Case report

Acinar cell carcinoma of the pancreas with and without endocrine differentiation

IT Virlos, IM Papazachariou and RCN Wiliamson

Department of Surgery, Hammersmith Hospital, London, UK

Background

Acinar cell carcinoma (ACC) is a rare pancreatic neoplasm, representing 1% of exocrine tumours and containing a variable endocrine component. Three recent cases of ACC are reported.

Case outlines

A 72-year-old man with painless obstructive jaundice had a 5-cm mass in the head of pancreas resected by Whipple's operation; histopathological examination showed a typical ACC. A 33-year-old man with weight loss and abnormal liver function had a dilated biliary tree but no mass on imaging. Pylorus-preserving pancreatoduodenectomy was performed, and histology showed a mixed acinar-neuroendocrine tumour. A 56-year-old man with weight loss and a palpable mass had a 15-cm mass in the distal body of pancreas, which was resected en bloc with the spleen and adherent stomach; it was a cystic ACC.

Results

Two patients are alive and free of disease at 30 months and 15 months, while the third patient with locally advanced disease died of myocardial infarction at 9 weeks.

Discussion

Acinar structures are the hallmark of this neoplasm, which carries a better survival rate than ductal cancer. Surgical excision prolongs survival and offers the best chance of cure.

Keywords

pancreas, acinar cell carcinoma, mixed acinar-endocrine carcinoma.

Introduction

Acinar cell carcinoma (ACC) of the pancreas represents a rare but distinctive clinicopathological entity [1,2], accounting for 1% of pancreatic exocrine malignant tumours [3,4]. It derives mainly from transformed acinar cells [5], but an endocrine component of the tumour may vary from a few scattered cells to more than 25% of the neoplasm; such tumours have been termed 'mixed acinar-endocrine carcinoma' [6]. We report three patients with ACC, one with mixed acinar-endocrine carcinoma, and review the clinical, diagnostic and pathological features of these tumours.

Case report

Case no. 1

A 72-year-old man presented in March 1997 with an acute onset of painless obstructive jaundice. Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated an irregular stricture 2 cm long in the lower common bile duct (CBD), and a stent was placed to relieve the jaundice (Figure 1). CT scan showed a 5-cm mass in the head of pancreas with loss of the fat plane suggesting possible tumour infiltration. Visceral angiography showed a well-circumscribed vascular lesion suggestive of duodenal leiomyoma (Figure 1). He had been on long-term anticoagulation since 1986 for recurrent deep vein thrombosis.

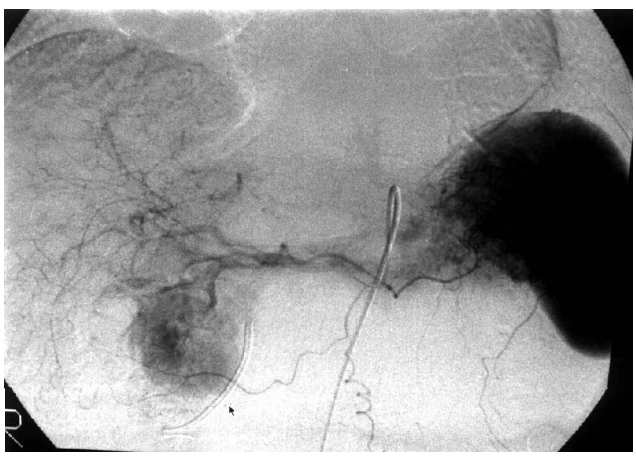

Figure 1. *Case no. 1. Late phase coeliac arteriogram showing an obvious tumour 'blush' in the head of the pancreas and the adjacent endoscopic stent (arrow).*

Correspondence to: *RCN Williamson, Professor of Surgery, Hammersmith Hospital, Department of Gastrointestinal Surgery, Du Cane Road, W12 0NN, London, UK*
e-mail: r.williamson@ic.ac.uk Tel: +44 208 3833210 Fax: +44 208 3833023

Laparotomy revealed a large but localised tumour, and pancreatoduodenectomy was successfully carried out to include a distal gastrectomy. Histopathological examination showed a typical ACC, and histochemistry was positive for lipase.

Immunohistochemistry was strongly positive for α-1-antitrypsin and α-1-antichymotrypsin and positive for cytokeratin. It was negative for neurone specific enolase (NSE) and chromogranin, but there was focal positivity for synaptophysin (Table 1). The lymph nodes were free of tumour. The patient remains well and free of overt disease 2 and a half years later.

Case no. 2

A 33-year-old man presented in November 1998 with a six-week history of pruritus, 12 kg weight loss, alteration in bowel habit and abnormal liver function tests: alkaline phosphatase (ALP) 1448 UL^{-1} (normal <115 UL^{-1}), alanine aminotransferase (ALT) 197 UL^{-1} (normal <40 UL^{-1}), γ-glutamyltransferase (γ-GT) 1136 UL^{-1} (normal <50 UL^{-1}) but normal bilirubin. CT scan showed both intra- and extrahepatic dilatation of the biliary tree, and ERCP confirmed a low CBD stricture (Figure 2). A liver biopsy raised the possible diagnosis of primary sclerosing cholangitis, but the patient developed pain and a fall in haemoglobin following the biopsy. With conservative treatment for probable intraperitoneal bleeding his symptoms gradually settled.

Since primary sclerosing cholangitis was an unconvincing explanation for the biliary stricture, the patient was referred to this Unit where laparotomy revealed an indurated mass in the lower head of the pancreas with no evidence of metastasis. Routine pylorus-preserving proximal pancreatoduodenectomy (PPPP) was performed. Histology showed a high-grade, malignant, mixed acinar/neuroendocrine carcinoma of the head of pancreas (3.5 cm in diameter). Some of the larger cells with a diffuse cytokeratin pattern were strongly positive for lysozyme and α-1 antitrypsin, representing the acinar part of the tumour. The smaller cells stained positively for chromogranin, representing the neuroendocrine part of the tumour (Table 1). Final diagnosis was confirmed by electron microscopy. Local excision was complete and there was no nodal involvement, but extensive venous invasion was present. It was decided to withhold adjuvant oncological treatment since the resection appeared complete, and the patient remains well 15 months later.

Table 1. *Immunohistochemical examination of ACC*

Case no:	1	2	3
Lipase	++	−	−
α-1-antitrypsin	+++	+++	−
α-1-antichymotrypsin	+++	−	+
Cytokeratin	++	++	+++
Lysozyme	−	+++	+
NSE	−	++	−
Chromogranin	−	++	+
Synaptophysin	+	−	−
CEA	−	−	+

Case no. 3

A 56-year-old man presented in May 1996 with a cerebrovascular accident (CVA) causing right hemiparesis and aphasia. There was a history of myocardial infarction and diabetes, and his mother had died of pancreatic cancer. He also reported recent anorexia and 6 kg weight loss. A large mass was palpable in the left upper quadrant, and CT showed a 10 cm mass with central cavitation replacing the distal body and tail of pancreas. In addition there was a

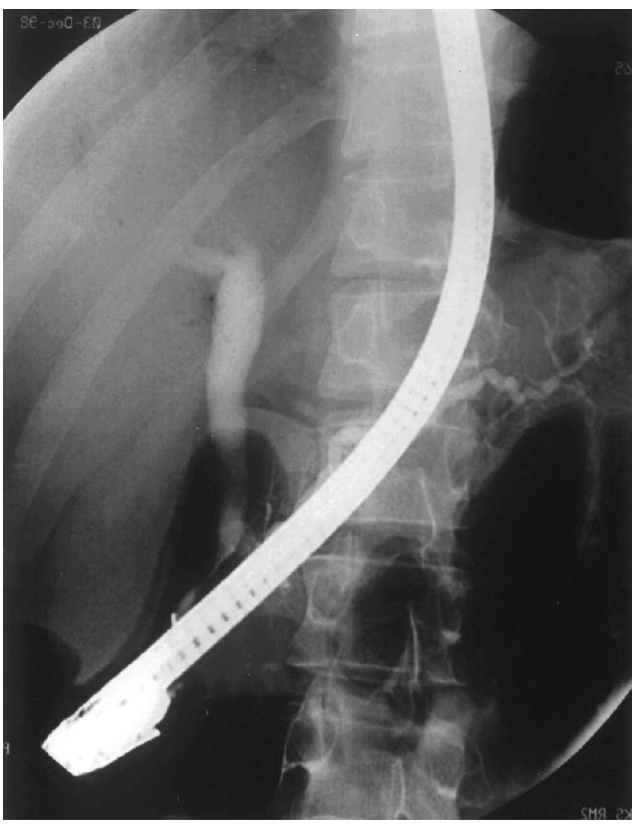

Figure 2. *Case no. 2. Endoscopic retrograde cholangiogram showing a low common bile duct stricture.*

15-mm low-density lesion in the spleen and a 4-mm diameter low-density lesion in the right lobe of the liver. CT-guided biopsy of the primary tumour showed poorly differentiated pancreatic adenocarcinoma. A 24-hr urinary level of adrenaline of 523 μg (normal < 190 μg/24 hr) suggested a possible neuroendocrine origin of the tumour. Angiography showed splenic vein thrombosis. Following an episode of upper gastrointestinal bleeding, endoscopy was performed to exclude ulceration of the tumour into the stomach.

Laparotomy revealed a massive tumour (15 cm in diameter) of the left pancreas, which was resected *en bloc* with the spleen and a portion of adherent stomach (greater curve). There was a penetrating gastric ulcer into the tumour cavity, which contained offensive material. Pathological examination showed a large cystic tumour with extensive haemorrhage and necrosis and the histological pattern of ACC. Local excision was complete, but vascular and neural invasion were present with direct involvement of the stomach and splenic capsule. Immunohistochemical staining was strongly positive for cytokeratin and carcinoembrionic antigen (CEA) and weakly positive for α-1-antichymotrypsin, lysozyme and chromogranin (Table 1). Postoperatively he developed septicaemia and adult respiratory distress syndrome. He remained in the intensive therapy unit for 8 weeks and required tracheostomy and then transcatheter embolisation for a bleeding colonic lesion that was probably angiodysplastic. Eventually he returned to the surgical ward in good health and eating normally. Discharge home was approaching when he suffered a massive myocardial infarction, from which he died 10 days later.

Discussion

Acinar cell carcinoma (ACC) accounts for 1% of pancreatic exocrine malignant tumours [3,4]. This malignancy shows a male predilection with a peak age in the seventh decade [1]. Most of these tumours arise from the head of the pancreas (56%), followed by the tail (36%) and the body (8%). In two of our patients the ACC was located in the head, while the third was in the distal body and tail. The symptoms of patients with ACC are usually non-specific, for example the anorexia and weight loss seen in two of our patients. Unlike ductal adenocarcinoma, ACC may not cause jaundice even when the tumour is located in the head of pancreas [1]. A specific syndrome of subcutaneous fat necrosis, panniculitis, polyarthralgia and blood eosinophilia [1,7,8] is encountered when lipase is secreted in excess from the tumour. This syndrome was not manifested by any of our patients.

Macroscopically these tumours are typically solid [1,9]. Other features of ACC include haemorrhage and necrosis [1] (seen in two cases) and the very rare cystic variant [10,11] (seen in the third). The microscopic appearance of ACC is distinctive. Acinar structures are the hallmark of this neoplasm under the light microscope. A glandular and trabecular pattern has been described, as well as vascular and perineural invasion. The identification of zymogen granules is the most characteristic ultrastructural finding, and fibrillary internal structures may be present within the granules [1]. Klimstra and colleagues [1] consider cytological uniformity to be a consistent feature of ACC. Nevertheless, cytological pleomorphism can rarely occur [12]. Immunohistochemical positivity in ACC has been reported mainly for trypsin, but also for chymotrypsin, lipase, α-1-antitrypsin, cytokeratin, lysozyme and rarely for amylase [1,2,5,13,14]. In addition, ACC can show positivity for various tumour markers such as alpha-fetoprotein [15], carcinoembryonic antigen [15,16] and CA 19-9 [15].

It is usually a straightforward matter to differentiate ACC from ductal adenocarcinoma. Macroscopic distinguishing features of ACC include circumscription, a fleshy consistency and polypoid growth into the duodenum; zymogen granules are seen but not the true dense desmoplastic stroma of ductal carcinoma [1]. Since tumours exhibiting both ductal and acinar features have been reported in man [17,18] as well as in a transgenic animal model [19], antibodies against pancreatic enzymes can be used to confirm an acinar cell origin. This evidence implicates acinar cells in the pathogenesis of ductal adenocarcinoma [19]. On the other hand, ACC may resemble endocrine tumours morphologically [20]; a minor endocrine component may be detected immunohistochemically in up to 40% of cases (as in case no. 2). Although the diagnosis can be reached clinically, confirmation of ACC is based on immunohistochemistry and electron microscopy, which demonstrate pancreatic enzymes and zymogen granules [1,5].

Surgical resection (pancreatectomy) offers the only chance of cure and prolongs survival [1,21,22]. The resectability rate of ACC is 64% [1], much higher than that of ductal adenocarcinoma (10–20%) [21,22]. Chemotherapy can be used either preoperatively (intra-arterially) [23] to reduce the tumour size or as palliative treatment

alone or in combination with radiotherapy [1]. When present, metastases from ACC are usually limited to the liver and lymph nodes [1,7,24], but the spleen [3], lung [5,18] and adrenal gland [18] are other potential sites. Only one of our patients has had locally advanced disease with direct invasion of the stomach and spleen. Although 1-year survival is just over 50%, ACC is a very aggressive tumour with an overall 5-year survival rate (5.9%) [1] similar to that of ductal adenocarcinoma (6.1%) [22]. Age above 60 years, symptoms of lipase secretion and size >10 cm are associated with a shorter survival time [1]. Two of our patients are still alive at 2½ years and 1 year, but both had localised and relatively small tumours. The third patient with a large and invasive tumour (>15 cm) had a prolonged postoperative course and died of myocardial infarction at 12 weeks.

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