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Expression of progesterone receptors in solid-cystic tumour of the pancreas:

a clinicopathological and immunohistochemical study of ten cases

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Abstract. A role for sex hormones in the pathogenesis of solid-cystic tumour (SCT) of the pancreas is suggested by its predilection for young fertile women. Controversial data have been provided for the presence of progesterone receptors (PR) and/or oestrogen receptors (ER) in SCT. We report the immunohistochemical detection of PR in ten cases of SCT. Eight were from young women. The remaining two were from a post-menopausal woman and a young boy. All cases showed PR immunoreactivity in the large majority of neoplastic cells, whereas none exhibited ER positivity. In one tumour two types of cell populations were noted, the more anaplastic invasive-type being PR negative, whereas the more typical was PR positive. PR immunoreactivity in the absence of ER may simply reflect a lower sensitivity of ER antibody failing to reveal the biochemically detectable ER, or that the PR in cells of SCT are constitutively synthesized in an oestrogen-independent way, as in T47D breast carcinoma cell line, meningioma cells and some gastric cancer cells. Our findings support the hypothesis of a possible pathogenetic role of progesterone in SCT, independent of the patient's sex and age.

Key words: Pancreas – Solid-cystic tumour – Progesterone receptor

Introduction

Solid-cystic (papillary-cystic) tumour (SCT) of the pancreas is a distinctive low-grade malignancy that primarily occurs in girls and young women (Frantz 1959). It has occasionally been reported in older women (Lieber et al. 1987; Matsunou et al. 1990), in males (Choi et al. 1988; Friedman et al. 1985; Klöppel et al. 1991; Lieber et al. 1987; Matsunou et al. 1990; Stoemmer et al. 1991; Warshaw et al. 1990) and in extrapancreatic sites (Ishikawa et al. 1990; Kim et al. 1990; Klöppel et al. 1991). Histogenesis remains controversial. Data have been provided for a ductal (Boor et al. 1979; Compagno et al. 1979; Cubilla and Fitzgerald 1979; Hamoudi et al. 1970; Lieber et al. 1987), acinar (Bombi et al. 1984; Morohoshi et al. 1983, 1987) or pluripotential pancreatic cell (Matsunou et al. 1990; Miettinen et al. 1987; Schlosnagle and Campbell 1981; Sclafani et al. 1991) origin. Usually SCT has a favourable clinical course but invasion of vital structures and metastases have been reported in 16% of patients (Sclafani et al. 1991). The pathogenetic role of sex hormones is suggested by the predilection of SCT for young, fertile women. However, the search of progesterone receptors (PR) and/or oestrogen receptors (ER) in SCT has led to conflicting results (Carbone et al. 1989; De Lagausie et al. 1988; Ladanyi et al. 1987; Pettinato et al. 1992; Stoemmer et al. 1991; Wrba et al. 1988), probably due to the heterogeneity of the assay techniques employed.

In the present study we report the immunohistochemical finding of PR positivity and ER negativity in ten cases of SCT.

Materials and methods

Seven cases of SCT from the files of the Department of Pathology of Verona University were reviewed. Three other cases were received in consultation. The clinicopathological data of the patients are summarized in Table 1. Cases 4 and 2 had been previously

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Table 1. Clinicopathologic data

Case	Age (years) sex	Location size (cm)	Presentation	Onset	FNAB	Treatment	Follow-up
1	69/F	Head/10	Incidental	None	Negative	Whipple's	NED 2.5 years
2	26/F	Head/6	Abdominal pain and mass	6 months	n.d.	Whipple's	Died 16 months[a]
3	17/F	Head/7	Abdominal pain	3 months	Positive	Whipple's	NED 1 year
4	25/F	Head/25	Abdominal pain and mass	5 months	n.d.	Whipple's	NED 20 years
5	37/F	Tail/8	Abdominal mass	1 month	n.d.	Distal pancreatectomy	NED 10 months
6	39/F	Head/10	Dyspepsia	4 years	Positive	Whipple's	NED 6 years
7	14/M	Head/8	Abdominal pain	2 months	Positive	Whipple's	NED 3 years
8	49/F	Head/5	Abdominal pain	1 month	n.d.	Whipple's	NED 4 years
9	20/F	Head/4	Dyspepsia	3 months	Positive	Tumorectomy	NED 5 months
10	23/F	Head/12	Abdominal mass	2 months	n.d.	Whipple's	NED 3 months

FNAB, Fine needle aspiration biopsy; n.d., not done; NED, no evidence of disease;
[a] Death was due to septic shock following cholangitis

Table 2. Antibodies: their sources and dilutions

Antibody	Source	Dilution
Monoclonal		
CAM 5.2	Becton-Dickinson, Mountain View, Calif., USA	1:10
KL1	Immunotech, Marseille, France	Undiluted
Vimentin	Amersham, Buckinghamshire, England	1:10
Neurofilaments 70–200 kDa	Dakopatts, Denmark	1:40
Chromogranin A	Enzo, New York, USA	1:5000
Synaptophysin	Boehringer, Mannheim, Germany	1:20
Lipase	Chemicon, USA	1:10000
Amylase	Biogenex, USA	1:10
Trypsinogen	Chemicon	1:4000
Oestrogen receptor	Abbott Laboratories, Wiesbaden, Germany	Undiluted
Progesterone receptor KD68[a]	Abbott Laboratories	1:5
Progesterone receptor LET126	Transbio, Paris, France	1:50
Progesterone receptor Li417	Transbio	1:25
Polyclonal		
Neuron-specific enolase	Miles, Scientific Santa Barbara, Calif., USA	1:100
Insulin	Dakopatts	1:5
Glucagon	Dakopatts	1:10
Somatostatin	Dakopatts	1:20
Pancreatic polypeptide	Dakopatts	1:10
Alpha-1-antichymotrypsin	Dakopatts	1:2500
Alpha-1-antitrypsin	Dakopatts	1:200

[a] Used undiluted on frozen tissue sections

misdiagnosed in 1972 and 1976 as non-functioning islet cell tumours. Five patients had a preoperative fine needle biopsy, with a diagnosis consistent with SCT in four cases, but inadequate material for diagnosis was obtained in one case.

All cases were stained with haematoxylin and eosin, periodic acid-Schiff (PAS) and Grimelius. Serial paraffin sections were immunostained by the ABC technique with the primary antibodies listed in Table 2. PR- and ER immunostaining was performed on paraffin sections in all cases and in three cases (nos. 3, 7 and 9; Table 1) also on frozen sections, using the peroxidase-anti-peroxidase complex staining technique. For the identification of PR we used three different monoclonal antibodies (mAbs; rat KD68 and mouse LET126 and Li417) recognizing different epitopes on the PR molecule (Green and Press 1987; Perrot-Applanat et al. 1985; Vu Hai et al. 1989), whereas mAb H222 was used for ER. With the rat mAb, the reaction was performed using all the reagents in kit form (ER-ICA and PR-ICA, Abbott Laboratories, North Chicago, Ill.) in accordance with the manufacturers' instructions. Double enzymatic pretreatment with trypsin and DNAse was performed before immunostaining for ER, according to Hiort et al. (1988). Normal pancreas served as positive control tissue for acinar and endocrine cell markers and breast carcinomas for ER and PR. Scoring of immunoreactive cells for the different antibodies is reported in Table 3.

Electron microscopic examination was performed in five cases (nos. 3, 5–7 and 9; Table 2). Fresh tissue was fixed in 2% cold glutaraldehyde, postfixed in 1% aqueous osmium tetroxide and embedded in epon-araldite mixture. Thin sections were stained with lead citrate and uranyl acetate and examined with a Zeiss EM 10 electron microscope.

Table 3. Histochemical and immunohistochemical findings

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Grimelius	−	−	−	−	−	−	−	−	−	−
CAM 5.2 (trypsin 5′)	−	−	−	−	−	−	−	−	−	−
CAM 5.2 (trypsin 30′)	+++	+++	++	+++	−	++	+++	++	+++	+++
KL1	+++	++	−	++	−	+++	+	−	+	++
Vimentin	+++	+++	+++	+++	++	++	+++	+++	+++	+++
Neurofilaments	−	−	−	−	−	−	−	−	−	−
Chromogranin A	−	−	−	−	−	−	−	−	−	−
Synaptophysin	−	−	−	−	−	−	−	−	−	−
Oestrogen receptor	−	−	−	−	−	−	−	−	−	−
Progesterone receptor	++	+++	+++	+++	+++	++	+++	++	+++	+++/−[a]
Neuron-specific enolase	++	+++	+++	++	+++	+++	+++	+++	+++	+++
Insulin	−	−	−	−	−	−	−	−	−	−
Glucagon	−	−	−	−	−	−	−	−	−	−
Somatostatin	−	−	−	−	−	−	−	−	−	−
Pancreatic polypeptide	−	−	−	−	−	−	−	−	−	−
Lipase	−	−	−	−	−	−	−	−	−	−
Amylase	−	−	−	−	−	−	−	−	−	−
Trypsinogen	−	−	−	−	−	−	−	−	−	−
Alpha-1-antichymotrypsin	++	++	+++	++	+++	+++	+++	+++	+++	+++
Alpha-1-antitrypsin	−/+[b]	−/+[b]	−/+[b]	−/+[b]	−/+[b]	−/+[b]	−/+[b]	−/+[b]	−/+[b]	−/+[b]

All negative; +, less than 25% positive; ++, 26%–50% positive; +++, more than 50% immunoreactive cells

[a] Pleomorphic and atypical cell component
[b] Clusters of cells with granular positivity

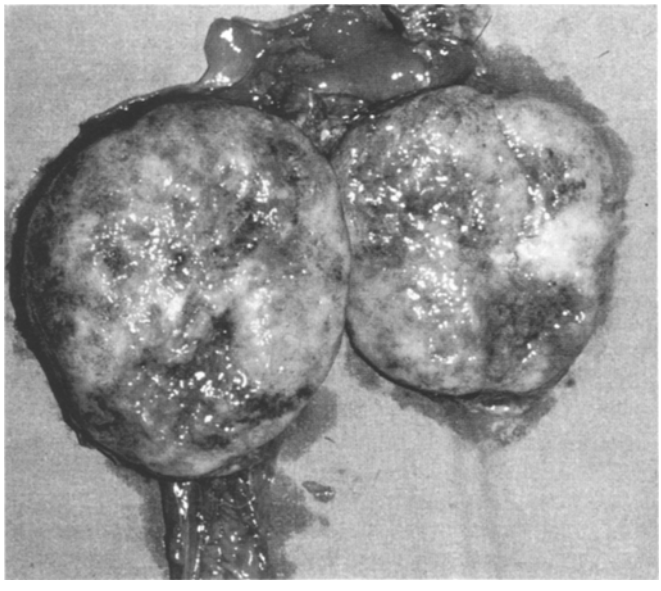

Fig. 1. Cross-section of a solid-cystic tumour of the pancreas characterized by a well-circumscribed, mainly solid mass with small areas of haemorrhage

Results

Macroscopically all tumours were well-circumscribed and exhibited variable proportions of solid and cystic areas (Fig. 1). Microscopically, all cases but one presented uniform features with a mixture of solid, pseudopapillary and cystic areas (Fig. 2). The tumour cells were monomorphous with round to oval nuclei and eosinophilic, granular cytoplasm. PAS-positive globules, stromal myxoid degeneration, necrotic changes and haemorrhage were characteristically present. Mitotic figures

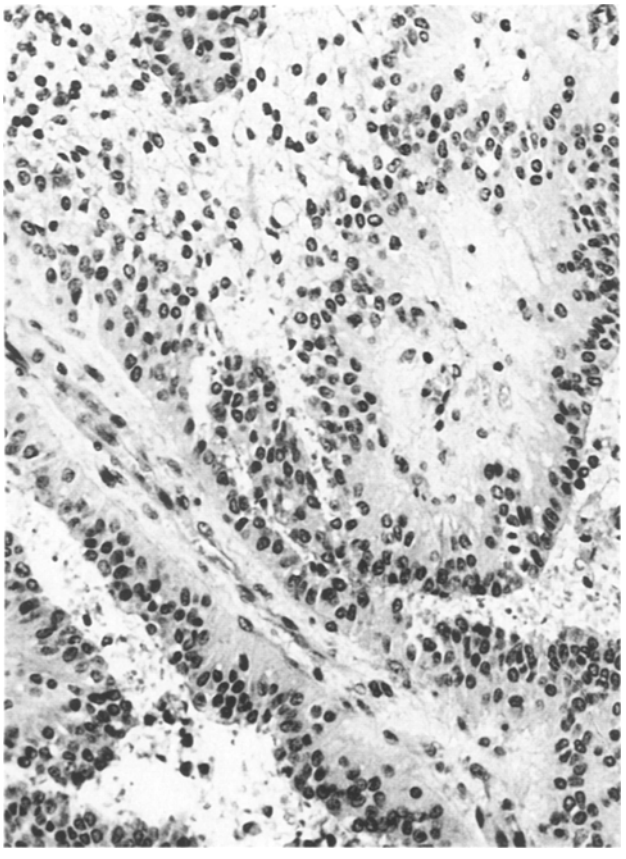

Fig. 2. Solid-cystic tumour of the pancreas: pseudo-papillary structures with thick, hyalinized fibrovascular cores. HE × 250

were extremely rare. In addition to these features, case 10 presented areas of pleomorphic and multinucleated tumour cells with nuclear atypia (Fig. 3), infiltration of the adjacent pancreatic parenchyma by both typical

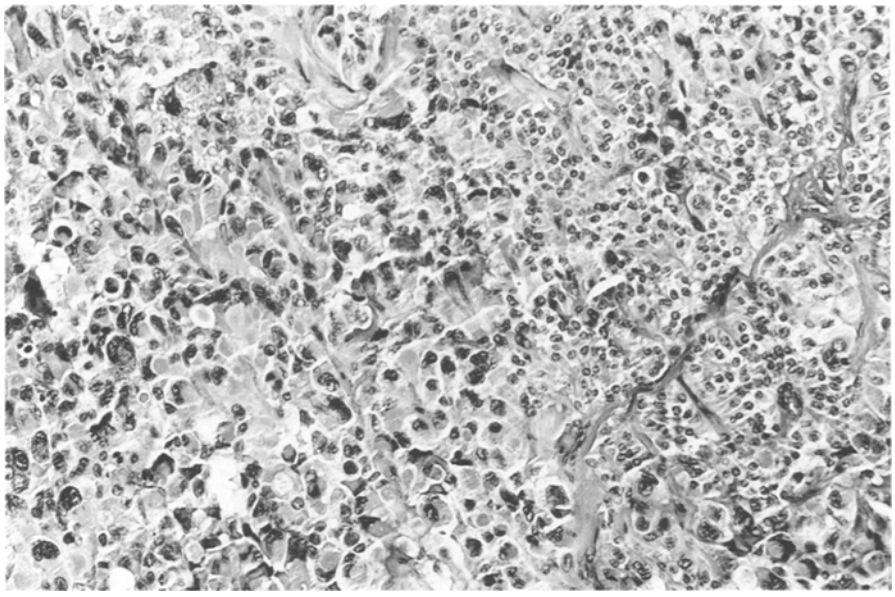

Fig. 3. Case 10 presents some areas with pleomorphic and atypical tumor cells *(left)* intermingled with more typical tumour cells *(right)*. HE × 100

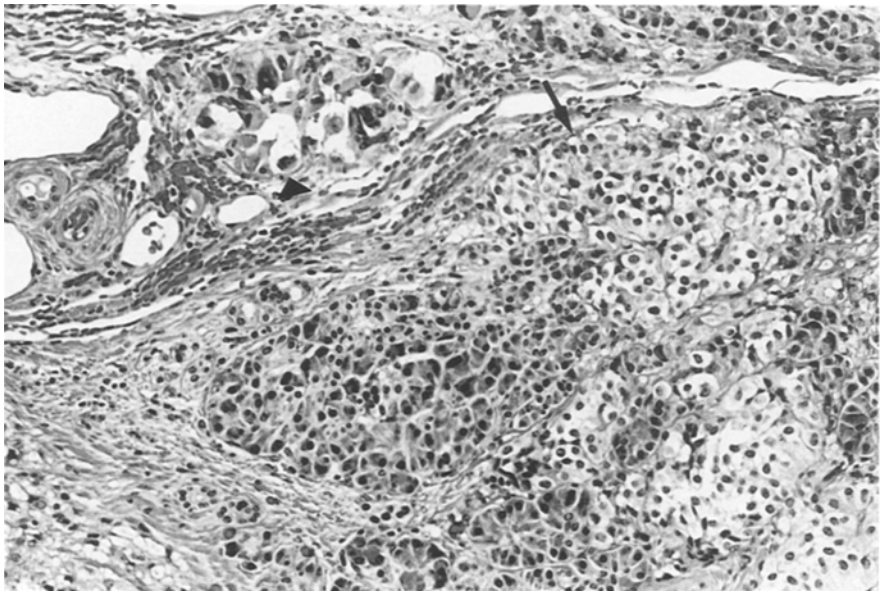

Fig. 4. Case 10. Margin of the lesion showing the typical cell component *(arrow)* directly infiltrating into the pancreatic parenchyma and capsular venous invasion constituted exclusively by pleomorphic and atypical cells *(arrowhead)*. HE × 100

(Fig. 4) and atypical cells and venous invasion constituted exclusively by atypical cells (Fig. 4). Neither necrosis nor mitoses were observed in this case.

The immunohistochemical findings, reported in Table 3, confirmed the diagnosis of SCT. Electron microscopy demonstrated a prevalence of ductular cells with minimal acinar and endocrine differentiation.

Independently of the patient's sex and age, PR immunoreactivity was detected in all ten cases. It was strictly confined to the nucleus of the vast majority of neoplastic cells, either in solid or pseudopapillary areas (Fig. 5a, b). The number of PR-immunostained cells did not significantly differ in frozen and fixed sections from the same tumour or when different mAbs to PR were used. However, the best results, with more intense nuclear staining and cleaner background, were obtained with KD68 rat mAb.

In case 10 the pattern of PR immunoreactivity differed in that pleomorphic cell clusters (Fig. 6) even within vessels (Fig. 7), were all negative, whereas the smaller, peculiar tumour cells were PR positive.

None of the tumours showed ER immunoreactivity on either frozen or fixed sections.

Discussion

In partial contrast with previous reports, in which both biochemical (Bigotti et al. 1989; Carbone et al. 1989; Ladanyi et al. 1987; Wrba et al. 1988) and immunocytochemical methods (Carbone et al. 1989; De Lagausie et al. 1988; Doglioni et al. 1990; Klöppel et al. 1991; Miettinen et al. 1987; Pettinato et al. 1992; Stoemmer et al. 1991; Wrba et al. 1988) were used, all our ten

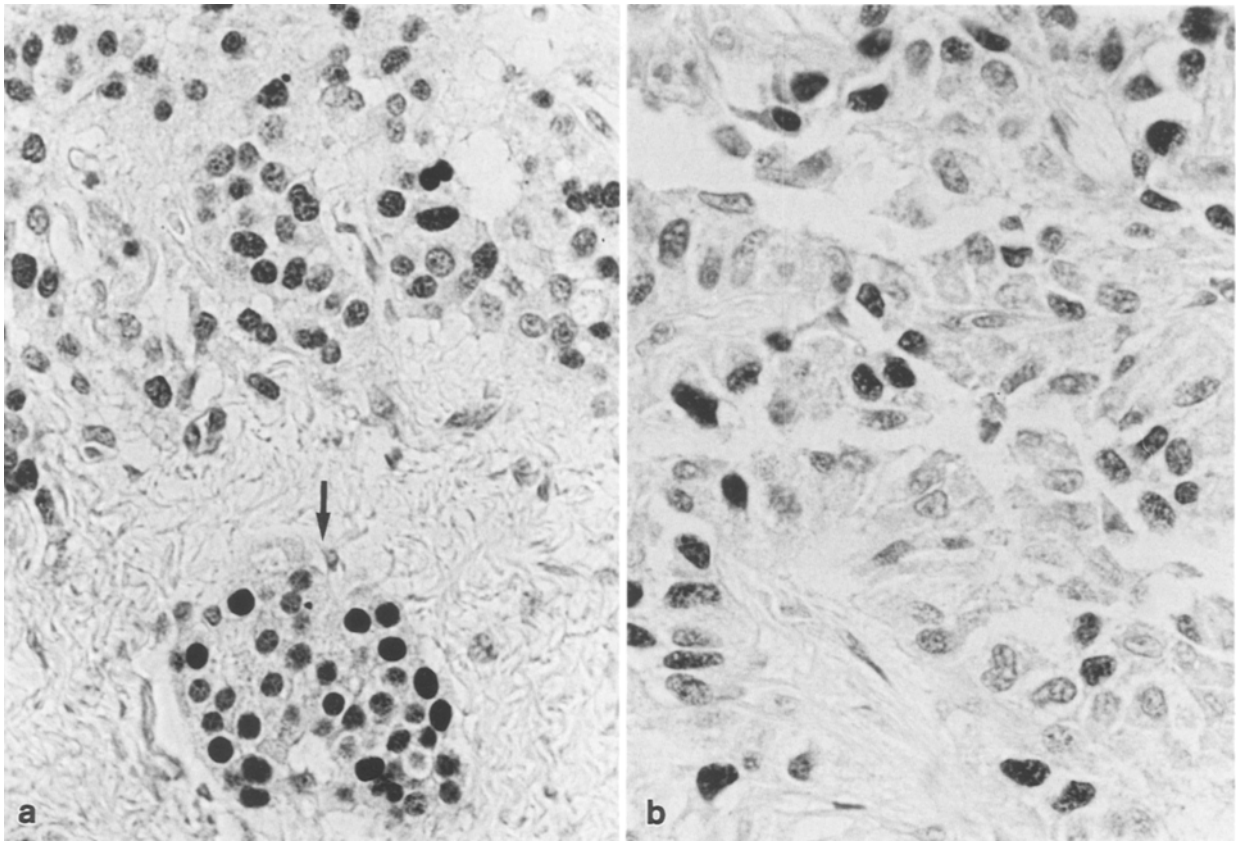

Fig. 5a, b. Nuclear immunoreactivity for progesterone receptors both in solid (**a**) and pseudopapillary (**b**) areas. The islet of Langerhans in the tumour capsule in **a** *(arrow)* shows strong nuclear positivity and serves as positive control. ×400

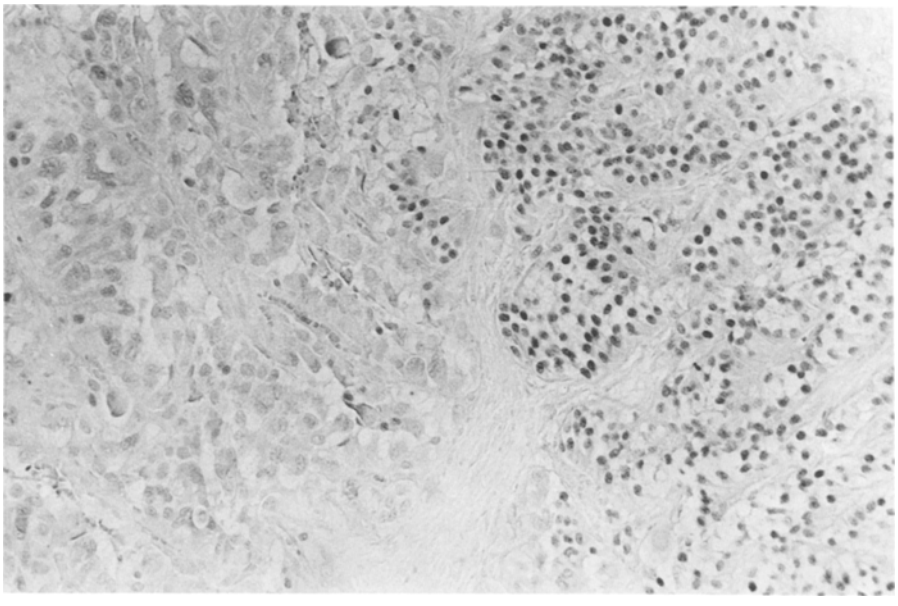

Fig. 6. Case 10. The pleomorphic and atypical tumour cells show negative reaction for progesterone receptors *(left)*, whereas the smaller and more typical tumour cells stain positively *(right)*. ×100

SCT showed PR positivity and ER negativity on immunostaining. By using biochemical methods, ER have been demonstrated in three of five tumour lysates (Bigotti et al. 1989; Carbone et al. 1989; Ladanyi et al. 1987; Wrba et al. 1988) and PR in all four cases tested (Carbone et al. 1989; Ladanyi et al. 1987; Wrba et al. 1988). However, the results in these reports differ considerably with regard to the receptor concentration among the different tumours and to their presence or absence in normal pancreatic tissue.

As in the present cases, immunohistochemical methods failed to demonstrate ER in the nine previously

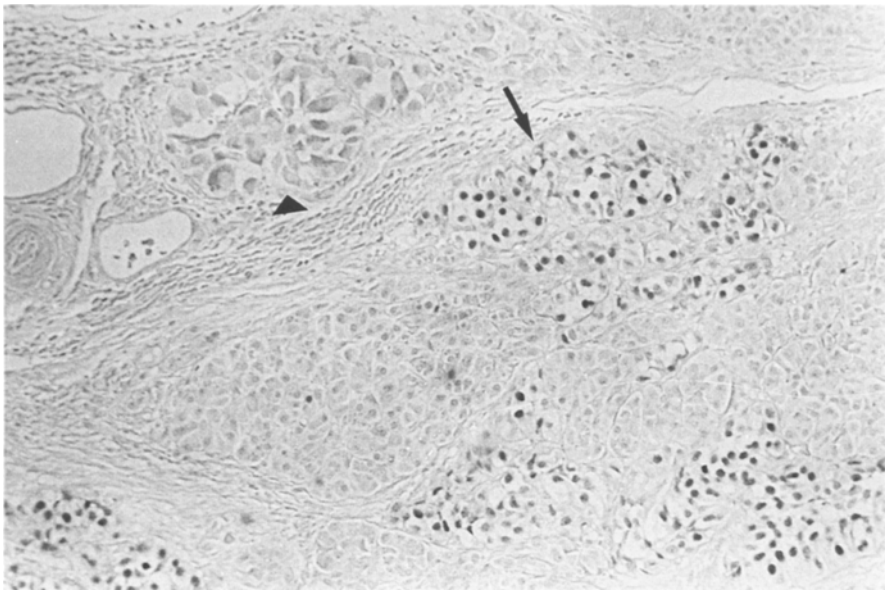

Fig. 7. Case 10. The pleomorphic and atypical cells invading a vascular space in the peripheral portion of the lesion (arrowheaded in Fig. 4.) show no progesterone receptor (PR)-reactivity *(arrowhead)*. The PR positivity is restricted to the typical cell component *(arrow)*, which infiltrated the pancreatic parenchyma. ×100

tested SCT (Carbone et al. 1989; De Lagauise et al. 1988; Doglioni et al. 1990; Klöppel et al. 1991; Miettinen et al. 1987; Wrba et al. 1988). In contrast positive PR immunoreactivity was reported, though only in a few of the tested cases (De Lagausie et al. 1988; Stoemmer et al. 1991), without specification of the antibodies used. Klöppel et al. (1991) and Pettinato et al. (1992) reported negative PR immunoreactivity, the former using KD68 mAb, the latter using a different mAb, both concluding that there is little evidence of a sex female hormone dependence of SCT.

Our finding of PR immunoreactivity in all ten cases, including the male patient, although better evidenced by KD68 mAb, has been confirmed by immunoreaction with two mouse mAbs LET126 and Li417. Immunohistochemical methods seem, thus, to represent a useful tool in evaluating the PR status in SCT.

PR positivity may support the hypothesis of a possible pathogenetic role of progesterone in SCT independent of the patient's age and sex. However, it is not possible to exclude that it simply represents an epiphenomenon, if one considers that PR are also expressed in pancreatic endocrine tumours (Viale et al. 1992) and in normal islets (Doglioni et al. 1990).

The synthesis of PR in sex hormone target tissues is considered to be induced by oestradiol (Leavitt et al. 1977). The absence of ER immunoreactivity in SCT may suggest that either the sensitivity of anti-PR antibody is greater than the anti-ER antibody, with the result that biochemically detectable ER cannot be immunocytochemically localized, or that the PR-positive cells of SCT represent a cell population in which PR are constitutively synthesized in an oestrogen-independent way, as in the normal endocrine cells of the islets of Langherans (Doglioni et al. 1990), T47D breast carcinoma cell lines (Horwitz et al. 1982), meningioma cells (Stojkovic et al. 1990; Tilzer et al. 1982) and some gastric cancer cells (Wu et al. 1990).

Recently, PR but not ER have been localized immunohistochemically in a large proportion of pancreatic endocrine tumours (Viale et al. 1992). The PR immunoreactivity in these endocrine tumours presents some differences with respect to those found in SCT. Only 58% of islet cell tumours showed PR immunoreactivity, which appeared more frequent in functioning than non-functioning tumours. PR immunoreactivity correlated significantly with the absence of metastases and lack of tumour invasion and should be regarded as a useful prognostic marker. Since none of our SCT showed malignant behaviour, it is conceivable that the expression of PR in SCT may have the same favourable prognostic significance. Analysis of the two cell populations in case 10 highlights their different behaviour with regard to PR, since the more anaplastic cells, which gave rise to vascular invasion, were PR negative whereas the more "typical" tumour cells were PR positive. PR negativity seems, thus, to correspond to a more aggressive malignant tendency on purely morphological grounds.

Information on the PR status in SCT might, thus, be useful in predicting malignant potential. It is not possible to rule out the hypothesis that PR negativity in atypical cells may simply reflect the inability to synthesize receptor protein or a resting phase in such cells. Follow-up of this and similar cases will probably clarify the issue.

The different cell populations in this particular case emphasize the value of the immunohistochemical methods in the detection of the different percentages and distribution of PR: the PR-negative cell component would have been missed with the steroid binding techniques on tissue homogenates.

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