JOP. J Pancreas (Online) 2007; 8(3):330-334.

CASE REPORT

Adenosquamous Carcinoma of the Pancreas with Clear Cell and Rhabdoid Components. A Case Report

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ABSTRACT

Context In as much as no such variant of this pancreatic tumour has been previously reported in the literature, we report an unusual case of an adenosquamous carcinoma of the pancreas characterized by clear cells and rhabdoid cells.

Case report A 75-year-old man presented with upper abdominal distention, dyspepsia, jaundice, and significant weight loss over a period of 3 months. Imaging of the abdomen showed a solid mass with cystic components in the region of the uncinate process of the pancreas. Endoscopic retrograde pancreatography showed mild to moderate dilatation of the intrapancreatic biliary tract and of the pancreatic duct, and a biliary stent was placed. The patient subsequently underwent a Whipple's procedure with curative intent. Histological evaluation of the pancreatic mass revealed an adenosquamous carcinoma displaying both clear cell and rhabdoid components.

Conclusions Assessing the predominant histology of pancreatic adenosquamous carcinoma variants such as those characterized by clear cells and rhabdoid cells may help select and improve upon therapies in this aggressive lesion.

INTRODUCTION

Adenosquamous carcinoma of the pancreas is an unusually rare, aggressive variant of pancreatic invasive ductal carcinoma with a worse prognosis and a higher potential for metastasis compared to its more conventional, exclusively glandular counterpart. Incidence is not known but autopsy and surgical specimen findings suggest that this lesion accounts for 1-4% of all exocrine malignancies of the pancreas [1]. The mass most commonly involves the pancreatic head, followed by the body and tail [2]. The presence of variable proportions of classic, often mucin-producing, columnar, glandular cells admixed with keratinized squamous epithelium in this neoplasm has led to the use of numerous nomenclature to describe this entity including adenoacanthoma, mixed squamous and adenocarcinoma, and mucoepidermoid carcinoma of the pancreas. Currently, there are several theories of the origin of this tumour including squamous metaplasia as a result of obstruction and inflammation [3], the less favored "collision theory" suggesting the coalescence of independently arising cell types, and malignant differentiation of pluripotent ductal cells into the two cell populations [4].

Patients typically range in age from 38-79 years (median 66 years) with the most common presenting symptom being abdominal pain, followed by anorexia and/or weight loss, obstructive jaundice, and general malaise. Multidisciplinary treatments including aggressive surgery, intraoperative radiation therapy, and locoregional chemotherapy may improve the survival of

patients but overall prognosis is dismal with a five-year survival rate of 3-5% reported. These tumours are often unresectable and cytologic material is often the only tissue available on which to base the diagnosis; however, a definitive diagnosis by fine needle aspiration and/or needle biopsy can be a challenge due to the presenting distribution and preponderance of the two cell populations.

For the pancreatic tumour to be histologically characterized as adenosquamous, the squamous cell component should account for 30% or more of the lesion, although variations do exist from microscopic field to field [5]. Carcinoma embryonic antigen (CEA) is present predominantly in the glandular component, while the squamous cells typically stain positively for low molecular weight cytokeratin. Molecular alterations may hold promise for preoperative diagnosis of this tumour as mutations in the *K-ras* oncogene have been identified in nearly half of adenosquamous carcinomas of the pancreas [6]. Adenosquamous carcinomas have been described in concert with other histological components. For example, a recent study reported an extensively infiltrative adenosquamous carcinoma with perineural invasion and involvement of peripancreatic lymph nodes, displaying a pronounced acantholytic pattern with osteoclast-like and pleomorphic giant cells within the squamous carcinoma component [7].

We describe a case of adenosquamous carcinoma of the pancreas displaying both clear cell and rhabdoid components, two components hitherto not previously described in adenosquamous carcinoma of the pancreas.

CASE REPORT

A 75-year-old man presented to the Emergency Department with a three-month history of epigastric distention, accompanied by dyspepsia, a modest right upper quadrant discomfort and a 9 kg weight loss. He then developed 2 weeks of painless jaundice, with dark urine and pale stools. He denied any fever or chills. His past medical history was significant for type 2 diabetes mellitus controlled with diet, mild hypertension, mitral regurgitation, right knee osteoarthritis, benign prostatic hyperplasia, and a frontotemporal lobe meningioma for which he had a craniotomy in 1994. The patient had no prior history of carcinoma. His family history was negative for malignancy. He was a 35-pack year ex-smoker (patient quit smoking on advent of recent symptoms) and drank alcohol on occasion. His only medication was enteric-coated aminosalicylic acid every other day and he had no known allergies. On examination, the patient was moderately jaundiced with skin and scleral icterus and his vital signs were stable. Cardiovascular and respiratory examinations were both unremarkable. There was no supraclavicular lymphadenopathy as well as no evidence of chronic liver disease. Abdominal examination revealed a 5-cm soft, non-tender right upper quadrant mass suggestive of Courvoisier's gallbladder. Abdominal ultrasound and computerized tomography scan showed a solid mass with a cystic component in the uncinate process of the pancreas. There was mild to moderate dilatation of the intrapancreatic biliary tract and of the pancreatic duct and no evidence of vascular invasion. The radiological examination found no other tumours in the gallbladder, liver, lungs, and abdominal or pelvic cavities. The patient underwent ERCP, which revealed an erythematous, edematous pancreatic papilla, and a biliary stent was placed with improvement of the patient's jaundice and appetite levels. He underwent an uncomplicated Whipple's procedure with intent to cure. However, 6 months following surgery, the patient developed extensive liver metastases on first-line systemic chemotherapy, sepsis, and succumbed to his illness.

Pathologic Description

On gross examination, a polypoid lesion measuring 1.5x0.8x0.8 cm was identified on the duodenal mucosal surface, 3 cm distal to

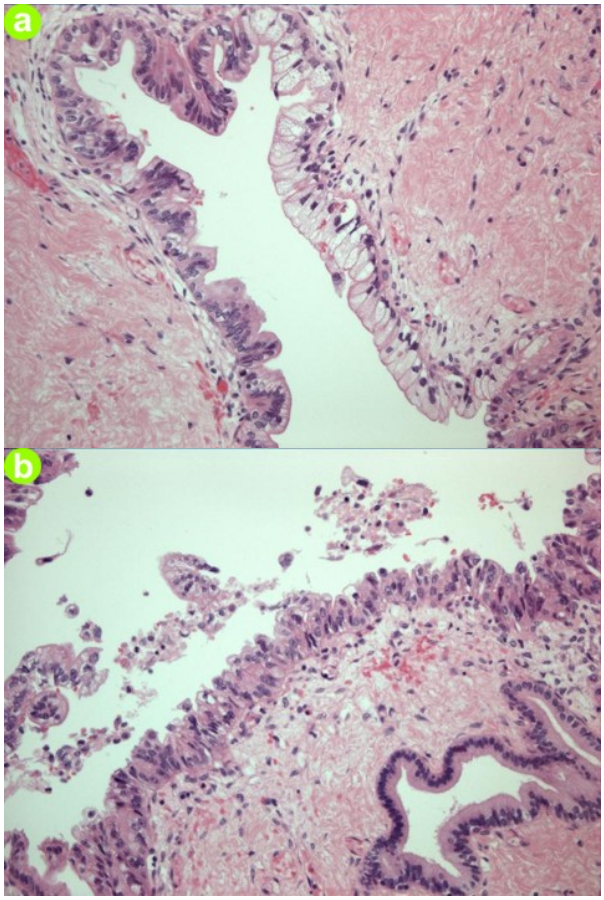

Figure 1. The typical lesions of PanIN 2 (**a.**) and PanIN 3 (**b.**) were present and also contained cells with clear cytoplasm. However, rhabdoid cells were not apparent in these lesions.

the ampulla. A white, solid tumour measuring 3.0x2.5x2.5 cm in the head of the pancreas and extending into the peri-ampullary area obstructed the distal common bile duct. This tumour was 2.5 cm from the distal lateral resection margin. Histological examination revealed a pancreatic parenchyma effaced by extensive fibrosis and chronic inflammation. Surviving ducts were dilated and lined by "proliferative" mucosa. This latter feature was typified by micro-papillary tufting of epithelium showing nuclear stratification and moderate cytologic atypia (Figure 1). These lesions ranged from PanIN 1a to PanIN 3. The cells varied in appearance from being clear to deeply eosinophilic/amphophilic. The invasive component had several appearances. There was a distinct clear cell component composed of sheets and nests of clear cells with pleomorphic nuclei, many of which had irregular, folded nuclear contours, imparting a

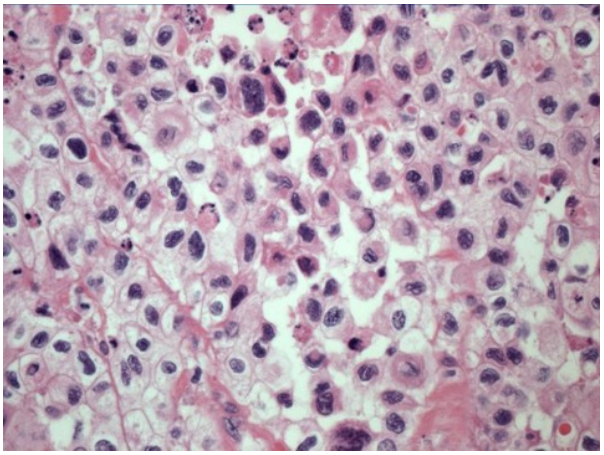

Figure 2. The clear cell component showed vacuolated cytoplasm and several nuclei had a convoluted, "wrinkled" appearance resembling a raisin ("raisinoid").

"raisinoid" appearance (Figure 2). Focal glandular differentiation was noted, with the ducts lined by clear cells as well as more conventional ductal lining cells. In other areas the infiltrating tumour had a high-grade squamous carcinoma appearance with marked pleomorphism, frequent mitoses and occasional dyskeratotic cells (Figure 3). Multinucleated tumour giant cells were associated with the squamous carcinoma. There was a transition from the clear cell component to the squamous foci. A third component, associated in particular with the clear cell areas, consisted of large cells with abundant, voluminous eosinophilic cyto-plasm, and eccentric large nuclei bearing prominent, acidophilic nucleoli (Figure 4a).

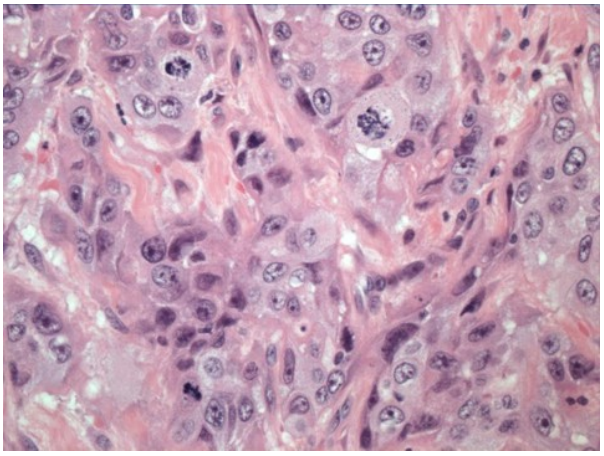

Figure 3. The squamous component was composed of squamoid cells with occasional dyskeratotic cells. Mitotic activity in this area was brisk.

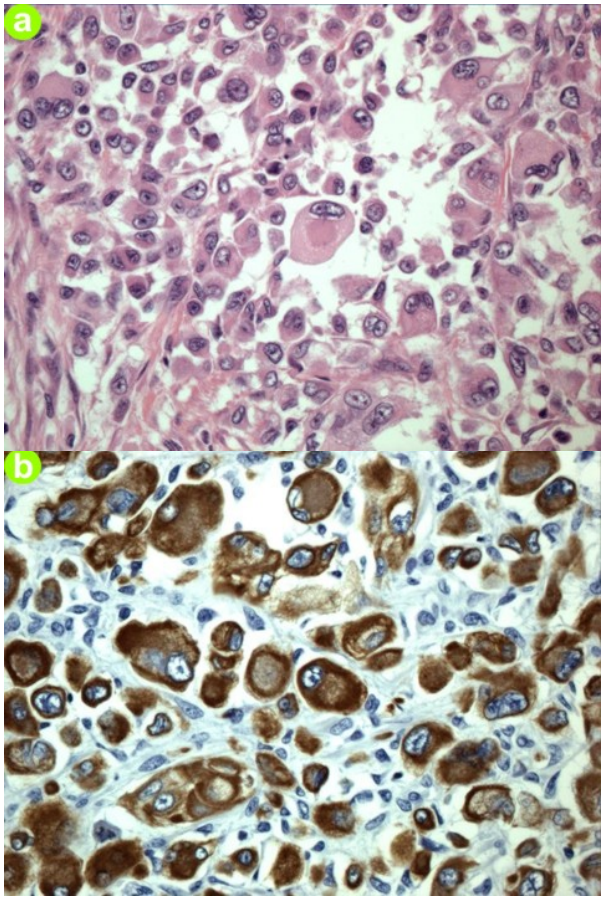

Figure 4. The rhabdoid cells were typified by large cells with abundant eosinophilic cytoplasm with paranuclear aggregation of filaments, eccentric nuclei and prominent nucleoli (**a.**). A cytokeratin stain highlights the cytoplasmic aggregation of intermediate filaments (**b.**).

Condensation within the cytoplasm with consequent displacement of the nucleus could be identified quite easily within this component. Several of these cells contained multiple nuclei. The clear cells contained glycogen and small amounts of mucin. All three components stained positively with cytokeratin markers (Figure 4b). The large eosinophilic cells were also vimentin positive and displayed paranuclear, dot-like accentuation of staining with cytokeratins and vimentin.

DISCUSSION

This case highlights for the first time an adenosquamous carcinoma of the pancreas characterized by the presence of clear cells with a rhabdoid component. Clear cell carcinoma of the exocrine pancreas is a rare tumour with very few cases reported previously. The molecular alterations and immunohistochemical profile of this lesion suggest that this tumour may have a ductal origin. Recently, foamy gland adenocarcinoma of the pancreatic or biliary tract and vacuolated cell adenocarcinoma of the pancreas have been described [8]. Both these subtypes have an aggressive clinical course similar to conventional ductal adenocarcinomas of the pancreas. It is in these two variations of pancreatic adenocarcinoma that the tumour cells show nuclei with irregular contours imparting a “raisinoid” appearance. Rhabdoid cells have been recognized in a wide range of epithelial and mesenchymal tumours, distinct from the prototypical malignant Wilm’s tumour of childhood. The rhabdoid phenotype is characterized by a large round to polygonal cell with eccentric nuclei, prominent nucleoli and abundant deeply acidophilic/eosinophilic, dot-like, hyaline filamentous cytoplasmic inclusions. It is currently believed that the rhabdoid phenotype represents a common clonal dedifferentiated end point in malignant tumours of varying histogenesis [9]. More recently, it has been suggested that rhabdoid changes may be a type of degeneration, or a preliminary stage before apoptosis or cell necrosis [10]. Ultrastructurally, the larger intra-cytoplasmic inclusions are located in a characteristic paranuclear or juxtanuclear location and consist of an accumulation of whorls of cytokeratin filaments approximately 10 nm in diameter, immunopositive for CK8, CK18 and vimentin. It is vital to recognize rhabdoid change histologically because, as in this case study, numerous studies have shown that its presence signals a neoplasm with aggressive behavior portending poor outcome in the majority of epithelial malignancies that have been encountered to date [11, 12, 13].
While there is still speculation as to the biological or prognostic relevance of pancreatic adenosquamous carcinoma variants, awareness of these morphologic nuances such as this case may have important diagnostic and, potentially, prognostic

ramifications which may, in the future, help select and improve upon adjunctive therapies and prolong survival in this aggressive lesion.

Received February 25th, 2007 - Accepted March 23rd, 2007

Keywords Adenocarcinoma, Clear Cell; Carcinoma, Adenosquamous; Rhabdoid Tumor

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Document URL: http://www.joplink.net/prev/200705/10.html

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