37	No	3	head	En		-	24	DF

Op, operation; F, femal; M, male; DP, distal pancreatectomy; S6, VI segmentectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; En, enucleation; MP, median pancreatectomy; DF, disease-free survival.

2. Wnt target genes and Ki-67 expression in SPT of the pancreas

All SPTs of the pancreas showed cytoplasmic and nuclear accumulation of β-catenin, frequent expression of cyclin-D1 and very low proliferation index. The β-catenin accumulation in the cytoplasm and particularly in the nucleus was observed in all tumors (Fig. 1). Ten tumors (83.3%) strongly expressed cyclin-D1, and the remaining two tumors had decreased expression of cyclin-D1 (Fig. 2). MMP-7 was detected in seven tumors (58.3%), and c-myc was detected in eight (66.6%) (Fig.3,4). The Ki-67 proliferative index was very low. Ki-67 expression less than 5% was observed in eleven patients. Among those, none expression of Ki-67 was noted in three patients (Fig. 5, Table 3).

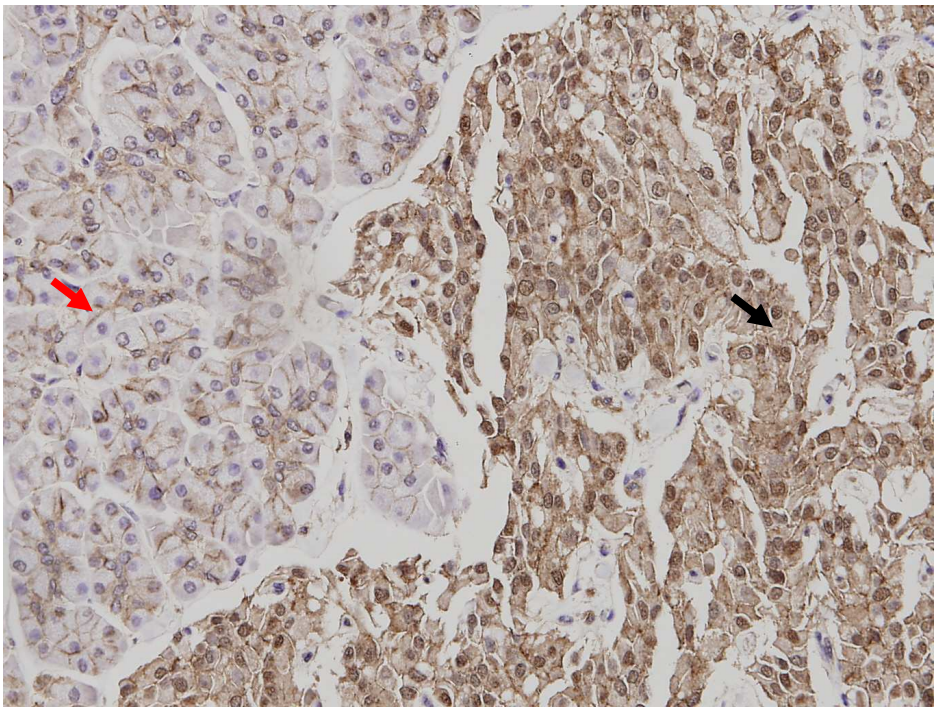

Figure 1. Expression of β-catenin, x200

All SPTs of the pancreas showed abnormal nucleus/cytoplsmic accumulation of β-catenin in tumor cells (black arrow). Note intercellular staining of β-catenin in normal pancreatic acinar cells (red arrow)

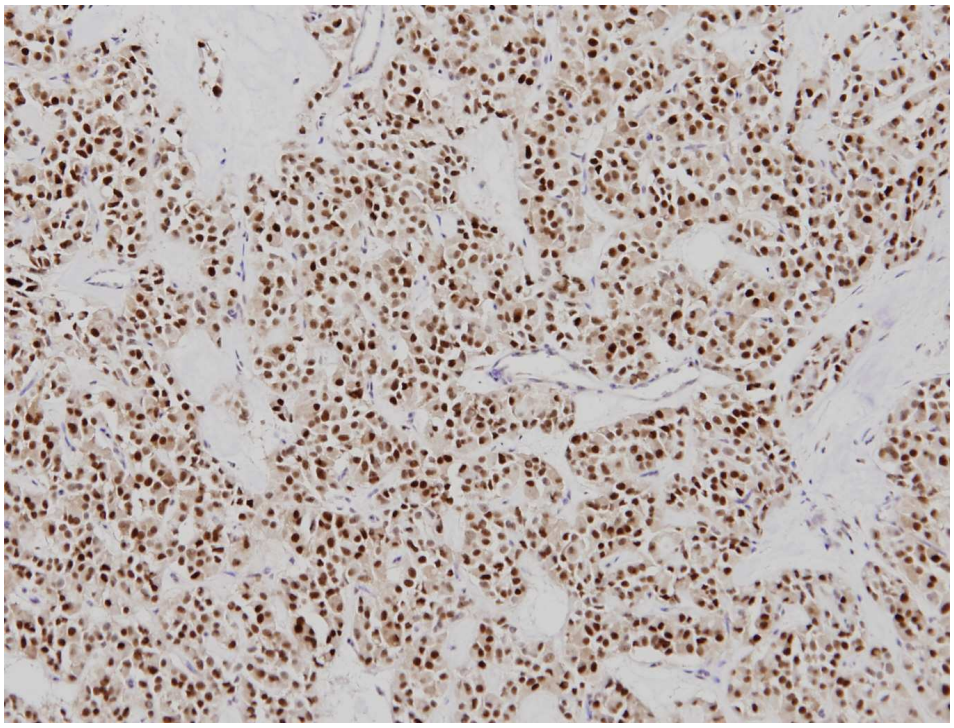

Figure 2. Expression cyclin-D1, X100

Frequent over-expression of cyclin-D1 was found in SPT of the pancreas. Note nuclear dense staining of cyclin-D1 in tumor cells.

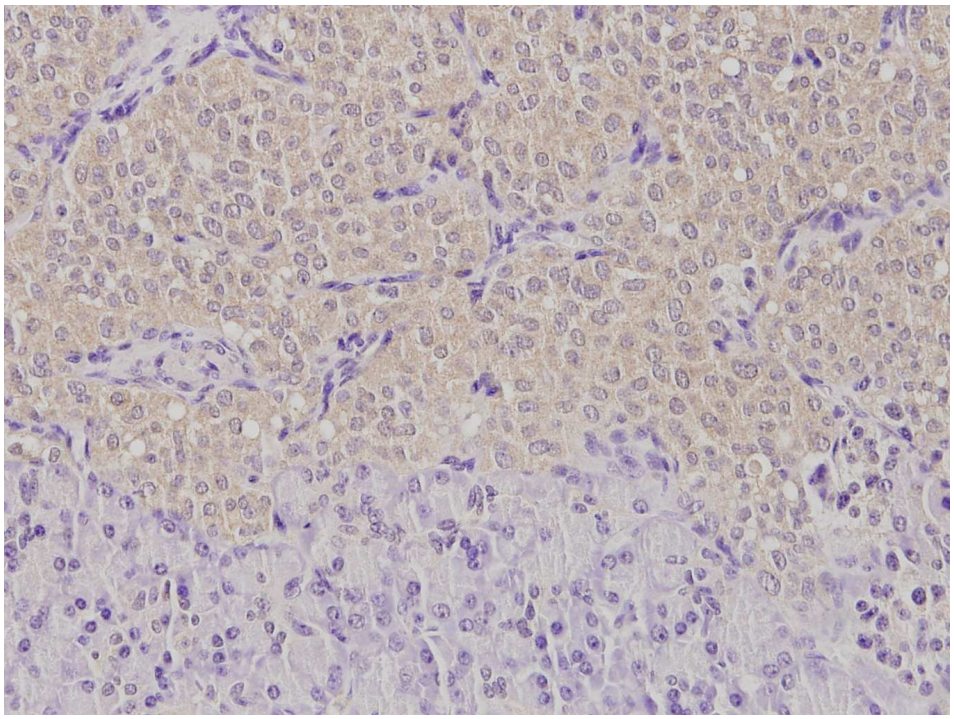

Figure 3. Expression of MMP-7, x200

Cytoplasmic MMP-7 expression was found in SPT of the pancreas.

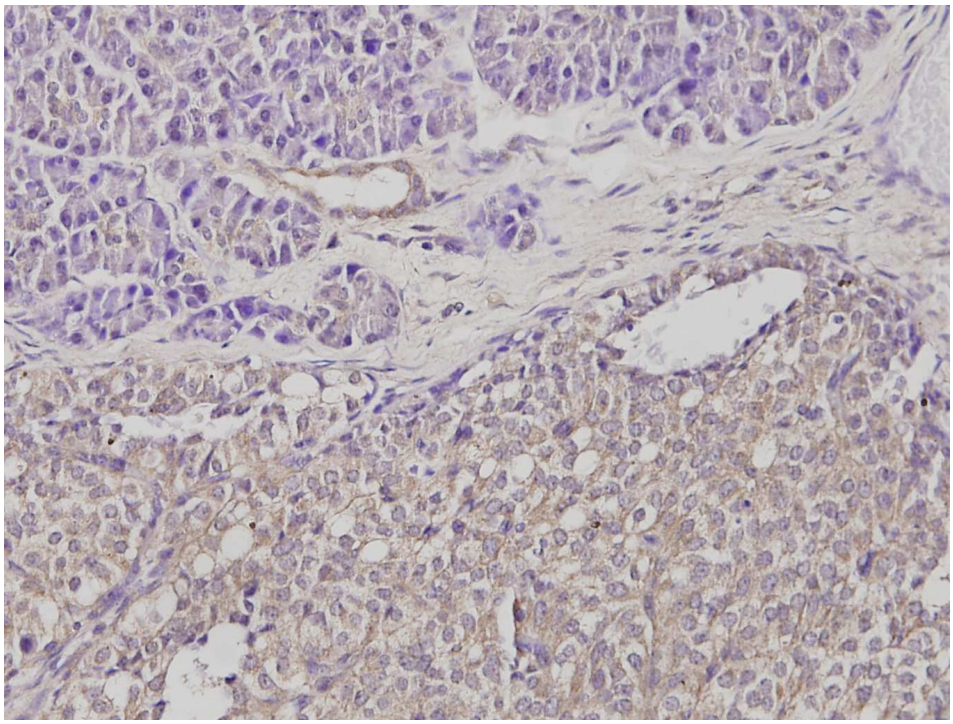

Figure 4. Expression of c-myc, x200

Cytoplasmic staining of c-myc was noted.

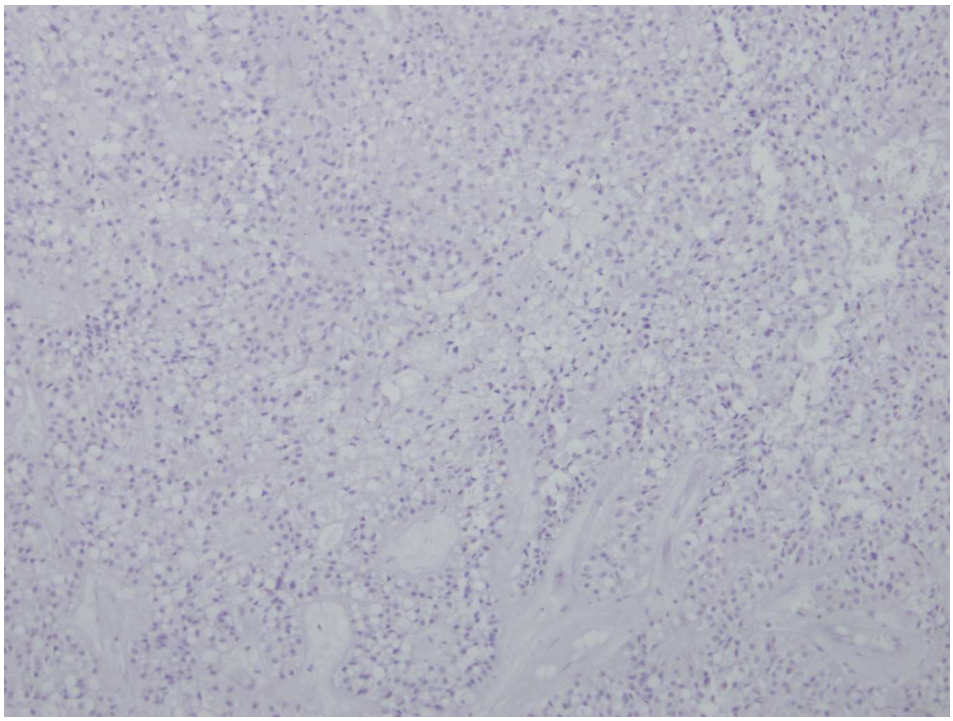

Figure 5-A. 0% expression of Ki-67, x100

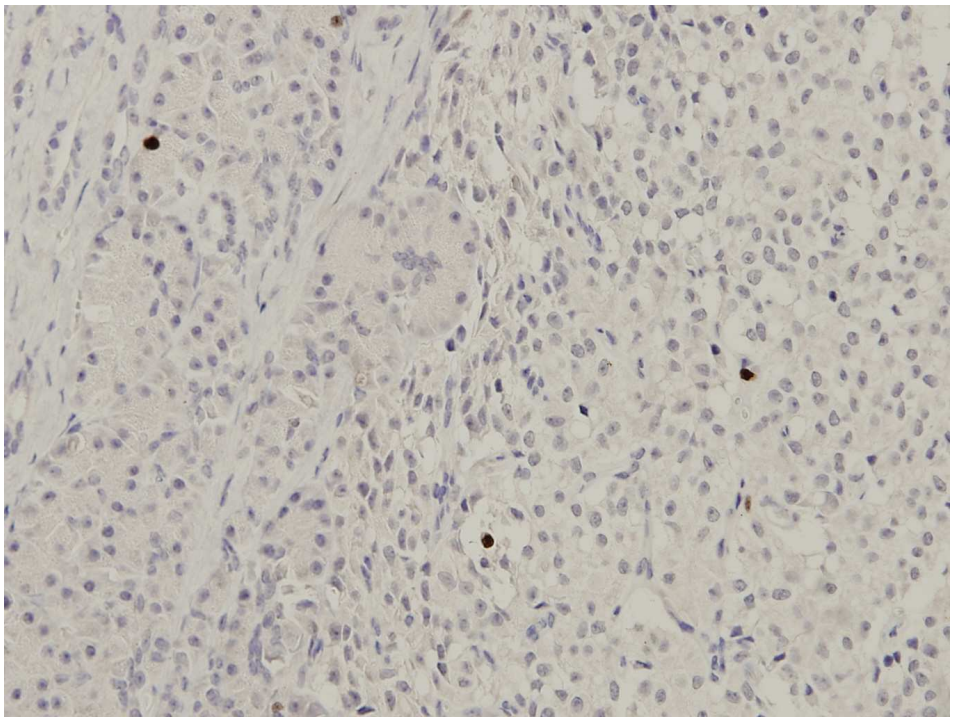

Figure 5-B. 1-2% expression of Ki-67, X200

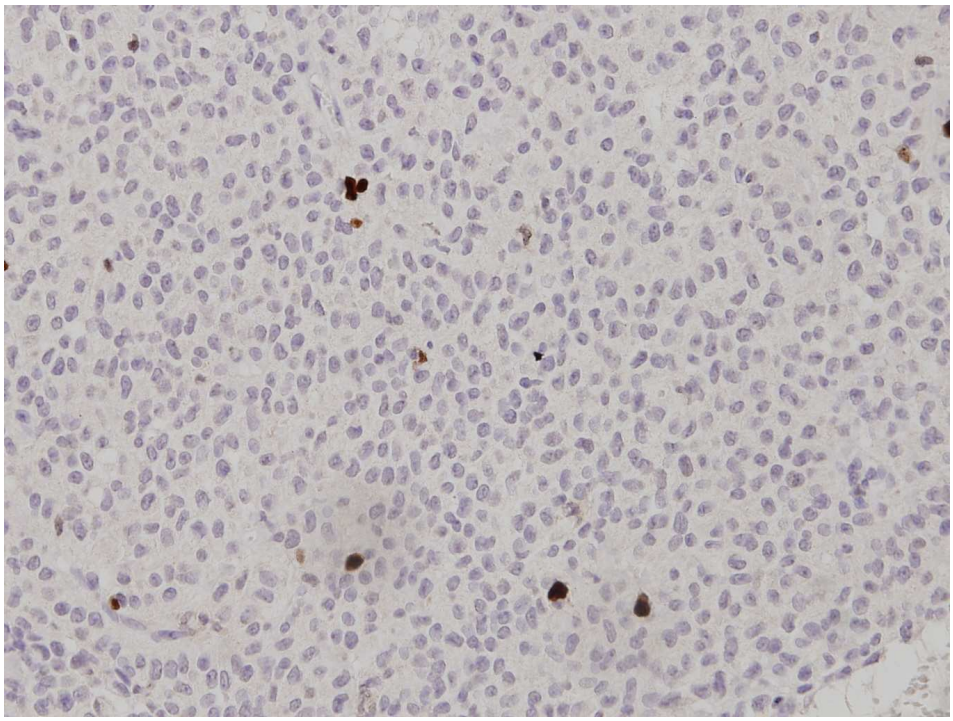

Figure 5-C. 2-5% expression of Ki-67, X200

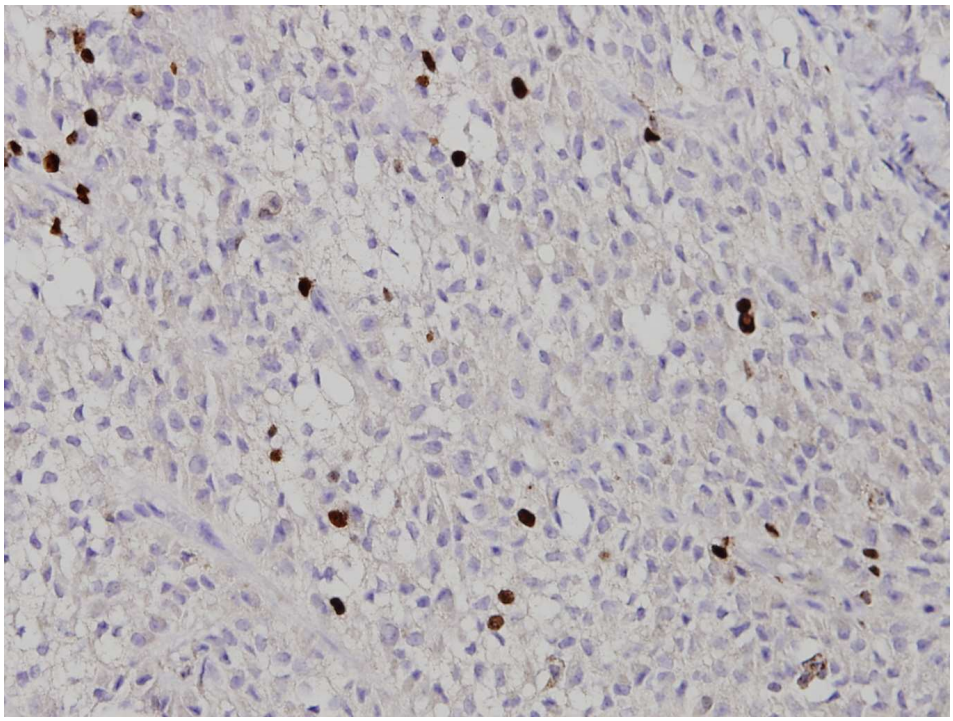

Figure 5-D. 5-10% expression of Ki-67, X200

Table 3. Summary of Wnt target genes and Ki-67 expressions in SPT of the pancreas

No.	Group	Size (cm)	ß-catenin	MMP-7	cyclin-D1	c-myc	Ki-67(%)
1	Tmp	4.7	+	+	+	+	0
2	Tmp	6	+	+	+	+	1-2
3	Tmp	10	+	0	+/-	+	0
4	Tmp	6	+	+	+	0	1-2
5	Tmp	10	+	+	+/-	0	0
6	Tmp	6	+	0	+	+	5-10
7	T	5	+	0	+	+	1-2
8	T	3	+	0	+	0	2-5
9	T	2.5	+	+	+	+	1-2
10	T	4	+	0	+	0	1-2
11	T	3.5	+	+	+	+	2-5
12	T	3	+	+	+	+	2-5

Tmp; SPT with malignant potential, T; SPT without malignant potential, 0; negative, +/-; week, + ; strong

3. Correlation of clinicopathologic variables and immunohistochemistry.

A. MMP-7, cyclin-D1, c-myc, and Ki-67 vs. SPT with malignant potential

Expression of Wnt target genes, MMP-7, cyclin-D1, and c-myc were not correlated with microscopic features suggesting the malignant potential of SPT in the pancreas (group Tmp, $p>0.05$). Interestingly, Ki-67 expression appeared to have some relationship with group Tmp. However, linear by linear association revealed that Ki-67 expression had no statistically significant inverse relationship with group Tmp ($p=0.058$, Chi-square with Fisher's Exact test, cf. $p=0.374$, linear by linear association, Table 4).

Table 4. Correlation between Wnt target genes, Ki-67 and SPT with malignant potential

Group	MMP-7		Cyclin-D1		C-myc		Ki-67(%)				Total
	0	+	+/-	+	0	+	0	1-2	2-5	5-10	
Tmp	3	3	-	6	2	4	-	3	3	-	6
T	2	4	2	4	2	4	3	2	-	1	6
Total	5	7	2	10	4	8	3	5	3	1	12
p-value	1.000		0.450		1.000		0.374*				

* Linear by linear association, cf. Chi-square with Fisher's Exact test, $p=0.058$

B. Tumor size vs. SPT with malignant potential

Tumor size was closely related to microscopic changes that suggested malignant potential. Larger tumors frequently displayed characteristics of SPT with malignant potential (p=0.026, Chi-square with Fisher's exact test, p=0.011, linear by linear association, Table 5).

Table 5. Correlation between tumor size and SPT with malignant potential

Group	Tumor size (cm)			Total	p-value
	<2	2-4	4<		
Tmp	5	1	-	6	0.026
T	-	4	2	6	
Total	5	5	2	12	

C. MMP-7, cyclin-D1, c-myc, and Ki-67 vs. tumor size.

MMP-7 and c-myc were not related to tumor size ($p>0.05$). In contrast, cyclin-D1 and Ki-67 expression was significantly related to tumor size ($p<0.05$, Table 6). Our results showed that small tumors strongly expressed cyclin-D1 and had a relatively higher proliferative index.

Table 6. Correlation between Wnt target genes, Ki-67, and tumor size.

Tumor size	MMP-7		Cyclin-D1		C-myc		Ki-67 (%)				Total
	0	+	+/-	+	0	+	0	1-2	2-5	5-10	
<2cm	2	3	-	5	2	3	-	2	3	-	5
2-4cm	2	3	-	5	1	4	1	3	-	1	5
>4cm	1	1	2	-	1	1	2	-	-	-	2
Total	5	7	2	10	4	8	3	5	3	1	12
p-value	1.000		0.015*		1.000		0.046*				

* Linear by linear association

IV. DISCUSSION

β-catenin, a multifunctional protein, links E-cadherin and α-catenin to the cytoskeleton, forming an E-cadherin-catenin complex that maintains normal epithelial polarity and intercellular adhesion and controls cellular differentiation and proliferation[27,28]. In normal adult epithelial cells, β-catenin is present in a submembranous location. In the absence of Wnt signals, levels of free cytoplasmic β-catenin are very low because β-catenin is phosphorylated by a complex that is composed of the adenomatous polyposis coli tumor suppressor (APC), AXIN, and a serine threonine glycogen synthetase kinase-3β (GSK-3β), which leads to subsequent degradation of β-catenin by a proteasome system[29]. During Wnt signal activation (or mutation of the APC gene, the AXIN, or the β-catenin gene itself), the phosphorylation of β-catenin by GSK-3β is inhibited, which results in high levels of β-catenin accumulation in the cytosol[30, 31]. The accumulated β-catenin binds to cytosolic T cell factor/ lymphoid-enhancer-factor (Tcf/Lef) transcription factors to translocate to the nucleus, which leads to the activation of important Wnt target genes, such as MMP-7, cyclin-D1, and c-myc[32-34]. Recent studies have demonstrated that overexpression of MMP-7, cyclin-D1, and c-myc are highly associated with accumulation of β-catenin in many types of tumors[35-39]. Abnormal cytoplasmic and nuclear β-catenin accumulation is already well known in SPT of the pancreas[25, 26, 40]

However, other Wnt target genes have rarely been evaluated from a clinical course viewpoint. In this study, we analyzed Wnt target gene expression through immunohistochemistry and tried to to correlate clinicopathologic features with their genes expressions. According to our clinical results, neither recurrence nor metastasis after surgery was noted during the follow-up period (median, 41.5 months; range, 24-157 months). Only one patient had simultaneous hepatic metastasis, which required a concomitant hepatic segmentectomy. The pathologic features that suggested malignant potential (patients No. 1-6), liver metastasis (patient No 1.), and even positive resection margin (patients No. 2, 5, and 11), could not predict malignant clinical course - namely metastasis and recurrence during follow up period. Based on our results, the inability to predict malignant clinical course may be explained by an very low Ki-67 proliferative index (Table 2). Our immunohistochemistry results showed increased expression of cyclin-D1 in all 12 patients (10 of 12 were strongly positive and the rest weekly positive). Cyclin-D1 participates in cell cycle control at the G1-S transition and has been shown to be one of the target molecules of the β-catenin/lef-1 complex[33]. Although overexpression of cyclin D1 generally indicated aggressive behavior of the tumor, our results showed SPT of the pancreas had overall low proliferation index detected by Ki-67 expression. Ki-67 expression less than 5% was observed in eleven patients. Among those, none expression of Ki-67 was noted in three patients (Table

3). Recent literature has discussed cyclin-D1 expression in SPT of the pancreas. Tiemann et al.[41] and Muller-Hocker et al.[42] suggest that overexpression of the cell cycle-activating protein D1 and subsequent counterbalancing upregulation of the cyclin-dependent kinase inhibitors p21 and p27 block hyperphosphorylation of the Rb protein. This is postulated to be the cause of the very low proliferation rate characterizing solid pseudopapillary neoplasms. In this study, we did not investigate the counterregulatory factors p21 and p27, but our results of frequent cyclin-D1 expression and low proliferation index seem to be indirectly supported by Tiemann and Muller-Hocker's conclusions. Very low proliferative power may result in long-term survival without recurrence or metastasis in SPTs of the pancreas with malignant potential.

Tang et al.[19] reported two cases of clinically aggressive SPT of the pancreas that showed high mitotic rates, with 30-40% of cells expressing Ki-67, compared with conventional SPT (less than 1% of cells express Ki-67). Some of the unusual pathologic features include a diffuse growth pattern, extensive tumor necrosis, significant nuclear atypia, and sarcomatoid features. In our clinical experiences, only one male patient died of tumor recurrence and metastasis within 3 years after surgery. His tumor pathology showed cellular atypia, peripancreatic tissue invasion, and lymph node metastasis. He could not be included in this study because his tissue was not available for examination. Robert et al.[5] also reported similar pathologic features with aggressive SPT of the pancreas.

These reports suggest that there is an aggressive variant of SPT. However, most SPT of the pancreas is believed to be less aggressive because of a very low proliferative index.

In patient No. 1 with simultaneous liver metastasis, MMP-7 was expressed in the resected specimen. Four of six patients (66.6%) who had SPT with malignant potential also expressed MMP-7. Therefore, MMP-7 may have a role in malignant behavior of SPT of the pancreas. To our knowledge, there have been no reports that have studied MMP-7 and c-myc in SPTs of the pancreas. Recent one study concluded there was a significant relationship between MMP-7 and p21 in Merckel cell carcinoma[43]. Considering the fact that there is correlation of p21 expression with cyclin-D1 over-expression in SPT of the pancreas and MMP-7 is one of the major Wnt target genes, the possible role of MMP-7 are highly suspected in SPT of the pancreas. Matrix metalloproteases are known to play an important role in tumor invasion by mediating the degradation of the extracellular matrix[44, 45]. Therefore, MMP-7 may be related to the invasive pathologic changes reflected in group Tmp or the metastastic behavior shown in patient No. 1. However, we failed to prove a correlation between MMP-7 and pathologic changes that suggested malignant potential (group Tmp). Instead, tumor size was closely related to SPT with malignant potential (Table 5, p=0.026); small tumors had a relatively higher proliferative index (Table 6, p=0.046). In the early stages of SPT of the pancreas, the role of MMP-7 may not be significant despite its

expression in tumor cells. However, its action to invasive and metastatic nature, combined with weak cell-to-cell adhesion (a result of abnormal β-catenin accumulation), may be involved in later tumor stages since larger tumors have tendency to posses malignant potential. Therefore, small SPT which has no microscopic characteristics of malignant potential may follow invasive behavior because of this possible unexpected role of MMP-7. The c-myc expression displayed similar patterns to those of MMP-7 ($p>0.05$, Table 2). The significance of these important Wnt target genes had not been previously studied with regard to SPT of the pancreas. Further research to correlate the clinical behavior of SPT of the pancreas with c-myc and MMP-7 expression will raise many interesting issues in the future.

We did not encounter any recurrences or metastases with SPT of the pancreas after surgical extirpation of the tumor, even if microscopic properties suggested malignant potential. However, Adair et al.[46] suggested that recurrence and metastasis cannot be completely excluded, even in the absence of pathologic features that suggest malignant potential. The aim of this study was to investigate whether or not we could explain the unpredictable clinical behavior of SPT of the pancreas by analyzing the immunohistochemistry of the tumor. According to our results, most SPTs of the pancreas expressed a low proliferative index. However, small SPTs of the pancreas displayed relatively higher Ki-67 expression comparing with larger tumor. This observation led us to

hypothesize that even small SPTs of the pancreas, though they do not show microscopic features that suggest malignant potential, may reveal malignant behavior in their clinical course if they have similar intracellular environments to SPTs that metastasize and/or recur (for example, in our study, if they have similar Wnt target gene expression to patient No.1). Therefore, we would like to emphasize the significance of long-term follow-up for all SPT patients after surgical resection. Similarly, Lai et al[47] concluded SPT of the pancreas should be considered as potentially malignant disease in all patients and regular follow up is mandatory by correlating clinicohistological, immunohistochemical and flow cytometric evaluation.

We failed to observe significant correlations between clinical course or pathologic features of SPT of the pancreas and MMP-7 and c-myc expression in our study. MMP-7 and c-myc expression were noted in both group Tmp and group T. Our study may be the first to observe the expression of MMP-7 and c-myc in SPT of the pancreas. We used several specimens of colon cancer, lung cancer, and skin cancer to control for the quality of MMP-7 and c-myc expression before staining the SPT of the pancreas. However, the volume of specimens was so small that there might be high chance of selection bias in our study. In order to validate this observation, it is necessary to examine these Wnt target genes in more larger-volume specimens. In addition, the detection of immunohistochemistry can be very subjective and may be

influenced by preparation conditions, which are another limitation of our study. In future studies, more quantitative methods may be necessary to precisely measure gene expression on DNA, RNA, and protein levels.

V. CONCLUSION

Current study shows that most SPTs of the pancreas have an abnormal accumulation of cytoplasmic and nuclear β-catenin, as well as frequent cyclin-D1 overexpression with very low proliferation index. It was observed that tumor size and pathologic features that suggested malignant potential were significantly correlated. The expression of Cyclin-D1 and Ki-67 (proliferative index) were relatively prominent in smaller tumors than larger ones. Other target genes of Wnt-signal pathway, namely MMP-7 and c-myc, were seems to be unevenly detected in both group with or without pathologic features suggesting malignant potential (group Tmp and group T). Therefore, very low proliferative index and MMP-7 expression may have something to do with unpredictable clinical course of SPT of the pancreas after surgical resection. Subtle changes in the intracellular environment, not pathologic (morphologic) changes, may elucidate the unpredictable clinical course of SPT of the pancreas. We would like to place great emphasis on long-term follow up regardless of pathologic features suggesting malignant potential and on aggressive surgical intervention with lower morbidity because most SPTs of the pancreas are believed to have lower proliferative index, which means promising long-term survival regardless of their pathologic status. The clinical perplexity of SPT of the pancreas will be resolved in front of developing clinical experiences and far

advanced molecular research in near future.

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ABSTRACT (IN KOREA)

췌장의 고형성가성유두상종양에 있어 Wnt 관련 유전자의 발현 양상 분석

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췌장의 고형성가성유두상종양은 매우 희귀한 종양으로서 아주 서서히 자라나고, 수술적 치료로 매우 좋은 예후를 보이며 젊은 여자에서 많이 발병한다는 것이 매우 잘 알려져 있다. 그러나 완전한 수술적 절제후의 임상경과에 대해서는 대부분은 예후가 좋으나 임상적으로 악성(재발 및 전이)과 양성을 예측할 수 없는 것이 특징으로 하는 특이한 췌장기원 종양이기도 하다. 본 연구는 β-catenin의 비정상적 발현과 관련이 있는 것으로 잘 알려져 있는 Wnt 신호 관련 유전자(MMP-7, cyclin-D1, c-myc)와 Ki-67의 발현의 정도를 고형성가성유두상종양에서 면역조직화학염색을 통해 분석함으로써 수술 그 발현양상에 따른 임상 및 병리학적 특성을 알아 보고자 하였다.

본 연구는 절제된 고형성가성유두상종양 12예를 대상으로 MMP-7, cyclin-D1, c-myc, 그리고 Ki-67의 발현을 면역조직화악염색으로 분석하고 그 결과를 임상적 양상과 비교 분석하였다. 일반적으로 췌장의 고형성가성유두상종양은 비정상적으로 β-catenin이 세포질과 핵내에 모두 발현하였으며(12/12), 흔한 cyclin -D1의 핵 내 발현(10/12)과 함께 전반적으로 낮은 증식도(Ki-67<10%)를 나타내고 있었다(12). 그러나 MMP-7과 c-myc은 비특이적으로 발현 됨을 알 수

있었다. 종양의 크기는 악성의 성향을 나타내는 조직학적 성향과 밀접한 관계가 있는 것으로 보였으며 cyclin-D1과 Ki-67 발현과는 역관계가 있는 것으로 보였다($p<0.05$). 매우 낮은 증식도와 이와 동반되어 발현되는 MMP-7은 수술 후 예측이 불가능한 본 종양의 특징을 설명할 수 있는 실마리를 보여주었다. 형태적인 모양보다는 세포 내 미세환경의 변화에 대한 기초적 연구가 특이한 본 종양의 궁금함을 풀어줄 것으로 사료되었다.

핵심 되는 말: 고형성가성유두상종양, 췌장, Wnt, β-catenin, MMP-7, cyclin-D1, c-myc, Ki-67, immunohistochemistry