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CASE REPORT

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Intraductal acinar cell carcinoma of the pancreas

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Abstract We describe a purely intraductal acinar cell carcinoma involving branch ducts of the pancreas in a 74-year-old man, which presented as recurrent episodes of acute pancreatitis. Endoscopic ultrasound examination revealed an intraductal mass bulging into the main pancreatic duct suggesting, pre-operatively, an intraductal mucinous papillary tumour. Gross examination showed several dilated branch ducts that contained haemorrhagic tumour material without any solid or true cystic formation within the pancreatic parenchyma. Using histology, a purely intraductal acinar cell carcinoma was observed, involving branch ducts only, associated with foci of carcinoma in situ in adjacent exocrine parenchyma. The main pancreatic duct was free of disease except for its communication with a cancerous branch duct. A concomitant neuroendocrine microadenoma was incidentally found during slide screening. Immunohistochemistry performed on the intraductal proliferation confirmed zymogen secretion with positive staining for alpha-1 anti-chymotrypsin and anti-trypsin and the persistence of diastase-periodic acid-Schiff positive granules in the apical pole of the tumour cells. Neuroendocrine markers were negative in the acinar cell carcinoma and positive in the neuroendocrine microadenoma. To our knowledge, this is the first report of an intraductal acinar cell carcinoma of the pancreas involving branch ducts and sparing the main pancreatic duct.

Keywords Pancreas · Intraductal tumour · Acinar cell carcinoma

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Introduction

Acinar cell carcinomas of the pancreas are rare neoplasms, accounting for approximately 1% of all exocrine pancreatic tumours [14]. This type of tumour is known to show aggressive behaviour, although its survival seems to be somewhat better than that of ductal carcinoma [7, 9, 14]. The tumour tends to occur in older patients, between the fifth and seventh decade, with a male predominance of 2:1 over females [4, 7, 9], and associated clinical features include subcutaneous fat necrosis, polyarthralgia and eosinophilia [9, 17]. We report a case of intraductal acinar cell carcinoma without any invasive component that showed foci of acinar carcinoma in situ in the adjacent exocrine parenchyma. In addition, there was a concomitant neuroendocrine microadenoma.

Clinical history

A 75-year-old retired farmer was admitted for recurrent episodes of acute pancreatitis over a 4-year period. His past medical history included a cholecystectomy 14 months prior to pancreatic surgery. Endoscopic ultrasound examination revealed a bulging intraductal mass in the main pancreatic duct at the junction of the body and neck of the gland. Upstream, the main pancreatic duct was moderately dilated and surrounded by changes of chronic pancreatitis in the adjacent parenchyma. No cystic formation was detected, and no other clinical symptoms or signs were observed. We decided to perform a segmental pancreatic resection. Because intraductal carcinoma was observed upon frozen section in the right surgical margin, the surgical procedure was then completed by an extended pancreatico-duodenal resection (Whipple's procedure). There were no post-operative complications and, 6 months later, the patient is alive and well, with no tumour recurrence.

Materials and methods

The surgical specimen was received fresh, fixed in 10% formalin and sampled in toto. Samples were embedded in paraffin and sections were stained with haematoxylin and eosin. Standard immunostaining methods were applied to formalin-fixed, paraffin-embedded tissue sections, using a peroxidase–antiperoxidase tech-

Table 1 Antibodies used in immunohistochemical analysis. *KL1* large spectrum cytokeratin; *EMA* epithelial membrane antigen; *CEA* carcinoembryonic antigen; *AFP* alpha fetoprotein

Antibody	Dilution	Source
KL1	1:200	Immunotech, Marseille, France
EMA	1:25	Dako, Glostrup, Denmark
CEA	1:100	Dako, Glostrup, Denmark
AFP	1:100	Dako, Glostrup, Denmark
Alpha-1 anti-chymotrypsin	1:100	Dako, Glostrup, Denmark
Chromogranin	1:25	Dako, Glostrup, Denmark
Gastrin	1:300	Dako, Glostrup, Denmark
Glucagon	1:150	Dako, Glostrup, Denmark
Insulin	1:25	Dako, Glostrup, Denmark
Pancreatic polypeptide	1:600	Dako, Glostrup, Denmark
Somatostatin	1:100	Dako, Glostrup, Denmark

nique. The antibodies used and their dilution are listed in Table 1. Antigen retrieval was performed using microwave heating in citrate buffer, pH 6.2, for all antibodies. Visualisation was performed using DAB staining (3,3-diaminobenzidine; Sigma Saint Quentin Flavier, France) in tris-buffered saline (TBS) containing 0.05% hydrogen peroxidase for 10 min. Sections were counterstained with haematoxylin and mounted with permount. Positive and negative controls were used for all antibodies.

Pathological findings

Gross description

The pancreas measured 10.5 cm in length, 3 cm in width and 4 cm in height. At 15 mm from the surgical resection margin of the initial medial pancreatectomy, a branch duct was found to be dilated (15 mm in circumference) and its lumen was plugged with haemorrhagic friable tumour material, which communicated with the main pancreatic duct. The latter was moderately dilated, with a cut section circumference of 10 mm. Some other branch ducts within the uncinate process contained similar material without dilatation. There was no obvious tumour in the pancreatic parenchyma, nor was there evidence of cyst formation. The ampulla of Vater was unaffected. The remaining pancreas showed mild changes of chronic pancreatitis.

Light microscopy

The tumour involvement was observed within the lumen of secondary ducts (Fig. 1), whereas the main pancreatic duct was spared. The intraductal proliferation displayed an acinar pattern with cells growing in well-formed acini, centring around a small identifiable lumen with sharp borders, and the cytoplasm was abundant and eosinophilic. The nuclei were basally orientated, typically round to oval, uniform and medium in size showing, mild cytological atypia (Fig. 1). The mitotic activity was low. The surgical specimen was examined in totality, and no infiltrating component or cyst formation was observed. Most of the ducts were involved, although in the isthmus, the lesions were plurifocal and discontinuous.

Adjacent to the intraductal tumour, foci of carcinoma in situ (Fig. 2), with hyperchromatic nuclei and increased nucleo-cytoplasmic ratio were observed in otherwise non-altered exocrine pancreatic acini. A concomitant neuroendocrine microadenoma was also found (Fig. 3), measuring 5 mm in diameter. Its architecture was typically trabecular, with a well vascularised and hyalinised partly calcified stroma. Changes of chronic pancreatitis were observed in the parenchyma of the head of the pancreas, and neither vascular invasion nor lymph node metastases were found. The surgical margins were free of tumour.

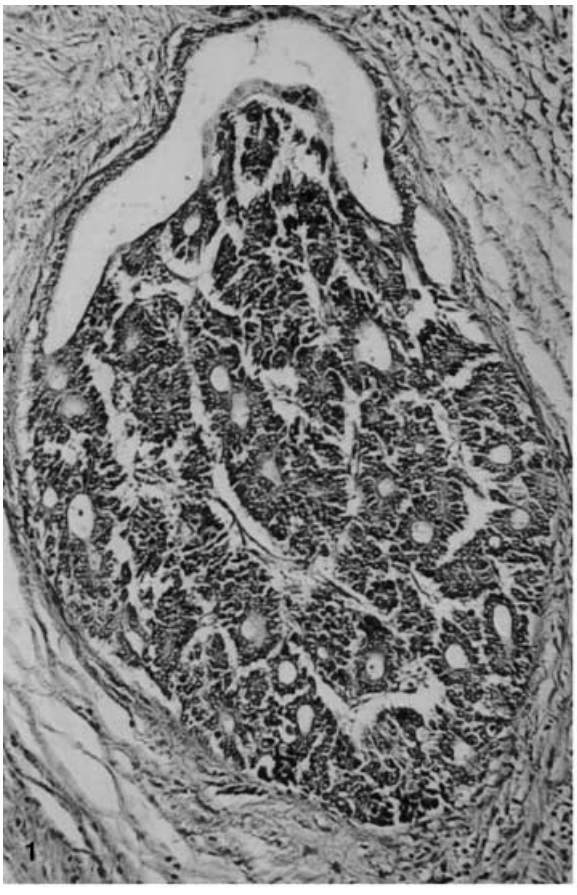
Special stains and immunohistochemistry

The intraductal proliferation showed periodic acid-Schiff (PAS) positive apical granules before and after diastase. Immunohistochemically, the intraductal tumour was positive for the epithelial markers Kl1 and epithelial membrane antigen (EMA) and negative for carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP). The apical part of the tumour cells stained strongly positive with antibodies against alpha-1 anti-chymotrypsin and trypsin (the latter antibody was kindly provided by Dr. Klöppel; Fig. 4), while the endocrine islets were invariably negative for these markers. The tumour cells were negative for chromogranin A and synaptophysin, whereas the cells from the neuroendocrine microadenoma showed intense cytoplasmic immunoreactivity for these markers. Antibodies against insulin, glucagon, gastrin and pancreatic polypeptide (PP) were negative.

Discussion

Acinar cell carcinomas are rare tumours of the pancreas. They commonly present as a voluminous tumour mass and are rarely cystic [3, 6, 14, 15]. To our knowledge, a predominant growth within pancreatic ducts without any invasive component has never been reported in acinar cell carcinomas. Intraductal pancreatic tumours are also rare. The majority of them represent intraductal papillary mucinous tumours (IPMT) of the pancreas [9, 14] and less commonly intraductal extensions of a primary ductal carcinoma or a metastasis (especially of a renal carcinoma) [1]. These possibilities were initially considered in this case upon examination of the endoscopic ultrasound images.

The peculiarity of this acinar cell carcinoma lay in its exclusive intraductal growth. Its histological diagnosis was based on the typical acinar pattern and the positive immunoreactivity for trypsin. A mixed acinar–endocrine carcinoma was excluded [4, 8], because neuroendocrine markers were negative. The presence of multiple foci of in situ acinar cell carcinoma in the adjacent exocrine parenchyma, situated at a distance from the intraductal tu-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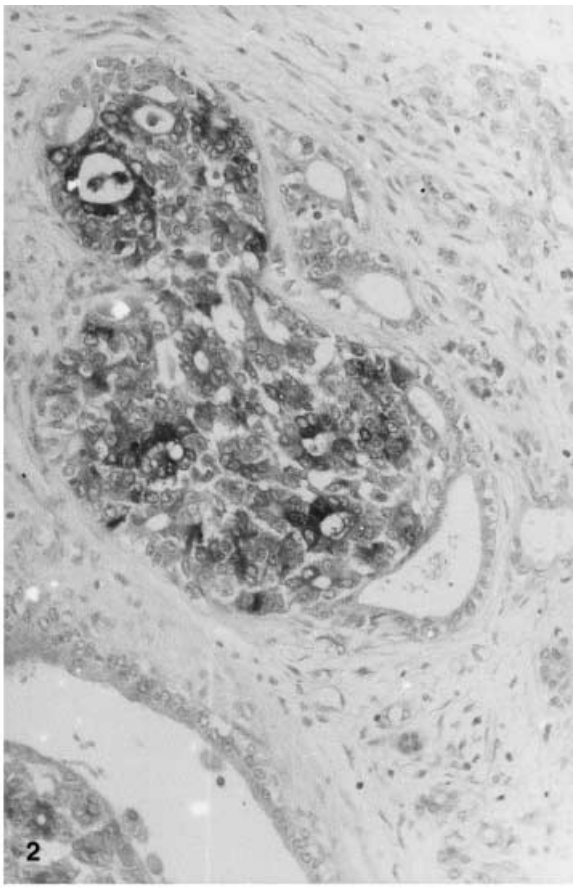
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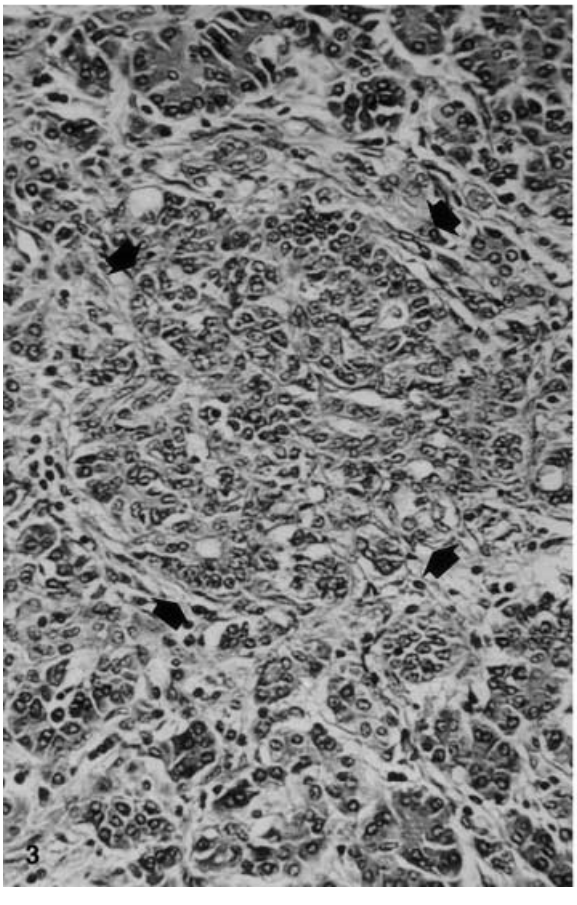
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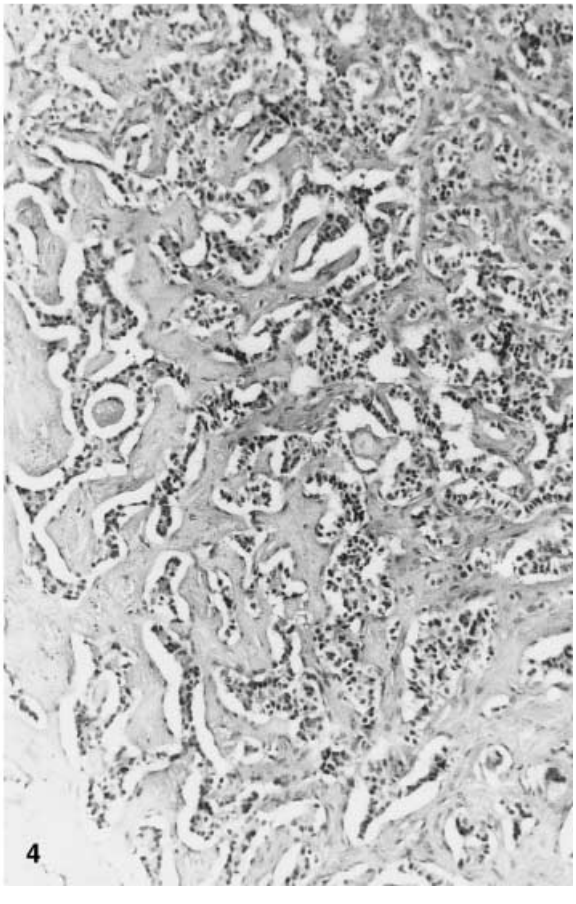
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◀ **Fig. 1** Purely intraductal growth of the tumour, displaying acinar features, with mild cytological atypia (haematoxylin and eosin, ×250)

Fig. 2 Carcinoma in situ within the adjacent pancreatic parenchyma (*arrows*; haematoxylin and eosin, ×400)

Fig. 3 Concomitant neuroendocrine microadenoma showing typical trabecular architecture (haematoxylin and eosin, ×250)

Fig. 4 Positive cytoplasmic immunoreactivity for the anti-trypsin antibody (haematoxylin and eosin, ×250)

mour, suggested that this intraductal acinar cell carcinoma originated from minute neoplastic acinar cell foci.

It has been demonstrated that atypical acinar cell nodules and adenomas can be induced in animal models by carcinogenic agents, such as azaserine, thus providing a good model for studying acinar cell malignant transformation [10]. A sequence of acinar cell neoplasia from atypical nodules, adenomas to carcinoma, has been observed in this animal model [11]. However, this sequence is still disputed in the human pancreas and, in recent large series of acinar cell carcinomas, the authors failed to show any concomitant acinar cell adenomas or nodules in the non-neoplastic pancreas [4, 7].

Finally, the incidental finding of a neuroendocrine microadenoma in association with the intraductal acinar cell carcinoma may support the hypothesis of a common primitive stem cell that could differentiate into all types of pancreatic cells to compose the pancreatic gland [2, 13]. Indeed, "endocrine-exocrine cells" have been described in both the foetal pancreas [16] and the postnatal pancreas [5, 12]. A minor endocrine component may be found in about 42% of acinar cell carcinomas [7], and true mixed acinar-endocrine carcinomas have recently been described [4, 8]. However, in this case of purely intraductal acinar cell carcinoma, endocrine markers were negative, and both tumours appeared distinct, suggesting two different genetic mechanisms. In conclusion, we have described a new type of acinar cell carcinoma, which grows within the ducts and has to be distinguished from IPMT.

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