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Solid and Cystic Acinar Cell Tumour of the Pancreas

A Tumour in Young Women with Favourable Prognosis*

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Summary. The clinico-pathological features of five cases with a distinctive pancreatic tumour are presented. The tumours, which occurred only in young women and an adolescent girl, were of large size (2.5–10 cm), had an uncharacteristic symptomatology and showed fibrous encapsulation with no evidence of metastases. The histological features include (1) solid areas with a monomorphic cell pattern and intracellular PAS positive globules, and (2) large foci of degeneration with cystic necroses, haemorrhages and cholesterol granulomas. Some tumour cells were positive for α_1-antitrypsin. The ultrastructural demonstration of zymogen-like granules suggests an acinar origin for the tumours. We therefore propose the term solid and cystic acinar cell tumour. This tumour resembles the so called pancreatoblastomas in small children in some respects. It must be clearly distinguished, on the other hand, from acinar cell carcinoma with its acinic structures and poor prognosis. This lesion is not included in the WHO classification of pancreatic neoplasms.

Key words: Pancreas tumours – Young women – Acinar cell origin – Classification – Prognosis

Introduction

The WHO-classification of epithelial pancreatic neoplasms distinguishes between papillary and cystic adenomas and carcinomas of tubulo-papillary, mucinous, adenosquamous, squamous, cystadenomatous, acinar and undifferentiated type (Gibson and Sobin 1978). The series, however, does not include some unusual tumours which have mainly occurred in children and adolescents and which have behaved quite differently from the common ductular, acinar or endocrine tumours of the pancreas (Taxy 1976; Horie et al. 1977; Cubilla and Fitzgerald

* Dedicated to Prof. Dr. G. Seifert in honour of his sixtieth birthday

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1979; Benjamin and Wright 1980). The reason for their not being included in the WHO-series is probably that, because of the small number of cases, their classification remains uncertain.

We observed this tumour in four young women aged 24 to 33 and in a 14-year-old girl. All five tumours showed identical behaviour and morphology. The aim of our study is to outline this clinico-pathological entity and review the literature on this subject.

Case Reports

Case 1. A 33-year-old woman was admitted to hospital with massive obesity and amenorrhoea of one years duration. The endocrinological examination revealed no abnormalities. However, sonography, computerized tomography (CT) and angiography of the pancreas and the left suprarenal gland demonstrated a tumour of about 5 cm in diameter in the pancreatic tail and another of about 4 cm in diameter in the left suprarenal gland. Subsequent laparotomy confirmed these findings and led to the removal of a fist-sized encapsulated tumour from the pancreatic tail and another tumour of walnut-size from the adrenal gland. The tumours were not connected with each other. The adrenal tumour was a non-functioning adrenocortical adenoma. No metastases were observed. The patient's condition is satisfactory one year after the operation.

Case 2. A 24-year-old woman was admitted to hospital because of undefined abdominal discomfort and a palpable tumour in the upper abdomen. Sonography and CT localized a large tumour in the head of the pancreas. There were no endocrine abnormalities. At laparotomy a tumour of fist-size was found attached to the pancreatic head. It was easily removed. One year postoperatively the patient is doing well.

Case 3. In a 32-year-old woman a vagotomy was performed because of a bleeding chronic duodenal ulcer. During this operation a pancreatic tumour, size of a walnut, palpated in the head of the pancreas, was removed. No metastases were found. Clinically the patient showed no endocrine abnormalities. One-and-a-half years after removal of the tumour the patient is doing well.

Case 4. A 30-year-old woman was admitted to hospital with the complaint of upper abdominal discomfort of 2-years duration. X-rays had shown calcification in the region of the pancreatic tail 4 years earlier. This finding was confirmed by CT. Subsequent laparotomy resulted in the removal of an encapsulated tumour in the pancreatic tail, which was as large as an apple. There were no metastases. Six months postoperatively the patient is doing well and shows no evidence of a tumour recurrence.

Case 5. A 14-year-old girl was admitted to hospital with a mass in the upper abdomen, which she had already noticed one year earlier. Endocrine abnormalities were excluded. By CT, sonography and angiography the tumour was localized in the pancreatic head. At the subsequent laparotomy a fistsize tumour was completely removed from the pancreatic head. There were no metastases. The postoperative course was uneventfull.

Methods

Light Microscopy. All five surgical specimens were formalin-fixed and routinely processed. Serial paraffin embedded sections were stained with haematoxylin and eosin, periodic acid Schiff (PAS), aldehyde fuchsin, phosphotungstic acid haematoxylin (PTAH), Gomori's method for reticulin and the silver technique of Grimelius and Masson-Hamperl.

Immunocytochemistry. Insulin, glucagon, somatostatin, pancreatic polypeptide (PP), gastrin and α_1-antitrypsin were visualized using the indirect immunoperoxidase method (insulin) or by using the unlabelled enzyme method (Sternberger 1979) as previously described (Klöppel et al. 1978). The dilution of the α_1-antitrypsin serum (DAKO Immunoglobulins, Denmark) was 1/500. The

Table 1. Clinico-pathological data

Case No.	Age/Sex	Symptoms	Location	Size (cm)	Metastases
1	33/F	No symptoms. Discovered by CT	tail	10 × 10	no
2	24/F	Abdominal mass. Abdominal discomfort	head	7 × 8	no
3	32/F	Found at vagotomy for duodenal ulcer	head	2.5 × 2.5	no
4	30/F	Abdominal discomfort for 2 years	tail	4 × 5	no
5	14/F	Abdominal mass	head	8 × 8	no

specificity of the reactions was tested as follows: (1) non-immune rabbit serum as first layer (2) specific antiserum absorbed with 50 µg of the antigen per ml diluted serum, (3) omission of 3.3′-diaminobenzidine-tetrahydrochloride or H_2O_2 from the incubation medium for the peroxidase reaction.

Apart from the five reported tumours, three ductular adeno-carcinomas, one cystadenocarcinoma, the liver metastases of an acinar carcinoma and normal parenchyma of the pancreas were stained for α_1-antitrypsin.

Electron Microscopy. Tumour pieces from case 1 were fixed in phosphate buffered glutaraldehyde (2.5%, pH 7.5) and postfixed in cacodylate buffered osmium tetroxide (1%). The tissue blocks were dehydrated in graded ethanol and embedded in Epon. Ultrathin sections were stained with uranylacetate and lead citrate, and examined in a Zeiss EM 10 electron microscope.

Formalin fixed tissue from cases 2 and 3 was cut into 1 mm cubes and postfixed in buffered 1% osmium tetroxide for 2 h. Further processing was as described above.

Results

Gross Features. The localization and size of the tumours are summarized in Table 1. Each of the tumour masses was round and encased in a fibrous tissue capsule, which separated it well from the normal pancreatic tissue. The tumours were fluctuant. The cut surfaces showed lobulated light brown tissue, mostly located at the periphery and a central zone of degeneration with haemorrhages and cavities filled with necrotic debris and surrounded by sclerotic tissue (Fig. 1). In case 5 the central necrosis of the tumour was so massive that there was only a small rim of solid tissue under the fibrous capsule. No connections of the tumours with the duct system of the pancreas were noted.

Microscopy. The well preserved tissue from the tumour periphery showed a solid pattern of polygonal cells, which were arranged around delicate fibrovascular stalks in pseudopapillary sheets (Fig. 2a) or pseudorosettes (Fig. 2b). In other areas the vessels were ensheathed by a hyaline stroma (Fig. 3). The single cells exhibited a well developed eosinophilic cytoplasm, containing polygonal to oval nuclei with a loose chromatin structure (Fig. 4a). Mitoses were very rare. Ocassionally there were large PAS-positive granules within or between the cells (Fig. 4). Apart from those eosinophilic cells there were single cells or clusters of them showing vacuolated cytoplasm with fine PAS-positive granu-

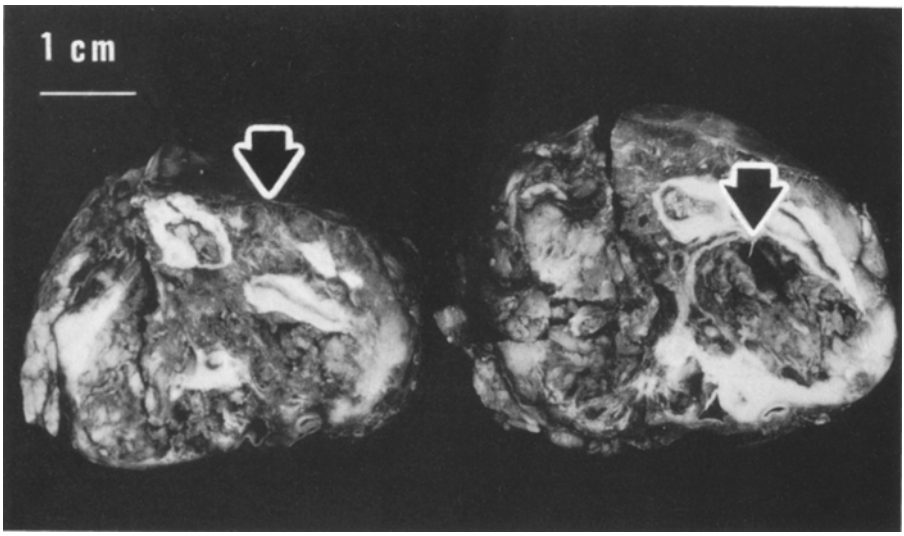

Fig. 1. Cut surfaces of the solid and cystic acinar tumour of the pancreas from case 4. Note the solid areas (*arrow*) and the cystic degenerative changes (*arrow*) surrounded by hyalinised tissue

larity (Fig. 5). Between these cells small cysts had often developed which were filled with amorphous, slightly PAS-positive material (Fig. 5). Adjacent to these viable tissues there were large areas with cystic and other degenerative changes such as haemorrhage, hyalinisation and cholesterol granulomas found in four of the five tumours. In addition, one tumour contained foci of calcification. Most conspicious were the cholesterol granulomas, which were mainly located at the periphery of the cystic areas (Fig. 6), but some small granulomas were also seen within the solid tissue. The tumours were seperated from the normal pancreatic parenchyma by a layer of connective tissue, which was sometimes invaded by tumour complexes. However, the surrounding tissue was not involved in any of these cases.

Immunocytochemistry. Testing with anti-insulin-, anti-glucagon-, antisomatostatin-, anti-PP- and antigastrin serum gave negative results. In contrast, staining with α_1-antitrypsin revealed a positive granular reaction in individual cells in each of the five tumours (Fig. 7). Positivity for α_1-antitrypsin was also found in the liver metastasis of an acinar cell carcinoma, while all the ductular carcinomas and the normal exocrine parenchyma were negative.

Ultrastructure. The closely packed cells occasionally formed small intercellular spaces resembling rudimentary acini. The cytoplasm contained numerous mitochondria (Fig. 8) some polyribosomes and single endoplasmic lamellae. Most conspicious, however, were large zymogen-like granules of various sizes (500–3,000 nm), which were very numerous in some of the cells (Fig. 8). At their periphery, the granules showed small degenerative vacuoles filled with pleomorphic cores (Fig. 9). Some of the zymogenlike granules were already trans-

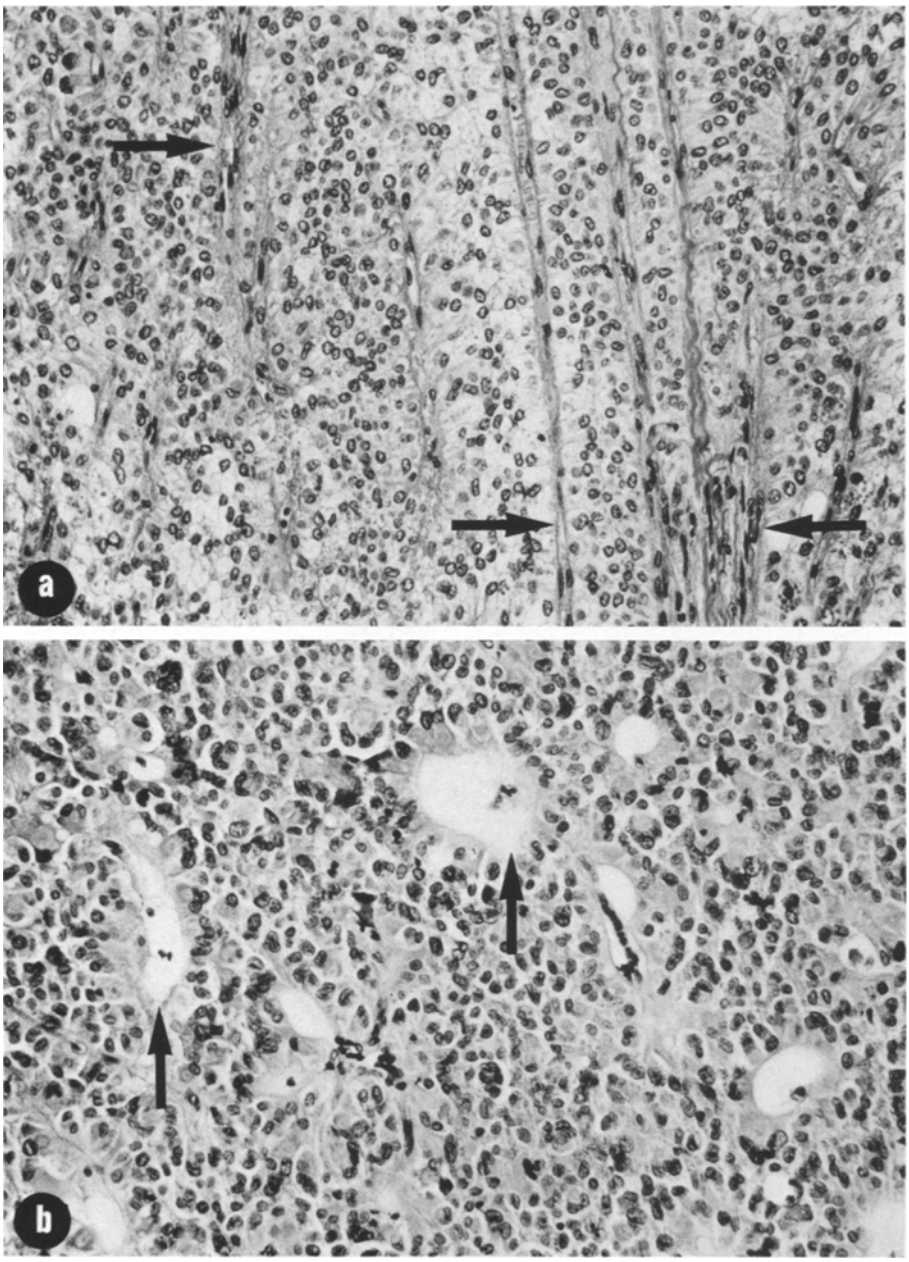

Fig. 2a, b. Acinar tumour of the pancreas with solid cellular pattern. **a** pseudo-papillary structures around fibrovascular stalks (*arrows*). **b** Pseudorosettes (*arrows*) simulating tubular structures. PAS, ×250

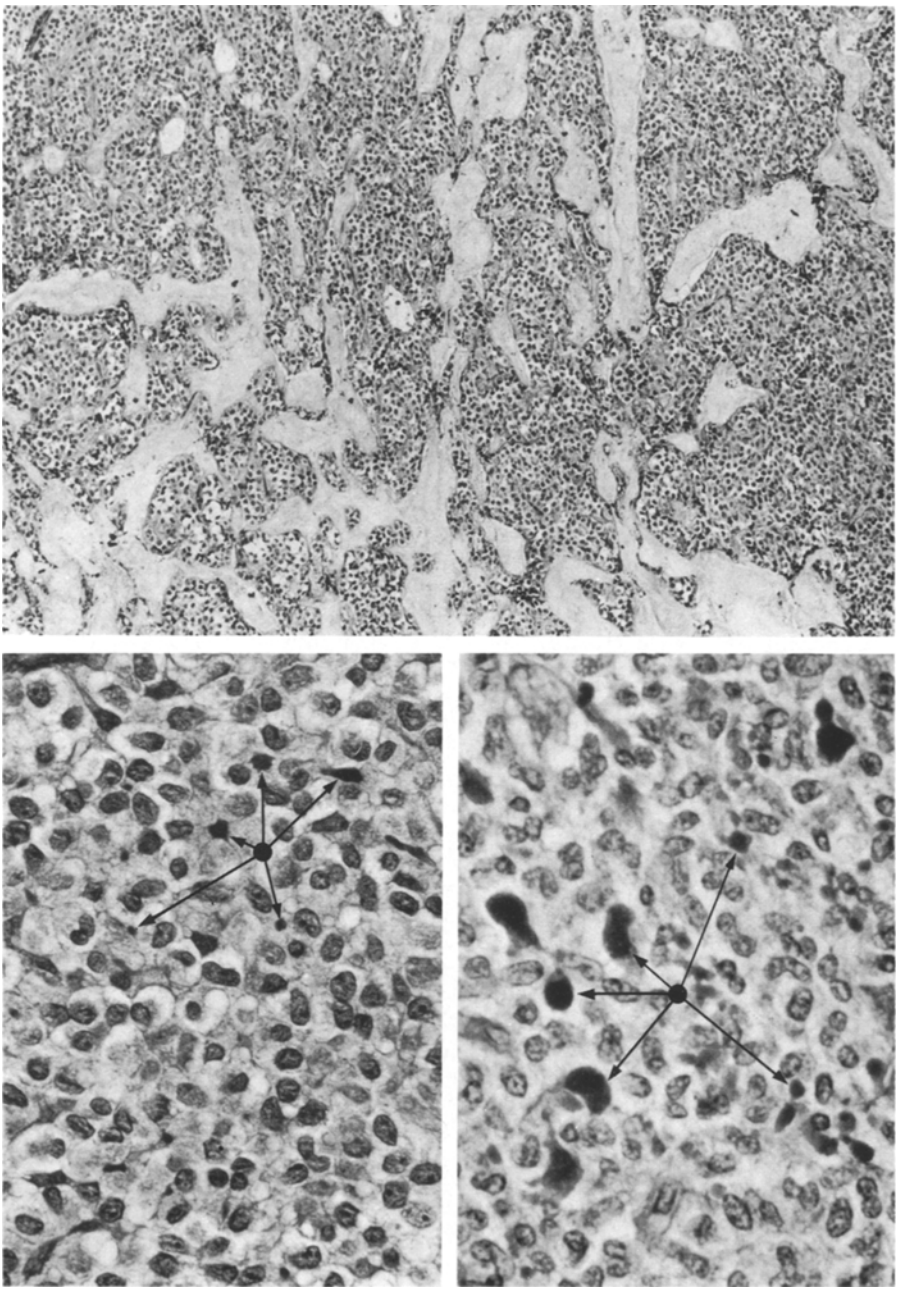

Fig. 3. Solid areas of an acinar tumour showing markedly hyalinised stroma. PAS, ×140

Fig. 4. High power views of closely packed cells in acinar tumours. Note the PAS-positive globules within and between the tumour cells (*arrows*). PAS, ×640

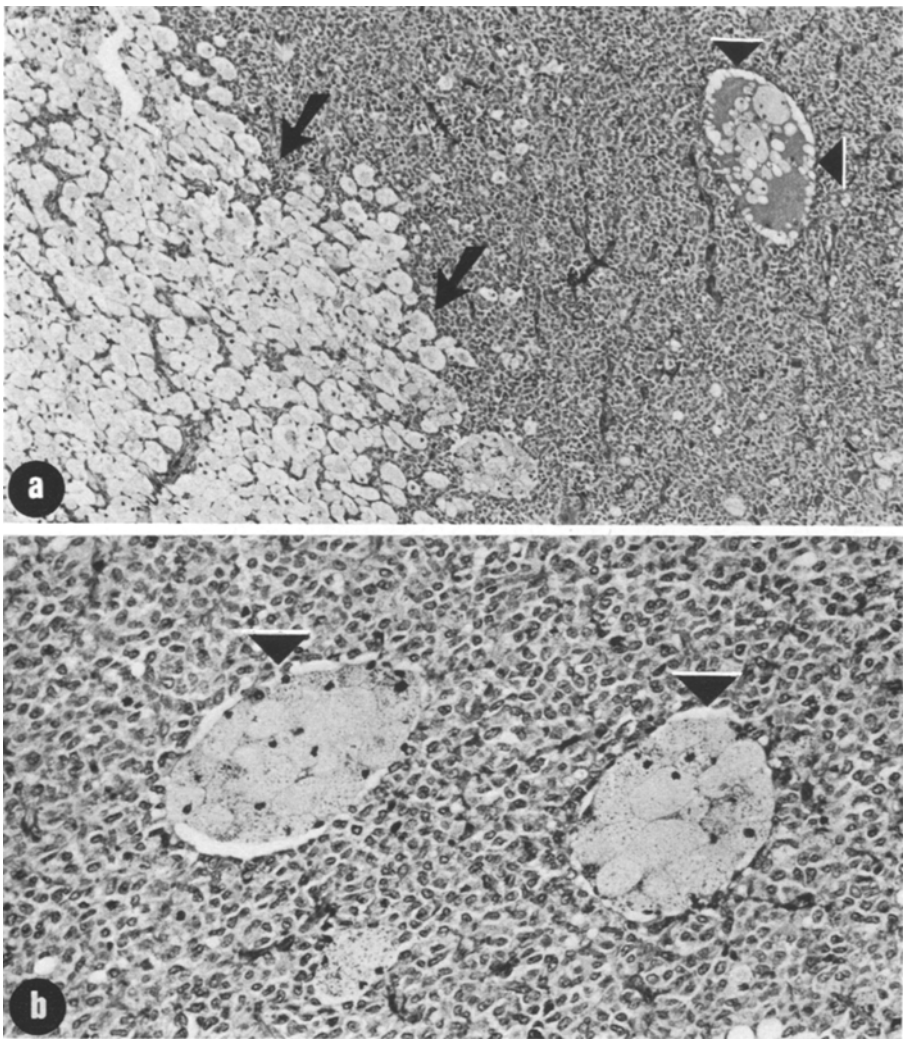

Fig. 5a, b. Solid acinar tumour with groups of vacuolated cells (*arrows*). **a** The tumour tissue contains a small cyst with remnance of vacuolated cells (*arrow heads*). **b** Groups of vacuolated cells showing a fine PAS-positive granularity of the cytoplasm (*arrow heads*). PAS, ×140 and 250

formed to vacuoles containing only zymogen debris. Exocytotic processes were not observed. The nucleus was irregularly formed and showed only little heterochromatin and a small nucleolus. Those cells, which histologically were characterized by clear cytoplasm, had cytoplasm showing numerous lysosomal vacuoles with spotty (lipid) degradation remnants at the ultrastructural level.

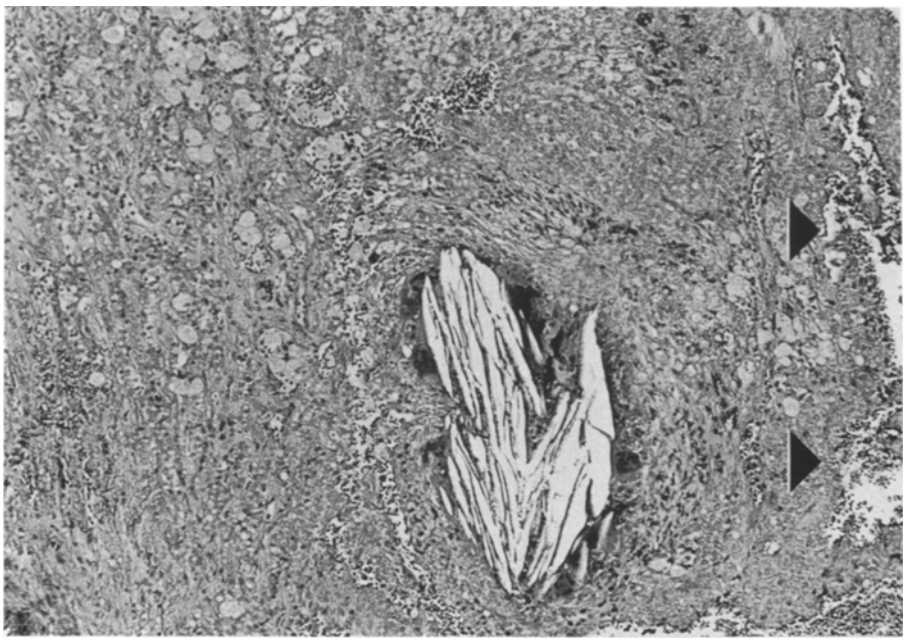

Fig. 6. Cholesterol granuloma at the edge of cystic necrosis with haemorrhages (*arrow heads*). HE, × 140

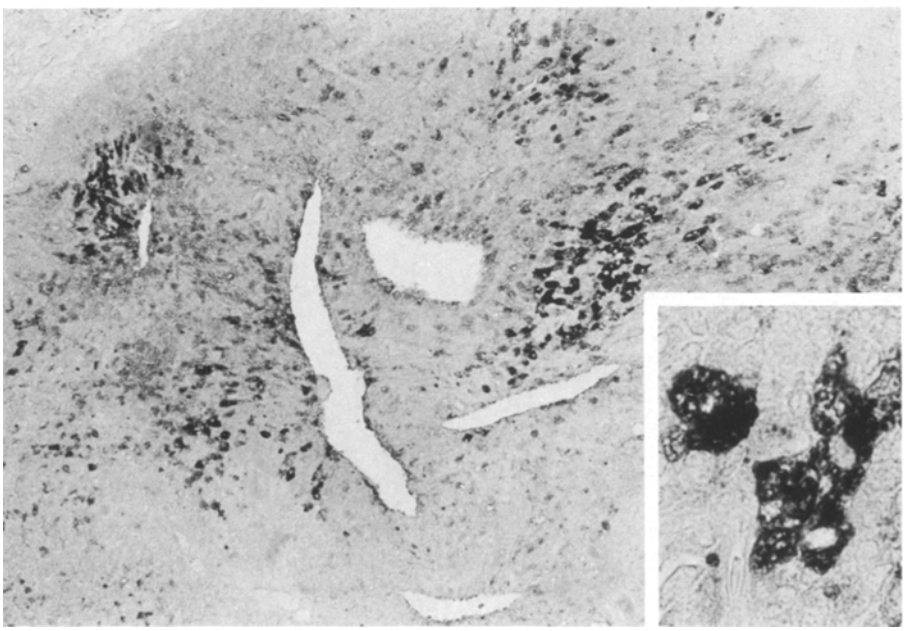

Fig. 7. Positive immunocytochemical staining (PAP-method) for α_1-antitrypsin in a solid and cystic acinar tumour. Positive cell clusters with a granular reaction product (*inset*). × 140 and 640

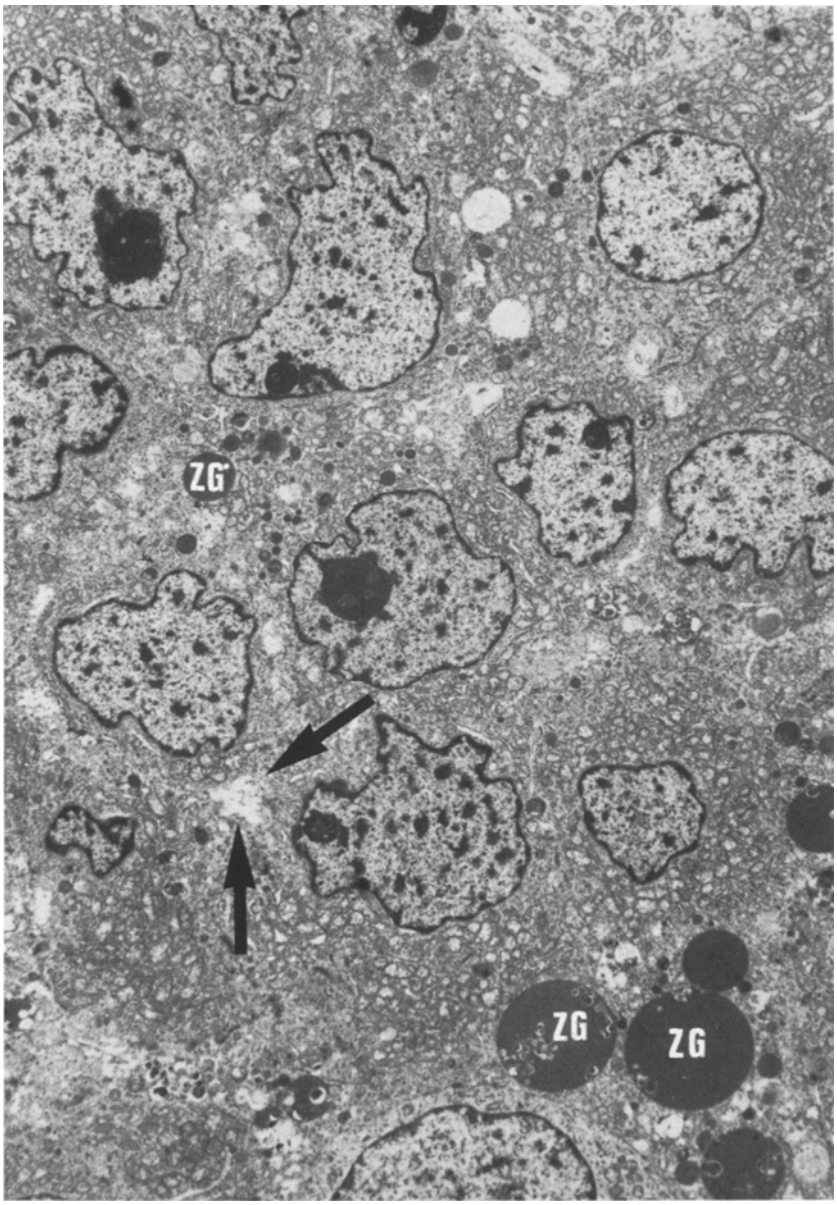

Fig. 8. Low power electron micrograph showing closely packed cells with small acinar lumen (*arrow*). The cells are rich in mitochondria. Some of the cells countain large zymogen-like granules (*ZG*) ×4,370

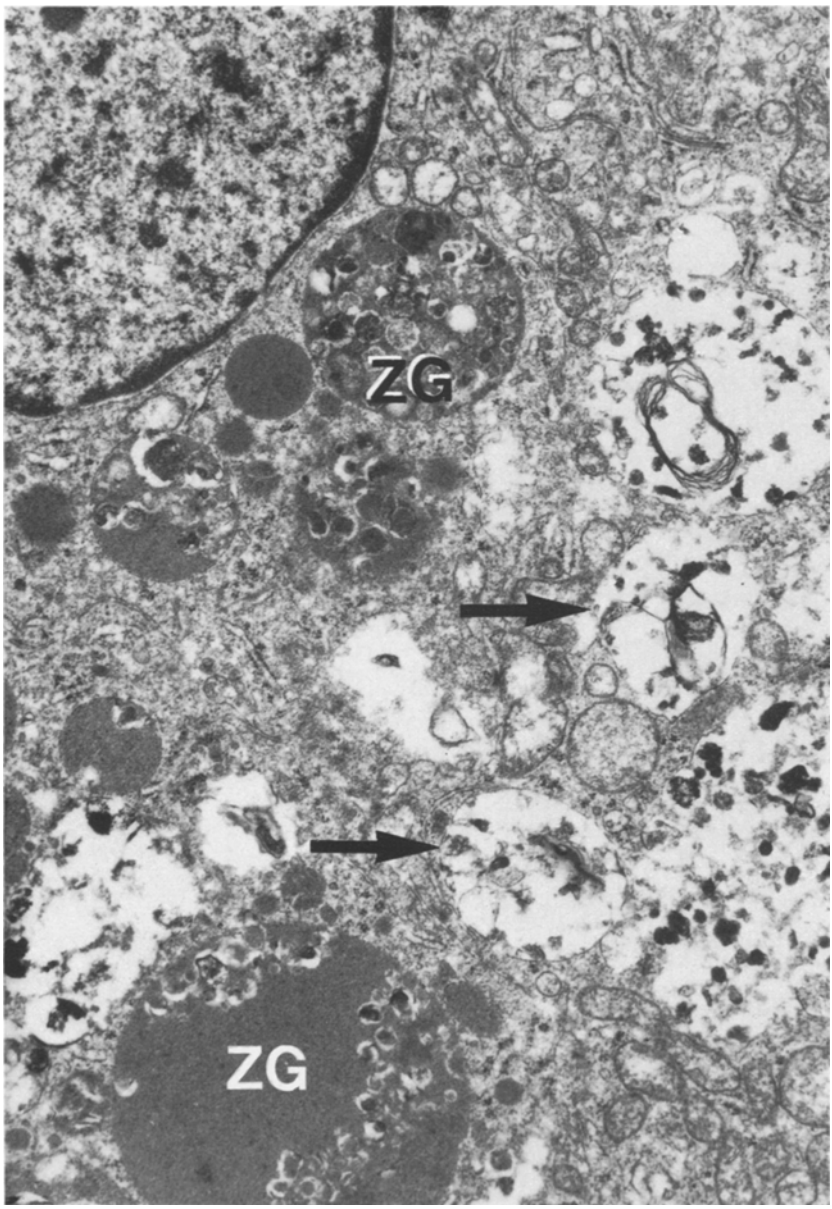

Fig. 9. Ultrastructural appearance of zymogen-like granules (*ZG*) in a solid and cystic acinar tumour. Almost all granules showed degenerative lesions with disintegration of the zymogen content (*arrows*). × 7,820

Discussion

The five pancreatic tumours we studied had the following clinico-pathological features in common: occurrence in young women, uncharacteristic discomfort in the upper abdomen, slow growth, remarkable size, good encapsulation, solid and pseudopapillary cell patterns, well developed vascularization and widespread degenerative changes including cystic necroses, haemorrhage, cholesterol granulomas and hyalinization. All the tumours lacked tubular or true papillary structures. Further, they failed to stain with any of the known pancreatic hormones or with gastrin.

On the basis of these findings a ductular or endocrine nature of the tumour can be excluded. Acinar origin is strongly suggested by the ultrastructural demonstration of zymogen granules. As further evidence of this, we recently succeeded in the immunocytochemical demonstration of lipase in one of the tumours (Roth and Klöppel, unpublished observations). Though this finding has yet to be confirmed in the other tumours, it seems reasonable to classify these neoplasms as acinar tumours. This raises the question of their distinction from those tumours which are listed in the WHO-series as acinar cell carcinomas (Gibson and Sobin 1978). These acinar neoplasms in young women have to be related to a number of reports in the literature, showing similar or identical features.

In reviewing the relevant literature tumours identical with ours were found described as "papillary epithelial neoplasm of pancreas in a child" (Hamoudi et al. 1970), "adenocarcinoma of the pancreas in childhood" (Benjamin and Wright 1980; Taxy 1976) and "papillary and cystic neoplasms" (Cubilla and Fitzgerald 1979; Boor and Swanson 1979). These names indicate that the neoplasms were observed predominantly in children and were mostly considered to be adenocarcinomas. Altogether we accumulated nine cases of this type from literature (Nanson 1954; Warren 1955; Frantz 1959; Hamoudi et al. 1970; Taxy 1976; Cubilla and Fitzgerald 1979; Boor and Swanson 1979; Benjamin and Wright 1980, 2nd case) two of which are mainly characterized in this retrospective view by their clinical and gross features (Nanson 1954; Warren 1955) while their histological descriptions are rather inconclusive. All of the neoplasms occurred in adolescent girls or young women. The large non-metastasising tumours were predominantly located in the pancreatic head. It appears from the reports that all the patients except one where the tumour reccurred seven years after the operation (Cubilla and Fitzgerald 1979) were cured by tumour resection. The longest postoperative course, 21 years without evidence of recurrence, was reported by Frantz (1959)

Similar although not identical tumours have been described in small children (Becker 1957; Frable et al. 1971; Horie et al. 1977; Cubilla and Fitzgerald 1979; Benjamin and Wright 1980, 1st case). Horie et al. (1977) observed two of these neoplasms and called them pancreatoblastomas. These tumours are distinguished from ours by the following features: a predominant occurrence in small children of both sexes, occasional malignancy, organoid tumour structures with partly acinic patterns and scattered squamoid corpuscles and mesenchymal elements. Because of this variable mixture of tissue elements, these

tumours were designated pancreatoblastomas, similar to nephroblastomas and hepatoblastomas (Horie et al. 1977).

A distinct separation must be made between our solid acinar neoplasms and the acinar cell tumours which are listed in the WHO-classification (Webb 1977; Gibson and Sobin 1978). The latter tumours, which mostly occur in adults (Becker 1973; Webb 1977) and only rarely in children (Moynan 1964; Mah et al. 1974; Wilander et al. 1976; Osborne et al. 1977), are almost all malignant and occur equally in both sexes (Webb 1977). Histologically the tumours exhibit a variably developed acinar and partly trabecular pattern (Schreiber and Probst 1977; Cubilla and Fitzgerald 1979). The cytoplasm of the cells is granular and slightly PAS positive, showing typical zymogen granules on electron microscopy (Burns et al. 1974; Webb 1977). The acinar cell carcinoma lacks encapsulation, pseudopapillary patterns, solid vacuolated cell complexes and degenerative lesions (cholesterol granulomas, hyalinisation and haemorrhage) which distinguish the solid and cystic acinar cell tumour. Furthermore, some acinar cell carcinomas may secrete lipase and may thereby induce a generalized panniculitis and arthralgia snydrome (Wuketich and Pavlik 1963; Burns et al. 1974; Schreiber and Probst 1977).

On the basis of these considerations it is obvious that the acinar cell tumours represent a heterogenous group. Since their distinction is of prognostic relevance we propose the following designations: (1) acinar cell carcinoma, a tumour with malignant behaviour "forming epithelial structures resembling pancreatic acinar tissue" (WHO-classification), (2) solid and cystic acinar cell tumour, a tumour in young women with favourable prognosis when it can be completely removed (Frantz 1959), and (3) pancreatoblastoma, a tumour in small children which also seems to have a good prognosis, only one malignant case has been observed (Cubilla and Fitzgerald 1979).

The exclusive occurrence of the solid and cystic acinar tumours in young women makes it likely that genetic and hormonal factors play a decisive role in their aetiology. The wide-spread degenerative lesions which make the solid acinar tumours so cystic may be induced by degeneration of the zymogen granules in the cells, with subsequent release of enzymes. Activation of these enzymes would then initiate the breakdown of cells, finally leading to necrosis, cholesterol crystalisation, haemorrhage and focal hyalinisation.

It is not known why some tumour cells contain α_1-antitrypsin. Since α_1-antitrypsin was also found in an acinar cell carcinoma but not in ductular carcinomas, it may serve as a marker for acinar cell tumours in general.

In summary, we observed solid and cystic acinar cell tumours of the pancreas in young women and although the number of cases observed is still limited, we feel that they represent a clinico-morphological entity with a favourable prognosis.

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Addendum: Since this paper was submitted, we observed two other cases (28-year-old and 35-year-old women) with identical tumours as described above. One case has a postoperative course of 6 years without evidence of recurrence. Moreover, another case report of this tumour type was published (Alm et al. (1981) Acta Pathol Microbiol Scand Sect A 89:125–132).

References

Becker V (1973) Bauchspeicheldrüse (Inselapparat ausgenommen). In: Doerr W, Seifert G, Uehlinger E (eds) Spezielle pathologische Anatomie, Bd 6. Springer, Berlin-Heidelberg-New York

Becker WF (1957) Pancreatoduodenectomy for carcinoma of the pancreas in an infant: report of a case. Ann Surg 145:864–870

Benjamin E, Wright DH (1980) Adenocarcinoma of the pancreas of childhood: a report of two cases. Histopathology 4:87–104

Boor PJ, Swanson MR (1979) Papillary-cystic neoplasm of the pancreas. Am J Surg Pathol 3:69–75

Burns WA, Matthews MJ, Hamosh M, Vanderweide G, Blum R, Johnson FB (1974) Lipase secreting acinar cell carcinoma of the pancreas with polyarthropathy – a light and electron microscopic, histochemical and biochemical study. Cancer 33:1002–1009

Cubilla AL, Fitzgerald PJ (1979) Classification of pancreatic cancer (nonendocrine). Mayo Clin Proc 54:449–458

Frable WJ, Still WJS, Kay S (1971) Carcinoma of the pancreas, infantile type. A light and electron microscopic study. Cancer 27:667–673

Frantz VK (1959) Tumour of the pancreas. In: Atlas of tumor pathology VII, fasc. 27 and 38. Armed Forces Institute of Pathology, Washington DC,

Gibson JB, Sobin LH (1978) Histological typing of tumours of the liver, biliary tract and pancreas. WHO, International Histological Classification of Tumours, No 20. World Health Organization, Geneva

Hamoudi AB, Misugi K, Grosfeld JL, Reiner CB (1970) Papillary epithelial neoplasm of pancreas in a child. Cancer 26:1126–1134

Horie A, Yano Y, Kotoo Y, Miwa A (1977) Morphogenesis of pancreatoblastoma, infantile carcinoma of the pancreas. Report of two cases. Cancer 39:247–254

Klöppel G, Bommer G, Commandeur G, Heitz Ph (1978) The endocrine pancreas in chronic pancreatitis. Immunocytochemical and ultrastructural studies. Virchows Arch [Pathol Anat] 377:157–174

Moynan RW, Neerhout RC, Johnson TS (1964) Pancreatic carcinoma in childhood. J Pediat 65:711–720

Mah PT, Loo DC, Tock EPC (1974) Pancreatic acinar cell carcinoma in childhood. Am J Dis Child 128:101–104

Nanson EM (1954) An unusual case of carcinoma of the head of the pancreas. Br J Surg 41:439–441

Osborne BM, Culbert SJ, Cangir A, Mackay B (1977) Acinar cell carcinoma of the pancreas in a 9-year-old child: case report with electron microscopic observations. Southern Med J 70:370–372

Schreiber D, Probst HJ (1977) Sekretorisch aktives Karzinom des exokrinen Pankreas. Fallbericht und Literaturübersicht. Zentralbl Allg Pathol Pathol Anat 121:114–121

Sternberger LA (1979) Immunocytochemistry, 2nd edn. J Wiley, New York – Chichester – Brisbane – Toronto

Taxy JB (1976) Adenocarcinoma of the pancreas in childhood. Report of a case and a review of the English language literature. Cancer 37:1508–1518

Warren KW (1955) Non-functioning islet cell carcinoma in an 11 year-old child treated by pancreatoduodenectomy. Lahey Clin Bull 9:155–159

Webb JN (1977) Acinar cell neoplasms of the exocrine pancreas. J Clin Pathol 30:103–112

Wilander E, Sundström C, Meurling S, Grotte G (1976) A highly differentiated exocrine pancreatic tumour in a young boy. Acta Paediatr Scand 65:769–772

Wuketich St, Paulik F (1963) Syndrom des metastasierenden lipasebildenden Pankreasadenoms. Zugleich ein Beitrag zur Differentialdiagnose der Pfeifer-Weber-Christianschen Krankheit. Arch Klin Exp Derm 216:412–426

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