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Definition and Histogenesis of Ovarian-type Stroma in Mucinous Cystic Neoplasms of the Pancreas

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Summary. **Objectives: The present study aimed to clarify the definitions and histogenesis of ovarian-type stroma (OTS) in mucinous cystic neoplasms (MCNs) of the pancreas.**

Methods: Expression and density of cells positive for estrogen receptor (ER) and progesterone receptor (PR) were immunohistochemically studied in 16 MCNs (6 adenomas, 10 carcinomas), 22 intraductal papillary mucinous neoplasms (IPMNs), 10 common-type invasive ductal carcinomas (IDCs) and 24 non-neoplastic pancreatic tissues.

Results: OTS comprised densely packed spindle-shaped cells with round or elongated nuclei. Stromal cells were diffusely positive for ER and PR in all 16 MCNs. OTS-like stromal cells in IPMNs and IDCs were negative or only sporadically positive for ER or PR in all cases. In non-neoplastic pancreatic tissue, ER- and PR-reactive stromal cells were scattered sporadically irrespective of site in the pancreas (head, body or tail) or sex.

Conclusions: OTS is an absolute marker for diagnosis of pancreatic MCNs and should be confirmed as ER- and PR-reactive on immunostaining in addition to findings from sections stained using hematoxylin-eosin. ER- and PR-reactive stromal cells may become hypersensitive to female sex hormone stimulation and start to proliferate and form OTS in the pancreas.

Key words—pancreatic tumor, mucinous cystic neoplasm, intraductal papillary mucinous neoplasm, ovarian-type stroma, estrogen receptor.

INTRODUCTION

Mucinous cystic neoplasm (MCN) of the pancreas is uncommon, comprising approximately 2~5% of all exocrine pancreatic tumors[1,2]. MCNs are characterized by a large, predominantly multilocular or unilocular cystic tumor with macroscopically smooth surface and thick fibrous capsule. The tumors occur almost exclusively in the distal (body and tail) pancreas of middle-aged women, generally showing no communication with the pancreatic ductal system, and displaying columnar, mucin-producing epithelium supported by ovarian-type stroma (OTS)[1,2].

MCN and intraductal papillary mucinous neoplasm (IPMN) have been considered as a single entity due to histological similarities[3-5]. However, OTS has recently been included as a specific feature of MCN, and can be used to distinguish MCNs from IPMNs and other pancreatic neoplasms[1]. OTS reportedly consists of densely packed spindle-shaped cells with round or elongated nuclei and sparse cytoplasm, as seen in ovarian stroma[1]. OTS, however, changes into hypocellular and fibrotic or hyaline stroma in some

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Abbreviations—ER, estrogen receptor; IPMN (IPMA, IPMC), intraductal papillary mucinous neoplasm (adenoma, carcinoma); MCN (MCA, MCC), mucinous cystic neoplasm (cystadenoma, cystadenocarcinoma); OTS, ovarian-type stroma; PR, progesterone receptor.

areas with secondary changes in large mucinous cystadenoma (MCA) or in invasive areas of mucinous cystadenocarcinoma (MCC)[1] and such stroma is very similar to that of common-type invasive ductal carcinoma (IDC). Moreover, OTS-like stroma is seen in invasive areas of common-type IDCs of the pancreas. OTS detected only using hematoxylin-eosin (HE) thus does not represent an objective finding in some situations.

To objectively define OTS, diffuse reactivity of spindle cells for estrogen receptor (ER) and progesterone receptor (PR) is indispensable, but such staining has not always been performed in previous reports[3,4]. Even when such staining has been used, frequency of ER and PR diffuse immunoreactivity for MCNs has varied among previous studies, and has generally been very low in all except one report (Table 1)[4–9]. These discrepancies between papers may be due to the use of varying definitions for OTS in HE sections, or to differences in techniques or antibodies used in immunostaining.

Regarding the etiology of OTS, ectopic ovarian stroma incorporated during embryogenesis in the pancreas is hypothesized to release hormones and growth factors causing nearby epithelium to proliferate and form cystic tumors[1,5]. Since the left primordial gonad and dorsal pancreatic primordium lie side-by-side during the fourth and fifth weeks of development, this hypothesis could explain the predilection of MCN for the body-tail region of the pancreas[1]. However, no reports have described the presence of small foci of ectopic OTS in the pancreas or whether ER-/PR-reactive stromal cells are present in the normal pancreas or in pancreatitis.

The present study objectively refined the definition for histological characteristics of OTS, and studied histogenesis of OTS and frequency of ER and PR overexpression in MCNs compared with ER and PR status in intraductal papillary mucinous carcinomas (IPMCs), IDCs, chronic pancreatitis and normal pancreatic tissue.

MATERIALS AND METHODS

Case selection

We selected 16 MCN cases after macroscopic and microscopic examination based on the criteria

Table 1. Summary of past studies into ER and PR immunoreactivity in mucinous cystic neoplasms

Author	Year	Ovarian-type stroma in HE section	ER		PR		Antigen enhancement
			Positivity: % (n)	Source	Positivity: % (n)	Source	
Kirby RE[6]	1995	ND	0% (0/26)	Abbott Diagnostics, Abott Park, IL, USA.	15% (4/26)	Cell Analysis Systems, Elmhurst, IL, USA.	ND
Fukushima N[7]	1997	100%	11% (1/9)	Novocastra, Newcastle, UK. Dilution 1 : 40	ND		Microwave
Zamboni G[5]	1999	86%	22% (22/54)	Dakopatts, Denmark. Dilution 1 : 30	48% (26/54)	Dakopatts, Denmark. Dilution 1 : 30	ND
Thompson LDR[4]	1999	100%	23% (15/65)	Dako, Carpinteria, CA, USA. Dilution 1 : 20	71% (46/65)	Novocastra, Newcastle, UK. Dilution 1 : 20	Microwave
Nobukawa B[8]	1999	100%	100% (6/6)	Nichirei, Tokyo, Japan.	100% (6/6)	Nichirei, Tokyo, Japan.	ND
Izumo A[9]	2003	100%	62% (21/34)	Immunotech, Marseille, France. Dilution 1 : 10	82% (28/34)	Nichirei, Tokyo, Japan. Dilution 1 : 10	Microwave
Ours	2004	100%	100% (16/16)	Novocastra, Newcastle, UK. Dilution 1 : 100	100% (16/16)	Novocastra, Newcastle, UK. Dilution 1 : 100	Autoclave

ND, not described; ER, estrogen receptor; PR, progesterone receptor.

Table 2. Clinicopathological features of MCN, IPMC and IDC of the pancreas

	MCN (n=16)		IPMC (n=22)	IDC (n=10)
	Adenoma (10)	Carcinoma (6)		
Sex (male: female)	0:10	0:6	15:7	6:4
Age in years; mean (range)	44.1 (31-67)	45.7 (27-71)	63.9 (22-80)	65.4 (51-76)
Location (head/body/ tail)	0 /3 /7	0 /3 /3	20/ 2/ 0	5/ 3/ 2
Tumor size in mm; mean (range)	66.0 (25-110)	83.2 (45-190)	37.6 (7-90)	45.8 (15-110)

MCN, mucinous cystic neoplasm; IPMC, intraductal papillary mucinous carcinoma; IDC, invasive ductal carcinoma.

Table 3. Clinicopathological data of 16 mucinous cystic neoplasms of the pancreas

Case number	Diagnosis	Age at diagnosis	Sex	Location	Tumor size (mm)	Number of blocks/case	Surgical treatment	Follow-up (months)	
1	MCC, invas.	71	F	Body	54	10	DP	Alive	104
2	MCC, invas.	51	F	Tail	70	8	DP	DOD	80
3	MCC, invas.	49	F	Body	45	10	DP	Alive	57
4	MCC, non-invas.	27	F	Body	70	11	DP	Alive	60
5	MCC, non-invas.	34	F	Tail	190	149	DP	D*	51
6	MCC, non-invas.	42	F	Tail	70	30	DP	Lost	
7	MCA	64	F	Tail	110	16	DP	Alive	104
8	MCA	40	F	Tail	60	12	SR	Alive	66
9	MCA	67	F	Tail	25	12	DP	Alive	48
10	MCA	44	F	Tail	70	7	DP	Alive	46
11	MCA	33	F	Tail	55	15	DP	Alive	41
12	MCA	34	F	Tail	40	12	DP	Alive	22
13	MCA	49	F	Tail	80	46	DP	Alive	13
14	MCA	45	F	Body	80	16	DP	Alive	8
15	MCA	31	F	Tail	60	25	DP	Alive	2
16	MCA	34	F	Tail	80	21	DP + LRLT	D†	0

MCC, mucinous cystadenocarcinoma; invas./non-invas., invasive/non-invasive; MCA, mucinous cystadenoma; DP, distal pancreatectomy; SR, segmental resection; LRLT, living related liver transplantation; DOD, died of the disease; D*, died of ovarian cancer; D†, surgical death; Lost, lost at follow-up.

proposed in the blue book of the Word Health Organization, which included OTS as a necessary characteristic in HE-stained sections[1]. The cases had all been surgically resected and collected at Niigata University Hospital, Nagaoka Red Cross Hospital or Niigata Hospital of the Niigata Cancer Center. Clinicopathological information for these cases is shown in Tables 2 and 3, and all patients were Japanese. Of the 16 cases, one showed communication between the main pancreatic duct and tumor cyst.

To compare frequency and grade of ER- and PR-positive stromal cells between MCNs and other pancreatic neoplasms, 22 IPMC tumors (n=20 in pancreatic head; n=2 in pancreatic body), 10 IDC tumors (n=5 in pancreatic head; n=5 in pancreatic body or tail) were used. IDCs and IPMNs in this study were selected based on criteria proposed by World Health Organization[1]. Additional tissues from normal pancreas and chronic pancreatitis (14 males, 10 females; n=17 from pancreatic head, n=7 from pancreatic body or tail) were collected from another set of patients without pancreatic tumors.

Immunohistochemical staining

Conventional HE diagnosis was performed using a mean of 25 blocks/case (range, 7-149 blocks/case).

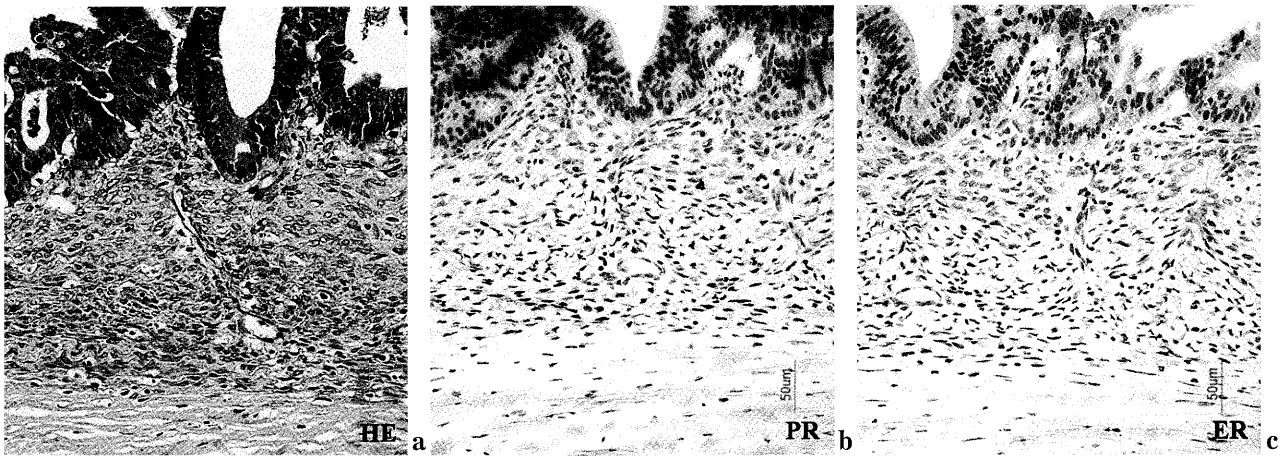

Fig. 1. Mucinous cystadenocarcinoma with ovarian-type stroma. Stroma is hypercellular and composed of spindle-shaped cells. Outside the stroma is a thick fibrous layer (outer layer of capsule) on HE staining (**a**). Immunostaining for PR (**b**) and ER (**c**) shows diffuse positivity in spindle cells.

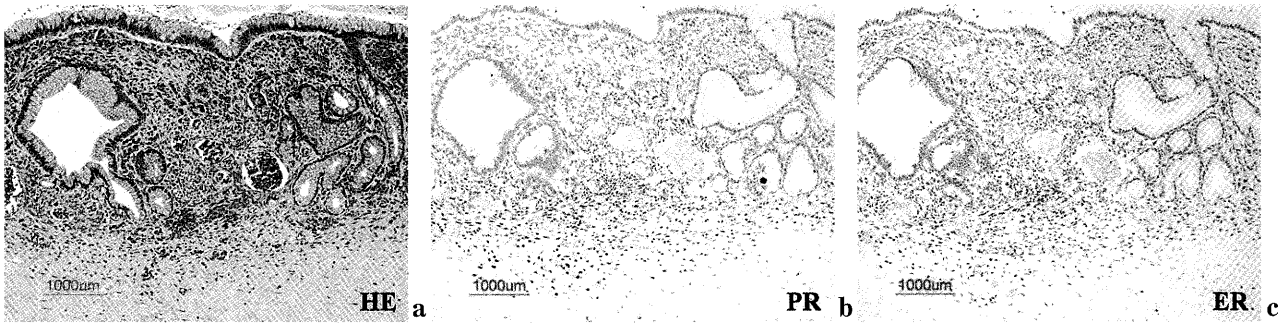

Fig. 2. Mucinous cystadenoma with variant-type stroma (**a**) indicating diffuse reactivity to PR staining (**b**) and ER staining (**c**).

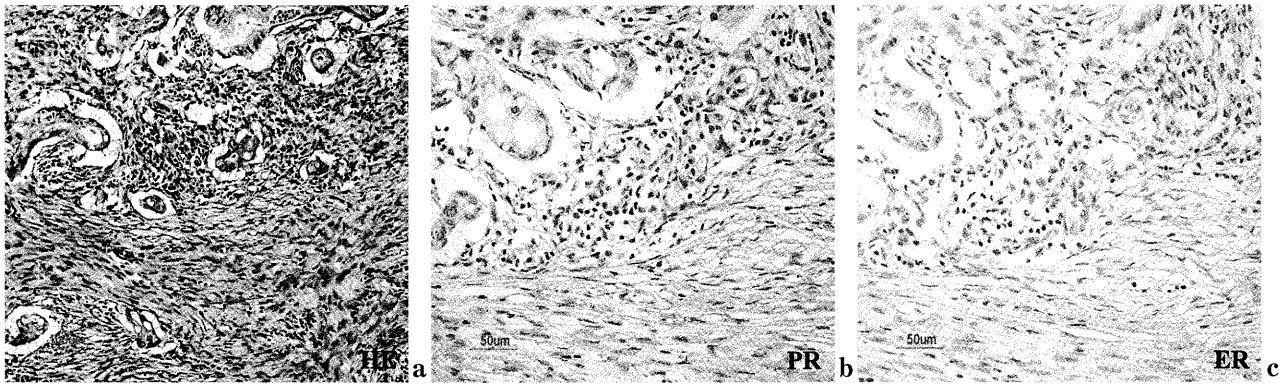

Fig. 3. Common-type invasive ductal carcinoma of the pancreas associated with cellular stroma like ovarian-type stroma (**a**). Spindle or ovoid stromal cells are all negative for both PR (**b**) and ER (**c**). Some cells display brown their cytoplasm (negative for ER, **c**).

For each case, 1-4 representative paraffin blocks were selected for immunohistochemical staining after complete observation of all HE sections. For immunohistochemistry, 3-μm sections were mounted on MAS-corted micro slide glass (Matsunami Glass Industries, Ltd, Japan).

For antigen retrieval, deparaffinized sections were treated by autoclaving in citrate buffer (pH 6.0) for 20

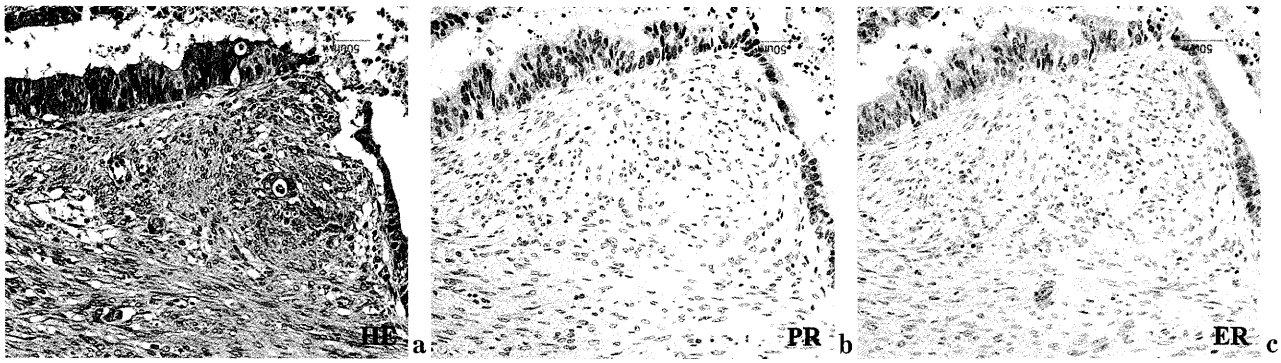

Fig. 4. Common-type invasive ductal carcinoma of the pancreas associated with cellular stroma like ovarian-type stroma (**a**). Spindle or ovoid stromal cells are all negative for both PR (**b**) and ER (**c**).

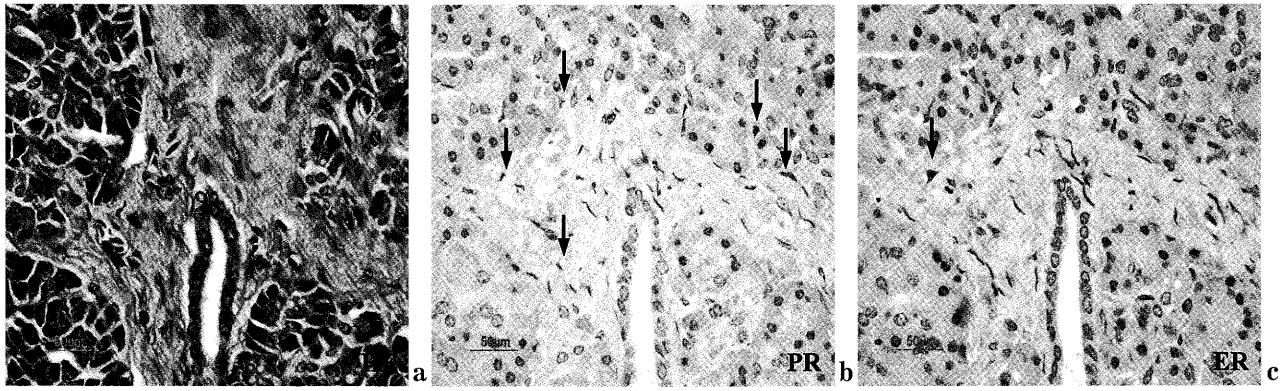

Fig. 5. Normal pancreatic tissue with mild fibrosis around an intralobular duct (**a**). A small number of PR-positive (**b**) and ER-positive (**c**) stromal cells are seen.

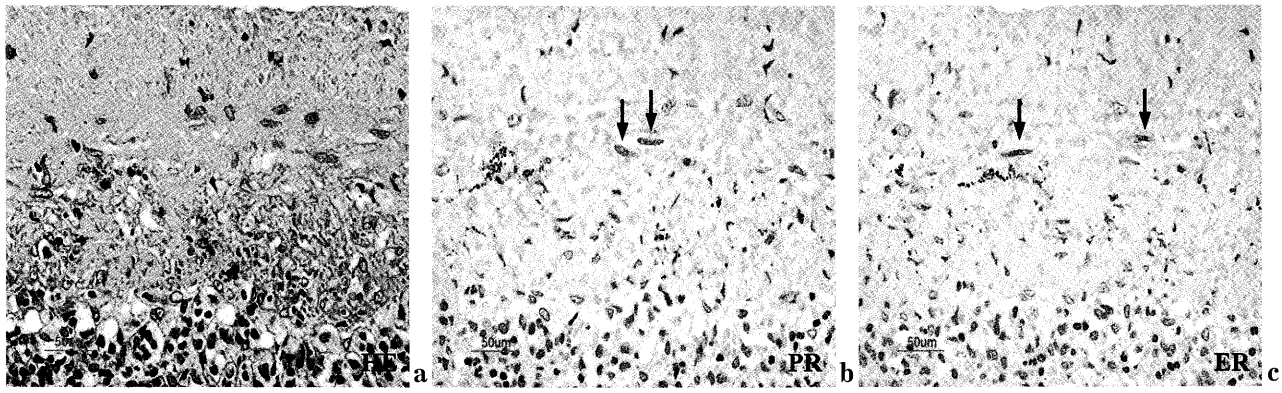

Fig. 6. Normal splenic capsule (**a**). A small number of PR-positive (**b**) and ER-positive (**c**) stromal cells are seen.

min and allowed to cool to room temperature. Endogenous peroxidase activity was blocked by 20 min of incubation with 0.3% hydrogen peroxidase in absolute methanol, then the sections were washed in tap water. Non-specific binding was blocked using normal serum (Nichirei, Tokyo, Japan). Sections were incubated with primary antibody overnight at 4°C, then for 30 min at room temperature with biotinylated secondary antibody (Nichirei, Japan), followed by treatment with a streptavidin-biotin-peroxidase kit (Nichirei, Japan). All sections were visualized using diaminobenzidene (DAB tablet, Wako Pure Chemical Industries. Ltd., Osaka, Japan). Finally, sections were lightly stained with hematoxylin. Immunohistochemical staining for ER and PR antigens is shown in Table 1. All nuclei stained brown

Table 4. Features of ovarian-type stroma in pancreatic mucinous cystic neoplasms

	Ovarian-type stroma in MCNs	Stroma in ductal carcinomas	Stroma in IPMNs	Stroma in SCNs
Inner layer of wall (stroma just beneath epithelial cells)				
Ovarian-type stroma (OTS) in HE section	Diffuse distribution	OTS-like stroma, focal	OTS-like stroma, focal	OTS-like stroma, focal
Density of spindle cells	Form a compact cellular layer Swollen spindle cells without or with few inflammatory cells	Sparse Swollen spindle cells with fibers/inflammatory cells	Sparse Thin spindle cells mixed with inflammatory cells, predominantly plasma cells	Thin fibrous stroma
Estrogen-receptor-positive cells	Many positive cells distributed diffusely	Negative or positive for only a few spindle cells	Negative or positive for only a few spindle cells	Negative
Outer layer of wall				
	Thick fibrous wall (collagen fibers and MSA positive fibers)		Thick fibrous wall (collagen fibers and MSA positive fibers)	

IPMN, intraductal papillary mucinous neoplasms; SCN, serous cystic neoplasm; MSA, muscle specific actin.

Table 5. Immunohistochemical expression of ER and PR in stromal cells of MCN, IPMC and IDC of the pancreas

Histology	Number of cases					
	ER positivity			PR positivity		
	Diffuse	Scattered	Negative	Diffuse	Scattered	Negative
MCN (n=16)	16	0	0	16	0	0
IPMC (n=22)	0	12	10	0	19	3
IDC (n=10)	0	2	8	0	9	1

ER, estrogen receptor; PR, progesterone receptor; MCN, mucinous cystic neoplasm; IPMC, intraductal papillary mucinous carcinoma; IDC, invasive ductal carcinoma.

were evaluated as positive, irrespective of staining intensity, and cytoplasmic reactivity was evaluated as negative.

Quantification of immunoreactive ER- and PR-positive cells

For each case, ≥200 stromal cells in the area of maximal positivity were evaluated under ×400 magnification[10]. Cases with ≥30% positive cells were interpreted as "diffusely positive", with <30% as "scattered" and 0% as "negative".

Statistical analysis

Fisher's exact test was used for statistical analysis, and a value of $P<0.05$ was considered statistically significant.

RESULTS

Conventional and immunohistochemical findings of OTS in MCNs

OTS in MCNs comprised hypercellular stroma with spindle-shaped cells displaying round-to-oval nuclei and little cytoplasm in MCCs and MCAs. This stroma was predominant just at the subepithelial zone, and outside of OTS a thick fibrous layer rich in collagenous connective tissue existed (Figs. 1 and 2). The walls of all MCNs thus exhibited distinct triple structures, with an innermost epithelial cell layer, an inner subepithelial layer of OTS, and an outermost layer of collagenous fibrous tissue. Distinct OTS was often located in the septa of multilocular cysts in MCNs. The most obvious feature of OTS in MCNs

Table 6. ER and PR positive stromal cells in normal and localized chronic pancreatitis

	Age, Sex (years)	Site of pancreas tested	ER	PR	Main lesion
1	58 M	Head	1+	1+	Bile duct cancer
2	60 M	Head	1+	1+	Bile duct cancer
3	62 M	Head	1+	1+	Retention cyst, pancreas
4	65 M	Head	1+	1+	Bile duct cancer
5	65 M	Head	1+	1+	Bile duct cancer
6	70 M	Head	1+	1+	Bile duct cancer
7	70 M	Head	1+	1+	Bile duct cancer
8	71 M	Head	1+	1+	Cholangitis
9	71 M	Head	1+	1+	Bile duct cancer
10	76 M	Head	1+	1+	Bile duct cancer
11	68 F	Head	1+	1+	Bile duct cancer
12	69 F	Head	1+	1+	Bile duct cancer
13	70 F	Head	1+	1+	Bile duct cancer
14	71 F	Head	1+	1+	Bile duct cancer
15	77 F	Head	1+	1+	Retention cyst, pancreas
16	79 F	Head	1+	1+	Bile duct cancer
17	84 F	Head	1+	1+	Bile duct cancer
18	65 M	Tail	0	1+	Gastric cancer
19	69 M	Tail	1+	1+	Gastric cancer
20	71 M	Tail	1+	1+	Retention cyst, pancreas
21	74 M	Tail	0	0	Gastric cancer
22	59 F	Tail	1+	1+	Gastric cancer
23	63 F	Tail	0	0	Gastric cancer
24	74 F	Tail	1+	1+	Gastric cancer

ER, estrogen receptor; PR, progesterone receptor.

Table 7. Immunohistochemical expression of ERs and PRs in normal pancreas and in pancreatitis

	Ductal epithelium	Acinar cells	Islet cells	Stromal spindle cells
ER	(−)	(−)	(−)	Few, scattered
PR	(−)	(−)	(+), Diffuse	Few, scattered

ER, estrogen receptor; PR, progesterone receptor.

was in distribution, i.e., diffuse distribution within the tumor from the capsule to the intracystic septa (Table 4).

Spindle cells in OTS displayed diffuse and strong positivity for PR and ER in all of 16 MUNs (Figs. 1, 2 and Table 4). However, staining intensity was generally weaker in ER staining compared with that of PR staining.

Conventional and immunohistochemical findings of stroma in IPMNs and IDCs

Stroma of IPMCs and IDCs was mildly cellular in spindle cells admixed with chronic inflammatory cells in all cases (Table 4), but were partly hypercellular in some cases, particularly in the invasive areas (Figs. 3 and 4). Spindle cells in these areas, however, were either negative for both PR and ER staining (Table 5), or positive only in a scattered pattern.

ER- and PR-positive stromal cells in non-neoplastic pancreas

Normal pancreas and chronic pancreatitis tissue revealed few scattered positive stromal cells for ER and PR (Fig. 5 and Table 6). Number of positive cells was increased in chronic pancreatitis cases compared to normal pancreas, but was limited to a scattered pattern. Positive cells were seen in both the head and tail, and in men and women (Table 6).

ER- and PR-staining was negative for pancreatic ductal epithelium, and acinar cells and positive for a small number of stromal spindle cells. PR-staining was diffusely positive for islet cells in groups or even for single cells (endocrine cells) in pancreatic ducts, while ER-staining for these was negative.

Surprisingly, small numbers of ER- and PR-positive cells were also found in the splenic capsule (Fig. 6), but not in splenic parenchyma.

DISCUSSION

Recent studies have clarified that the most pathognomonic feature in MCN is the presence of OTS, which is found diffusely in the capsule and intracystic septa (Table 4)[1,2]. OTS has often only been diagnosed using HE staining, but OTS-like stroma can be seen in common-type IDC (Figs. 3 and 4) and IPMN. For correct histological differentiation of OTS from OTS-like stroma, ER or PR immunostaining is indispensable, as shown in this study. OTS displays diffuse ER-/PR-positivity, while OTS-like stroma displays either negative results or positive results only in a scattered pattern (Figs. 1, 2, 3 and 4). In previous studies, however, staining for ER and PR has not been always performed[4].

MCNs and IPMNs have sometimes been considered a single entity due to the lack of knowledge on the diagnostic importance of OTS and ER/PR immunostaining[3-5]. It is now evident that MCN is rarely found in men[11]. The many cases reported in men thus seem likely to represent IPMN rather than MCN[3,4,5]. For precise diagnosis of possible male cases of MCN, ER/PR immunostaining should be always performed.

Surprisingly ER/PR immunostaining in previous studies showed various rates of diffuse ER and PR reactivity in MCNs (Table 1). Rate of diffuse ER expression has been 0～100%, while that of PR has been 15～100%. Why have such big differences occurred? The following reasons may be involved: differences in definitions of MCN in HE-stained sections; differences in immunostaining antibodies used; differences in immunostaining technique; and whether or not studies were done with antigen enhancement. The present study suggests that OTS for pancreatic MCN displays diffuse positivity for ER and PR in 100% of cases.

This study is the first to report the presence of ER- and PR-immunoreactive stromal cells in IPMN, common-type IDC, normal pancreas and chronic pancreatitis. Density was sporadic and scattered in these tissues, and was completely different to that of OTS in pancreatic MCN (Fig. 5; Tables 5, 6 and 7). PR reactivity has been reported in islet cells, extrainsular endocrine cells and intraductal endocrine cells of the pancreas, but PR- and ER-positivity in pancreatic stromal cells has not been described[12-14]. Interestingly, ER- and PR-positive cells were also found sporadically in the fibrous capsule of normal spleen (Fig. 6).

OTS is supposedly derived from ectopic ovarian stroma incorporated into the pancreas during embryogenesis[5]. However, no reports of small foci of ectopic ovarian stroma have been made before now. We found that ER- and PR-reactive stromal cells are scattered in the stroma of IMPNs, common-type IDCs, pancreatitis tissue and normal pancreas tissue, irrespective of the site (head, body or tail) in the pancreas (Fig. 5; Tables 5, 6 and 7). These ER- and PR-reactive stromal cells thus become hypersensitive to stimulation by female sex hormones and start to proliferate and form OTS in the pancreas. This hypothesis, however, cannot fully explain why MCNs occur predominantly in the body and tail of the pancreas.

In conclusion, OTS represents an absolute marker for diagnosis of pancreatic MCNs and should be confirmed as ER- and PR-reactive on immunostaining, in addition to HE staining. Two hypotheses exist for the histogenesis of OTS: from ectopic ovarian tissue; or from ER- and PR-reactive stromal cells in the pancreas. Each theory has weak and strong points for explanations of OTS histogenesis, and further research is needed to clarify these issues.

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