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Acinar cell carcinoma of the pancreas. A histologic, immunocytochemical and ultrastructural study

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Summary. A rare case of acinar cell carcinoma of the pancreas is presented. Because of its unusual solid growth pattern, correct diagnosis required electron microscopic analysis and the demonstration of intracellular amylase by immunohistochemical stains. The presence of pleomorphic electron-dense cytoplasmic granules containing fibrillary internal structures is confirmed in this ultrastructural study. The differential diagnosis of acinar cell carcinoma from other neoplasms involving the pancreas, including neuroendocrine tumours, poorly-differentiated adenocarcinomas and neoplasms of putative acinar cell derivation, is discussed.

Key words: Acinar cell carcinoma, Pancreas, Histopathology, Immunohistochemistry, Electron Microscopy

Introduction

Acinar cell carcinoma comprises approximately 1% of all nonendocrine tumours of the pancreas. The neoplasm have an aggressive malignant course, and few patients survive for more than 1 year (Morohoshi et al., 1983).

In the present report, we describe a rare case of a pancreatic acinar cell carcinoma with a predominantly solid growth pattern. The diagnosis was resolved only after electron microscopic and immunocytochemical study.

Materials and methods

Case report

A 70-year-old man presented himself in October 1991 with epigastric pain, vomiting, and weight loss. In an effort to evaluate the abdominal complaint, a computed tomographic (CT) scan revealed a large, left-sided retroperitoneal mass, which extended itself from the tail of the pancreas up to the upper polar portion of the left kidney. The patient underwent a distal pancreatectomy, splenectomy, and left nephrectomy with complete excision of the tumour. The patient died of progressive disease in February 1992.

The tumour measured 7 cm at its greatest dimension and was well circumscribed and lobulated. On incising it showed a greyish-white colour, variegated for the presence of areas of haemorrhage and necrosis (Fig. 1).

Light microscopy

For light microscopic study, tissues were fixed in 10% formalin, embedded in paraffin, and stained using the following methods: haematoxylin and eosin (H & E), Mallory's phosphotungstic acid-haematoxylin (PTAH), alcian blue (pH 2.5) (AB), periodic acid-Schiff (PAS) with or without diastase digestion, AB-PAS, high iron diamine (HID), and Grimelius stain.

For immunohistochemical study, paraffin sections were stained with antibodies against wide-spectrum keratins, salivary amylase, alpha-1-antitrypsin (AAT), alpha-fetoprotein, carcinoembryonic antigen (CEA), chromogranin A, synaptophysin, neuron specific enolase (NSE), and S-100 protein. The immunostaining was visualized with the avidin-biotin complex method, using diaminobenzidine tetrahydrochloride as a peroxidase substrate. The antibodies were obtained from Dakopatts (Copenhagen, Denmark). Positive controls were performed on formalin-fixed and paraffin-embedded material with known immunoreactivity for the various antigens. Negative controls were obtained by omission of the primary antibody. All control stainings were negative.

Electron microscopy

For electron microscopy, the fresh specimens were fixed in 3% glutaraldehyde in 0.1M phosphate buffer (pH 7.0) for 1h, and postfixed in 1% osmium tetroxide

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for 30 min prior to dehydration and embedding in araldite resin. Semi-thin sections were stained with Giemsa's reagent for selection of fields. Thin sections were double-stained with uranyl acetate and lead citrate and were examined and photographed in a Siemens 101 electron microscope.

Results

On light microscopic examination, the tumour cells were distributed in cords, trabeculae and solid sheets (Fig. 2). A rich fibrovascular stroma separated the groups of cells. The tumour cells showed round nuclei with prominent nucleoli, and rare mitotic figures. Some neoplastic cells, located in perivascular areas, showed eosinophilic granules in the cytoplasm, which were diastase-resistant, PAS-positive, PTAH-positive, AB- and HID-negative. The Grimelius stain was negative. At the periphery of the neoplasia, a continuity with the normal pancreatic tissue was observed.

With immunohistochemistry, neoplastic elements showed an evident positivity for wide-spectrum keratin and AAT. Immunoreactivity for amylase was present in few cells (Fig. 3). Immunostains were negative for NSE, chromogranin A, synaptophysin, alpha-fetoprotein, CEA, as well as for insulin, glucagon, and somatostatin.

Electron microscopy revealed polygonal tumour cells which were tightly connected to each other by desmosomes. Occasionally, there were small luminal spaces between the cells, resembling acinar lumina. The tumour cells showed round to oval nuclei and abundant cytoplasm containing numerous zymogen-like electron-dense granules (diameter, 200-500 nm) and other organelles (Fig. 4). In addition, some cells displayed variable numbers of irregular, but mostly oval or rhomboid inclusions, which measured up to 3,400 nm (Fig. 5). They consisted of parallel arrays of filamentous material (Fig. 6). There were no degenerative changes of zymogen granules, such as myelin figures, areas of decreased electron density of the granule, fusion between zymogen granules and lysosomes. No evidence of neurosecretory-type granules was seen.

The final diagnosis was poorly differentiated acinar cell carcinoma of the pancreas.

Discussion

The tumour, in this case, was presented as a retroperitoneal mass in continuity with normal pancreatic tissue. By light microscopy, this lesion showed a solid growth pattern. On ultrastructural examination zymogen-like granules were found and the diagnosis of acinar cell carcinoma was made. Further evidence for this diagnosis included the immunohisto-chemical demonstration of wide-spectrum keratin, AAT, and alpha-amylase.

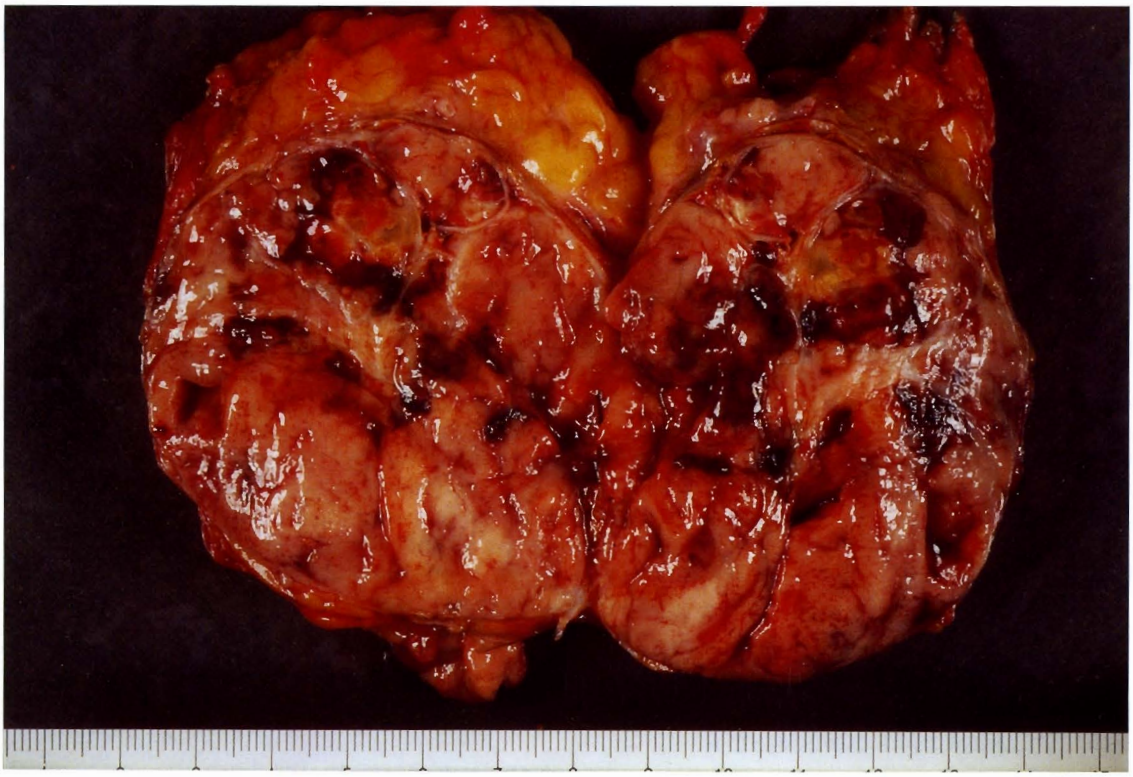

Fig. 1. Gross appearance of acinar cell carcinoma. The tumour is well circumscribed and lobulated. Focal areas of haemorrhage and necrosis are present.

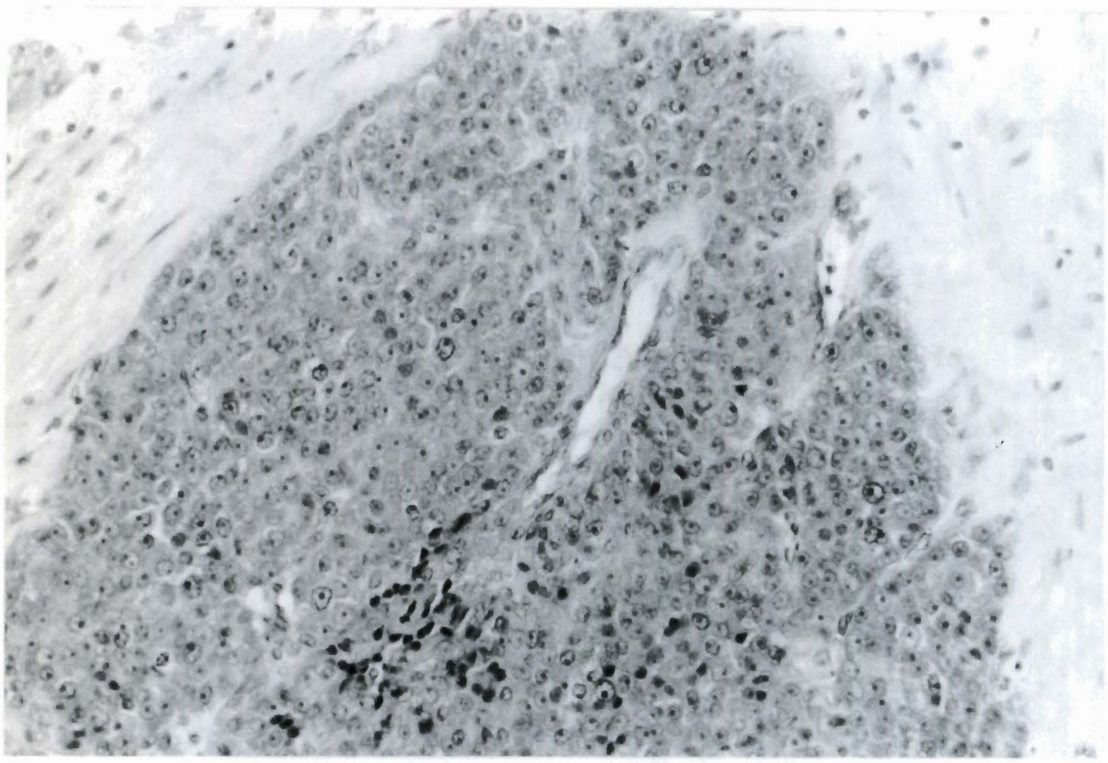

Fig. 2. The tumour cells show a solid growth pattern, simulating an endocrine tumour. The nuclei are usually centrally located and exhibit single, prominent nucleoli. H & E. x 380

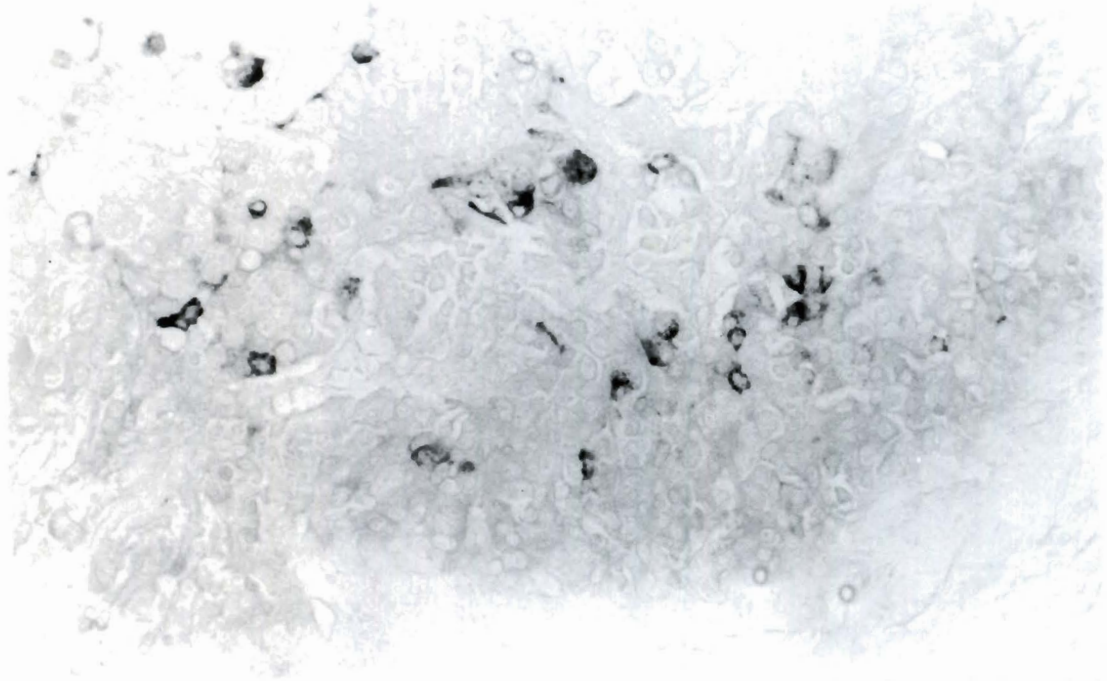

Fig. 3. Some tumour cells show amylase immunoreactivity in the cytoplasm. x 380

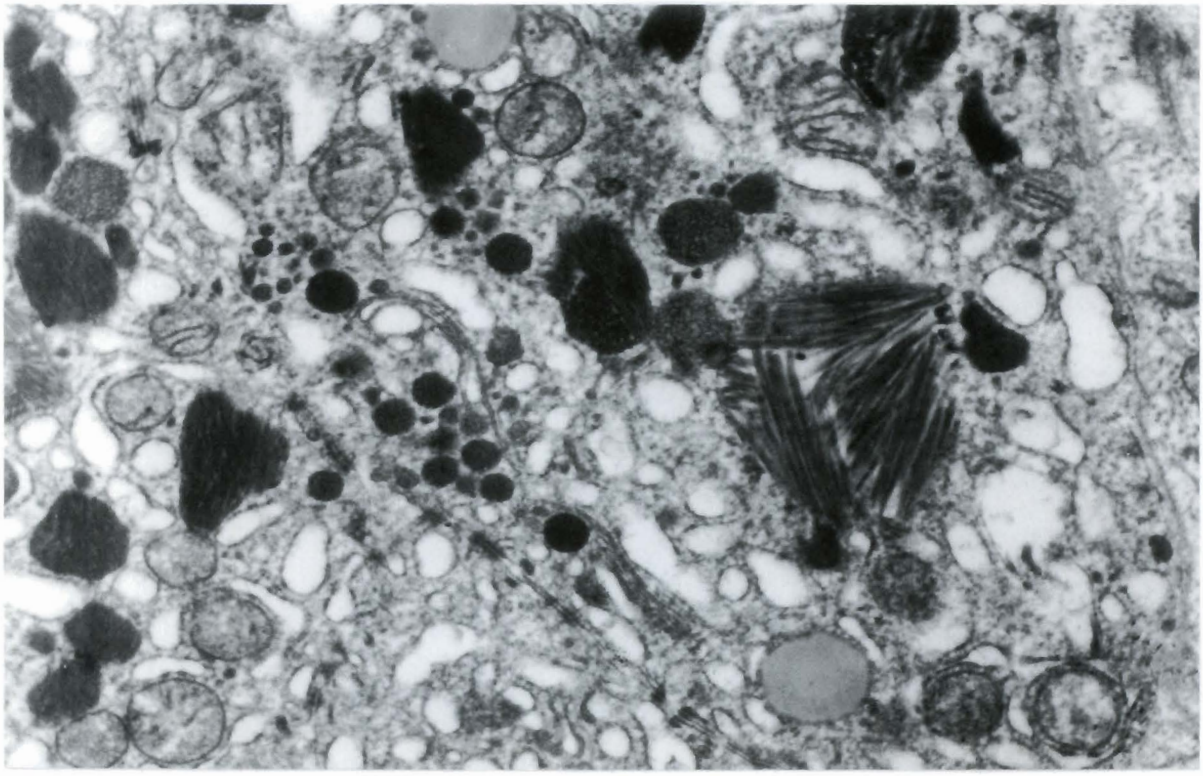

Fig. 4. Electron microscopic appearance of acinar cell carcinoma. Electron-dense zymogen granules are present, many of which are round and homogeneous, but pleomorphic granules are also evident. x 20,000

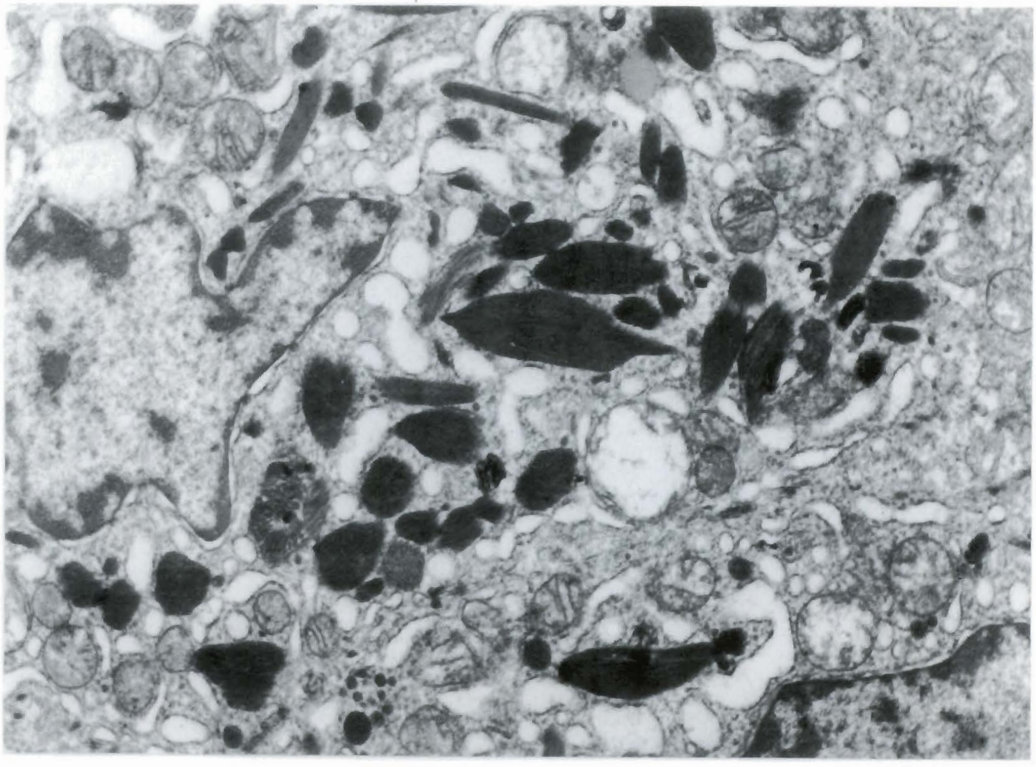

Fig. 5. Part of neoplastic cell containing mostly elongated formations with fine filamentous ultrastructure. x 20,000

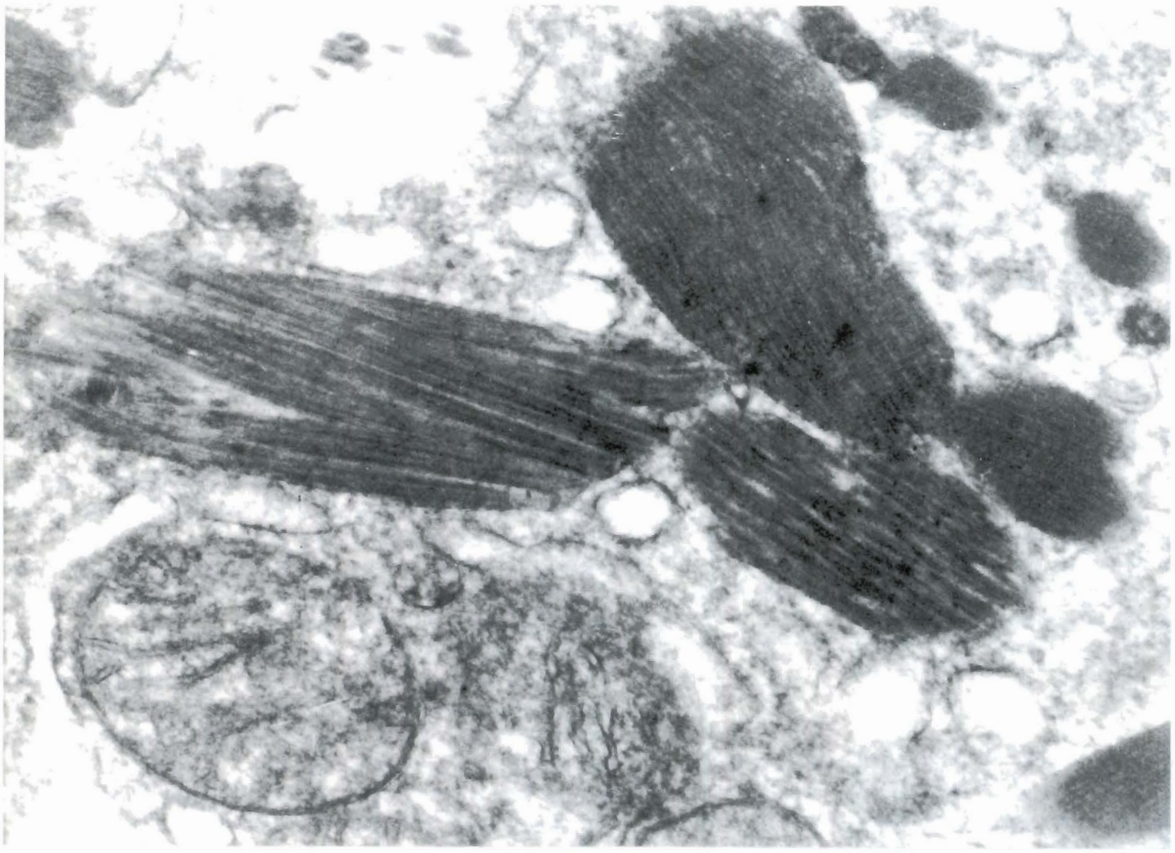

Fig. 6. Electron microscopic appearance of pleomorphic granules. At higher magnification, these granules are filled with what appear to be parallel filaments. x 50,000

Pancreatic cancer usually has a ductal phenotype, showing immunoreactivity with antibodies recognizing mucins, CEA (Batge et al., 1986) and showing no evidence of acinar cell phenotype (i.e. amylase negative). In our case, there was no histochemical, immunohistochemical nor ultrastructural evidence of ductal or ductular differentiation. Tumour cells contained no sialomucins in their cytoplasm, and at the ultrastructural level electron-lucent mucin granules were not seen. CEA reactivity was not expressed in our case.

Islet cell tumours must also be included in the differential diagnosis. Islet cell markers included antibodies against chromogranin A and somatostatin (Kim et al., 1990). In normal human pancreatic islets, chromogranin A reactivity was present in A-type and B-type islet cells; however, it was absent from somatostatin-producing D-cells and pancreatic polypeptide-producing cells (Grube et al., 1986). In the present case, an islet cell differentiation was ruled out, because there was no immunoreactivity for chromogranin A and somatostatin nor for insulin and glucagon. These data were also supported by electron microscopy, which failed to show neuroendocrine-type granules. Furthermore, common markers of neuroendocrine differentiation, such as NSE and synaptophysin (Gould, 1987), were negative. Thus, in our case, the tumour cells exhibited a pure acinar phenotype.

The differential diagnosis should also include other pancreatic neoplasms of putative acinar origin, such as pancreatoblastoma and solid-cystic tumour (Morohoshi et al., 1987). Pancreatoblastomas occur exclusively in young children and show a mixed histological pattern, characterized by monomorphic epithelial cells forming solid, trabecular, and acinar structures variably admixed with squamoid corpuscles and mesenchymal tissues (Horie et al., 1977). Solid cystic tumour occurs most frequently in young women and is almost invariably benign (Cubilla and Fitzgerald, 1975; Learmonth et al., 1985). Is is composed of uniform cells forming papillary and solid structures with thin vascular cores. Zymogen-like granules have been described in ultrastructural studies of solid-cystic tumours (Stommer et al., 1991). In our case, there were large irregular granules with fine filamentous ultrastructure, in addition to zymogen-like granules. Under appropriate physicochemical conditions, various resident or secretory long-chain molecules (usually proteins and, less often, polysaccharide moieties) can polymerize to form either filamentous or crystalline structures (Van Haelst and Pruszczynski,

1990). Electron-dense, fibrillary needle-like bodies have been recorded in the parotid gland of the rat (Toner et al., 1971). Altered serous granules, containing tubulo-filamentous structures, were also observed in acinar cells of a human parotid gland (Tandler and Riva, 1990). Recently, fibrillary granules have been observed in many out of 28 cases of acinar cell carcinoma of the pancreas (Klimstra et al., 1992). These authors underline the striking resemblance to zymogen granules in the 15-week foetal pancreas (Track et al., 1975; Lebenthal et al., 1986) and put forward the hypothesis that they may be an important diagnostic feature of acinar cell carcinoma of the pancreas. We confirm the presence of the fibrillary granules in the present case, and the utility of electron microscopy in the differential diagnosis of this tumour with respect to neoplasms of putative acinar cell derivation.

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