CASE REPORT

Undifferentiated (Anaplastic) Carcinoma of the Pancreas with Osteoclast-Like Giant Cells Showing Various Degree of Pancreas Duct Involvement. A Case Report and Literature Review

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ABSTRACT

Context Undifferentiated (anaplastic) carcinoma of the pancreas with osteoclast-like giant cells is exceedingly rare. The prognosis of undifferentiated carcinoma is worse than that of poorly differentiated ductal adenocarcinoma of the pancreas; however, undifferentiated carcinoma with osteoclast-like giant cells might have a more favorable prognosis. **Case report** We report the case of undifferentiated carcinoma of the pancreas with osteoclast-like giant cells, showing an intraductal growth pattern with various degree of pancreas duct involvement in the different areas. As a result, we were able to demonstrate the entire spectrum of changes, ranging from the early, minimal intraluminal growth to the partial or complete occlusion of the branches of the main pancreatic duct, and finally invasion and formation of the large necrotic/degenerated cysts. **Conclusions** Our findings support the epithelial origin of undifferentiated carcinoma of the pancreas with osteoclast-like giant cells. In early stages, the affected pancreatic duct epithelium was intermingled with nonepithelial component and had an immunoprofile distinctive from the epithelial lining of the uninvolved (normal) pancreatic ducts. Distinctive immunoprofile (CK 5/6, p63 and p53 positive) of the epithelial component and p63 and p53 positivity of the nonepithelial component should be explained and further investigated in the similar cases. Our findings support prior assertions that undifferentiated carcinoma of the pancreas with osteoclast-like giant cells may develop from carcinoma in situ within the main pancreatic duct or its branches.

INTRODUCTION

Undifferentiated (anaplastic) carcinoma of the pancreas is a rare aggressive tumor, which accounts for 2-7% of all pancreatic cancers [1, 2, 3, 4]. A number of terms have been used to describe variants of undifferentiated carcinoma of the pancreas, including pleomorphic carcinoma, pleomorphic giant cell carcinoma, sarcomatoid carcinoma, spindle cell carcinoma, anaplastic carcinoma, undifferentiated carcinoma [3, 4] and osteoclastic or pleomorphic giant cell tumors. Three major histological subtypes have been described: spindle cell carcinoma, pleomorphic carcinoma, and round cell carcinoma [5]. Undifferentiated carcinoma of the pancreas may contain osteoclast-like giant cells that are positive for CD68 and lysozyme without reactivity to epithelial markers [6, 7] similar to that previously described for giant cell tumor of bone [8]. Undifferentiated carcinoma of the pancreas with osteoclast-like giant cells, first described by Rosai [9], is exceedingly rare (less than 1% of all pancreatic malignancies).

Generally, the prognosis of undifferentiated carcinoma of the pancreas is worse than that of poorly differentiated ductal adenocarcinoma of the pancreas [5]. In a study of 35 cases [4], 29 patients died with an average survival of 5.2 months. Three patients in this series were alive at last follow-up, two without evidence of the disease (14.6 and 7.2 years, respectively), and one with recurrent tumor (follow-up 14.7 years). Ten-year survival has also been reported elsewhere [10], suggesting that undifferentiated carcinoma of the pancreas with osteoclast-like giant cells might have a more favorable prognosis than undifferentiated carcinoma of the pancreas without osteoclast-like giant cells [11].

Though there is limited data to support the differentiation of these lesions by CT or MRI alone, endoscopic US is able to demonstrate features unique to undifferentiated carcinoma of the pancreas [12, 13]. In contrast to the uniformly hypoechogenic appearance

Received December 5th, 2010 - Accepted January 14th, 2011

Key words Carcinoma; Giant Cells; Osteoclasts; Pancreas

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Document URL http://www.joplink.net/prev/201103/06.html

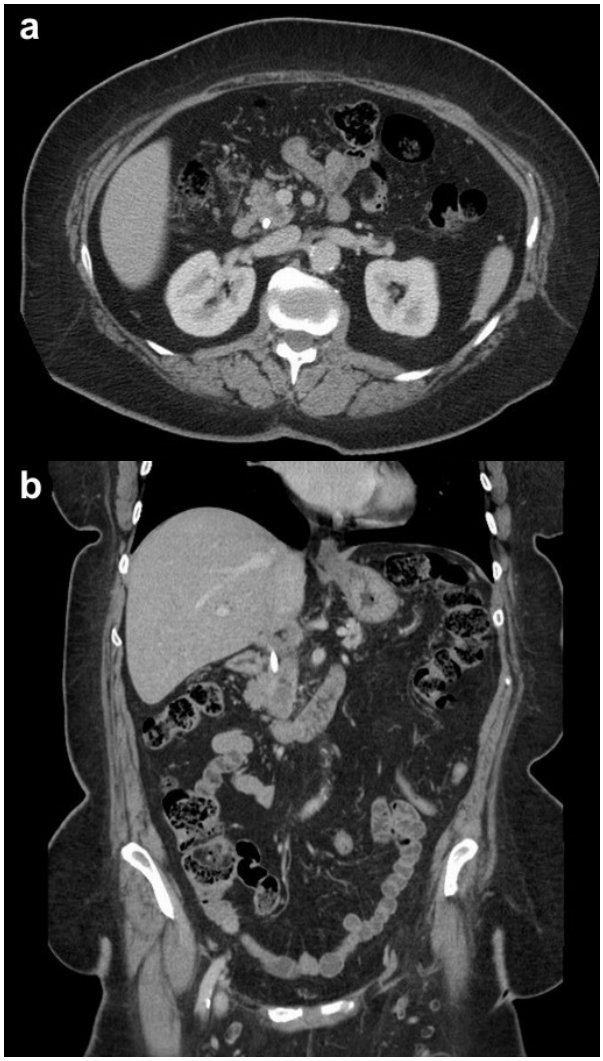

Figure 1. Computed tomography: coronal (**a.**) and sagital (**b.**) views of the mass.

of typical pancreatic adenocarcinoma, undifferentiated carcinoma of the pancreas tends to be markedly heterogeneous with both well demarcated hyper and hypoechoic areas, closely located within the same lesion [12]. Moore *et al*. [13] reported a series of five patients in whom a diagnosis of undifferentiated carcinoma of the pancreas was made by a combination of the endoscopic US findings with fine needle aspiration.

Similarly, the histogenesis of undifferentiated carcinoma of the pancreas with osteoclast-like giant cells is controversial as the tumor is often of advanced size and stage at the time of diagnosis [14, 15] and it is difficult to pathologically observe its relationship with the pancreatic duct [15].

We present a case of undifferentiated carcinoma of the pancreas with osteoclast-like giant cells with prominent intraductal extension, which is a unique feature and might help to better understand the pathogenesis of this rare entity.

CASE REPORT

A 68-year-old, Caucasian female presented to her family physician with episodes of spontaneously resolving painless jaundice. No nausea, vomiting, fevers, night sweats or abdominal pain was reported. An intentional weight loss of 4.5 kg was noted over two months. Past medical history was significant for type 2 diabetes mellitus, hyperlipidemia, hypertension, and osteoporosis. Past surgical history included an abdominal hysterectomy and open cholecystectomy. No allergies or significant social or family history was reported. Medications included hydrochlorothiazide, pravastatin and acebutolol. Of note, a trial of metformin began shortly before the initial episode of jaundice and its discontinuation coincided with resolution of the same.

Physical exam was unremarkable aside from jaundice. Laboratory investigations revealed elevated bilirubin at 160 μmol/L (reference range: 0-20 μmol/L) and moderately elevated transaminases. ERCP revealed abnormal papilla with a red, yellow mass protruding through the papillary orifice. The head and body portions of the main pancreatic duct were dilated as were both the common bile duct and intrahepatic bile ducts. An abrupt cutoff was noted in the distal common bile duct, suggesting a mass in the biliary tree. A biliary stent was therefore inserted to maintain patency. Biopsies obtained at the time revealed large atypical cells indicative of malignancy. A repeat CT showed a 2.0 cm mass in the uncinate process, without evidence of local or distant metastases (Figure 1ab). The patient underwent a standard pancreaticoduodenectomy. A mass within the uncinate process was easily palpated. Superior mesenteric vessels were not involved by tumor. No evidence of distant metastases was noted**.** The patient remained stable throughout the operation and postoperatively the patient recovered without complications. She was discharged from hospital on post-operative day 8.

Figure 2. Pancreaticoduodenectomy specimen. The main pancreatic duct (probe inserted) run separately from the longitudinally open, intact common bile duct. The pedunculated mass grows within the lumen of the distal portion of the pancreatic duct protruding through its orifice and forming a polypoid mass in the periampullary area, causing mechanical obstruction of the orifice of the common bile duct by occluding its opening.

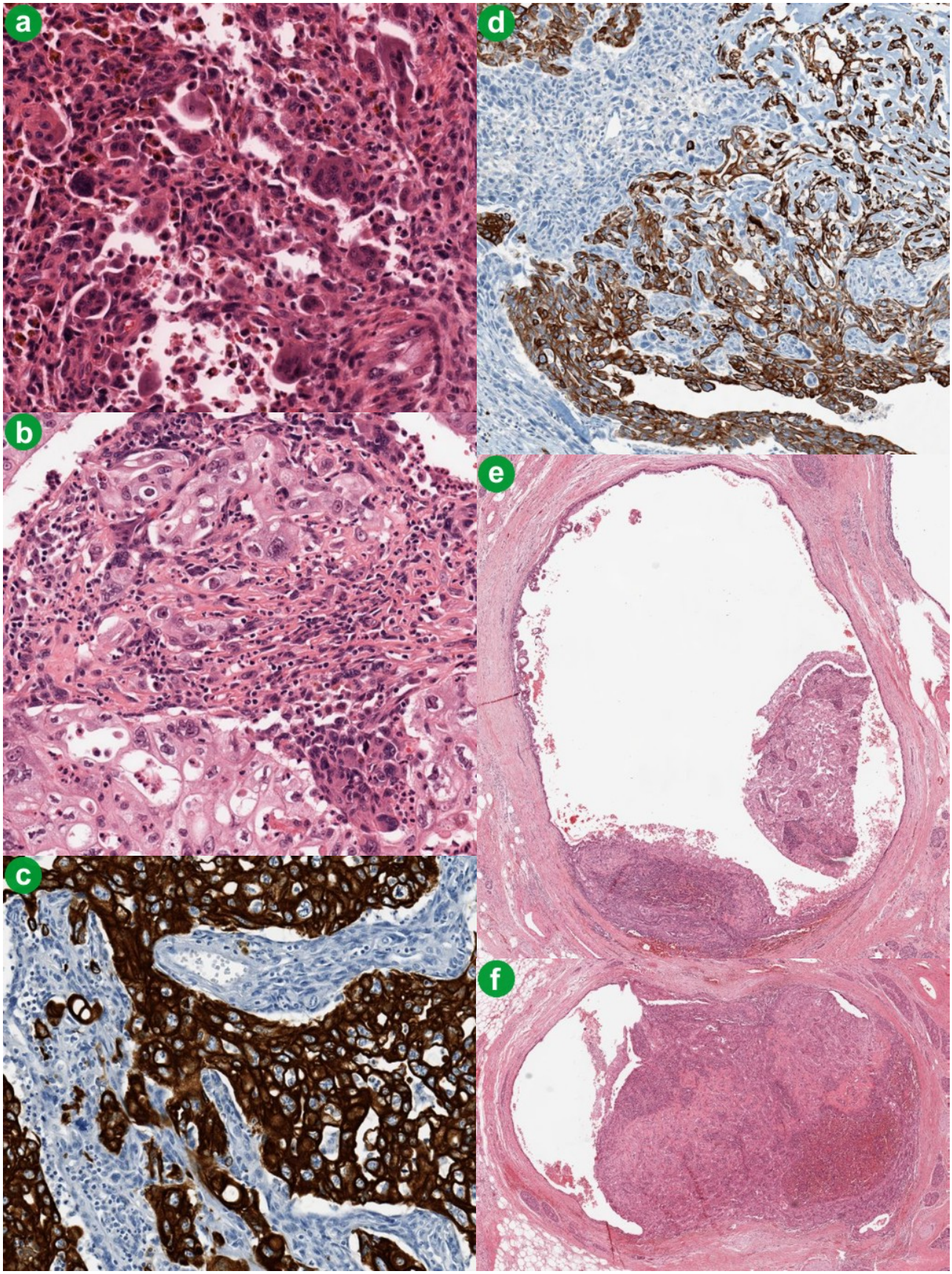

Figure 3. Histomorphologic findings. **a.** Mixture of the pleomorphic large cells, histiocyte-like mononuclear cells, atypical mononuclear cells and osteoclast-like giant cells (H&E, original magnification 20x). **b.** As above, but mixed with epithelial neoplastic cells (H&E, original magnification 20x). **c.** and **d.** Epithelial neoplastic cells strongly positive for pankeratin and cytokeratin 34 beta E12 (original magnification 20x). **e.** Early intraductal growth of the undifferentiated carcinoma of the pancreas (H&E, original magnification 2x). **f.** Pancreatic duct almost completely occluded by intraductal growth of the undifferentiated carcinoma of the pancreas (H&E, original magnification 2x).

Prior to fixation of the pancreaticoduodenectomy specimen, according to the previously described mapping protocol [16], components of the pancreatic resection margin, including uncinate (superior mesenteric artery) process resection margin, Posterior uncinate process dissection margin (posterior surface of the uncinate process) and superior mesenteric vein (vascular groove) dissection margin, were differentially inked. In situ assessment revealed that both common bile and main pancreatic ducts were dilated up to 1.2 cm and 0.6 cm in diameter, respectively. The main pancreatic duct was noted to run separately from the common bile duct and had its own duodenal opening. Growing along the lumen of the distal portion of the main pancreatic duct was a pedunculated, polypoid mass (2.5 cm in maximal dimension), protruding through its orifice and forming a polypoid mass in the periampullary area (Figure 2). Thus, contrary to the clinical impression an abrupt cutoff noted in the distal common bile duct was not related to the mass of the distal common bile duct, but was caused by pedunculated mass protruding through the orifice of the main pancreatic duct and causing mechanical obstruction of the common bile duct orifice at its opening. Otherwise, the common bile duct was intact. Further assessment revealed that the pedunculated mass was a part of a complex cystic hemorrhagic mass located within the uncinate process, measuring 3 cm in maximal dimension.

Microscopy revealed that the main bulk of the tumor was cystic/hemorrhagic and located within the uncinate process. At the same time, the tumor was intimately related to the main pancreatic duct and its branches. It grew along their lumen as an intraductal, pencil like growth and protruded into the lumen of the duodenum, forming a polypoid structure. Both components (cystic and intraductal) were predominantly comprised of non-epithelial component: pleomorphic large cells, histiocyte-like mononuclear cells, atypical mono nuclear cells and spindle cells with multiple, atypical and bizarre mitoses, as well as osteoclast-like giant cells (Figure 3a). Extensive sampling of the tumor revealed a minor epithelial component (Figure 3bcd), showing glandular differentiation within the intraductal pencil-like growth present in the main pancreatic duct and its branches **(**Figure 3ef**),** as well within the cystic component.

Two growth patterns were appreciated: invasive growth and intraductal extension. The former was large, hemorrhagic cysts, representing a necrotic/ degenerative process. The cysts were hemorrhagic, usually devoid of lining, and surrounded by a mesenchymal (non-epithelial) neoplastic component. There was a significant proportion of osteoclast-like giant cells, large pleomorphic cells, and hemosiderin, usually without an epithelial neoplastic component. However, extensive sampling demonstrated remnants of epithelial lining indicating its relation/origin to the branches of the main pancreatic duct. The latter pattern was intraductal/intraluminal neoplastic growth/ extension within dilated branches of main pancreatic duct with preserved epithelial lining (Figure 3e). Various degrees of pancreatic duct involvement (morphological heterogeneity), ranging from minimal intraluminal growth to complete occlusion of the lumen were noted. The cytologically abnormal epithelial lining within early intraductal involvement was focally lifted up and intermingled with the non-epithelial neoplastic component. The intraductal growth partially involving the lumen seems to be the finding of the tumor front, which represents the mode of early involvement of the duct by the tumor. It was clear that prominent intraductal extension of the tumor is an important and unique feature of this case.

Based on the morphological heterogeneity, it was clear that the two types of the growth pattern might represent different stages of neoplastic development with intraductal growth pattern more likely displaying early changes**.**

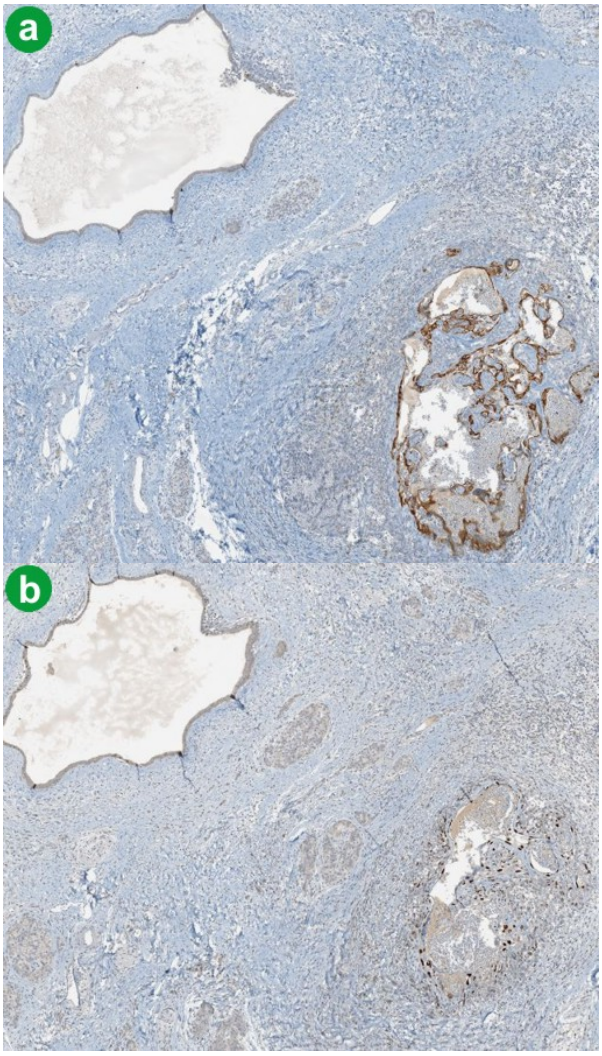

Figure 4. Comparison of the immunoprofile of the normal pancreatic duct (without intraluminal growth) with pancreatic duct involved by undifferentiated carcinoma of the pancreas. Left upper corner: normal pancreatic duct; right lower corner: pancreatic duct partially occluded by undifferentiated carcinoma of the pancreas, neoplastic epithelial component positive for CK 5/6 (**a.**) and P 63 (**b.**). (Original magnification 4x both).

The epithelial lining of the pancreatic duct with intraductal extension of the tumor (including epithelial neoplastic component intermingled with the nonepithelial component) had a distinct immunoprofile compared to normal branches of pancreatic duct without intraluminal growth. It was positive for cytokeratin (CK) 5/6 (Cell Marque D5&16B4, Rocklin, CA, USA), p63 (Cell Marque 4A4) and p53 (Ventana Bp53-11, Tucson, AZ, USA) (Figure 4ab). Staining for CD10 (Cell Marque 56C6), estrogen receptor (Ventana SP1), progesterone receptor (Ventana IE2), and inhibin (Dako R1, Carpinteria, CA, USA; 1/50 dilution) did not reveal ovarian like stroma, ruling out the possibility of the mucinous cystic neoplasm. Common markers such as CK 7 (Dako OVTL 12/30) and CK 20 (Cell Marque K520.8) had a similar pattern of the staining in normal branches of pancreatic and pancreatic ducts with intraluminal neoplastic growth. Overall, the epithelial component was positive for cytokeratin 34 betaE12 (Ventana 34be12), pankeratin (Ventana AE1/AE3/PCK26), CK 7, CK 5/6, p63, p53, epithelial membrane antigen (EMA) (weak) (Cell Marque E29), CEA (Ventana V9) and E-cadherin (Cell Marque ECH-6), but negative for CK 20, vimentin (Ventana V9), desmin (Ventana DE-R-11), actin (Cell Marque 1A4), calponin (Dako 1/50 dilution), CD10, CD117 (Dako ckit 1/100 dilution), estrogen receptor/progesterone receptor, inhibin and alpha antitrypsin (Cell Marque polyclonal). Interestingly, the epithelial component co-expressed (at least focally) CK 5/6 and p63, indicating the squamous/transitional or myoepithelial nature of the epithelial component.

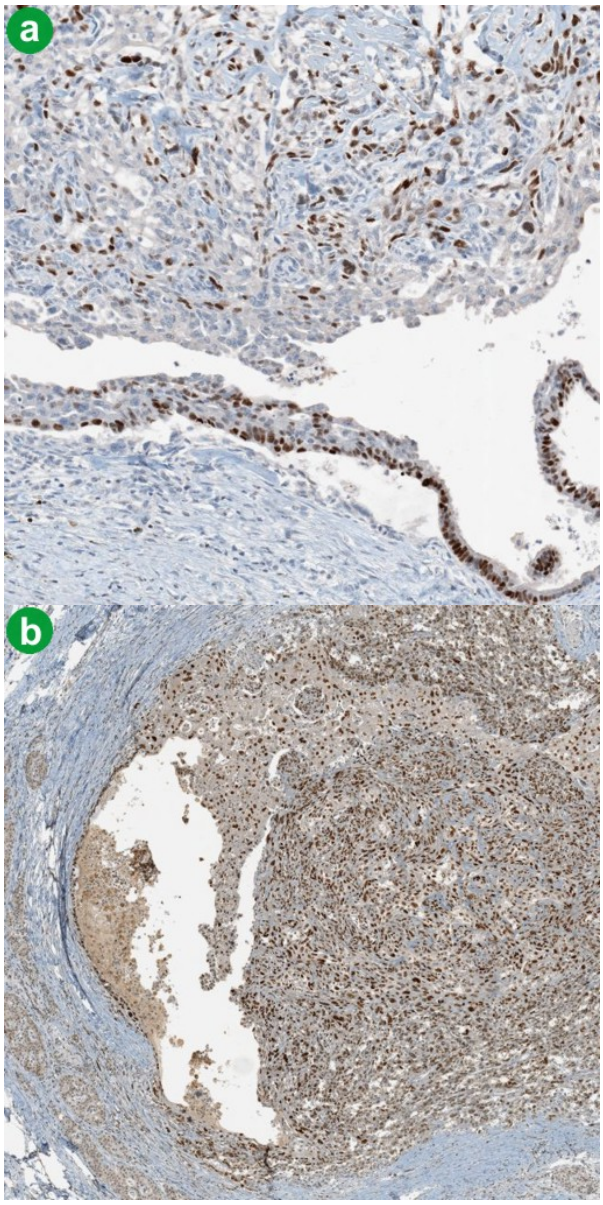

Figure 5. Intraductal growth of the undifferentiated carcinoma of the pancreas. Epithelial neoplastic component including the epithelial lining of the pancreatic duct and nonepithelial neoplastic components are positive for P63 (**a.** original magnification 10x) and P 53 (**b.** original magnification 4x).

The nonepithelial components of the tumor were positive for vimentin, desmin (focally), actin, p63, p53 (focally), calponin, CD10 (focally), CD117 (focally, weak) and alpha antitrypsin and negative for cytokeratin 34 betaE12, pankeratin, CK 7, CK 5/6, CK 20, EMA, CEA, estrogen receptor/progesterone receptor, inhibin and E-cadherin. CD68 (Ventana Kp-1) was positive in the osteoclast-like giant cells and large histiocytes-like cells. Both neoplastic components (epithelial and nonepithelial, excluding osteoclast-like giant cells) were strongly positive for Ki-67 (Ventana 30-9), p63 and focally p53 (Figure 5ab). CD31 (Ventana 1A 10) and factor VIII (Cell Marque polyclonal) highlighted only the feeding vessels.

The tumor DNA was examined for the presence of seven different K-*ras* mutations in codons 12 and 13 using real-time PCR. K-*ras* mutation was detected.

The small pancreatic ducts (less than 5 mm in diameter), within as well as outside the tumor, exhibited PanIN ranging from 1A to 3. There was no perineural or lymph vascular space invasion. The mapped pancreatic resection margin, as well as, distal pancreatic and common bile ducts, duodenal and gastric resection margin were all negative for malignancy. Fifteen regional lymph nodes were examined and were negative for metastatic disease. Since the tumor invaded the outer layers of the duodenal wall, it was classified as pT3 undifferentiated carcinoma of the pancreas. The patient is alive and well, with no evidence of disease 36 months postoperatively.

DISCUSSION

Undifferentiated carcinoma of the pancreas with osteoclast-like giant cells is a rare but known tumor. Based on the identification of atypical glandular differentiation, the presence of accompanying PanIN lesions, detection of K-*ras* mutation, and positivity for epithelial markers, the tumor is classified as a variant of pancreatic ductal carcinoma [4, 7, 17, 18, 19, 20, 21]. Recently, Bergman *et al*. [14] documented the initial steps in the evolution of these tumors and provided evidence for their ductal origin, including the

close association with PanIN 3 lesions. In the presented case, PanIN 2 and 3, which applies only to the small caliber ducts, were found, but the tumor presented within the main pancreatic duct and its branches. K-*ras* mutation, which is a characteristic finding in most pancreatic ductal adenocarcinoma [4, 14, 18, 20], was also present. E-cadherin expression within the epithelial component and loss of its expression within undifferentiated tumor cells, which is typical feature of the undifferentiated carcinoma of the pancreas [22], was also documented.

This case is unique due to the intraductal growth pattern with various degree of pancreas duct involvement and morphological heterogeneity of the lesion in the different areas. As a result, we were able to demonstrate the entire spectrum of changes, ranging from the early, minimal intraluminal growth to the partial or complete occlusion of the branches of the main pancreatic duct, and finally formation of the large necrotic/degenerated cysts as first described by Oehler *et al*. [23] as a "pseudocyst-like" lesion. In early stages, the affected pancreatic duct epithelium was intermingled with nonepithelial neoplastic component and had an immunoprofile (CK 5/6, p63 and p53 positive) distinctive from the epithelial lining of the uninvolved (normal) pancreatic ducts. This confirms the epithelial nature of the process, and also suggests the squamous/transitional, myoepithelial nature of the epithelial neoplastic component, or even origin from the reserve cells of the pancreatic ducts. Furthermore, even though the nonepithelial neoplastic component was negative for the epithelial markers, including CK 5/6, it still maintains positivity for p63 and p53. Both components were strongly positive for Ki-67.

Our findings contradict earlier assertions that coincidental entrapments of the preexisting epithelial structures, such as atypical ductal glands or dysplastic ducts, may have occurred independently from the tumor [14]. Our results support the association of tiny foci of the undifferentiated carcinoma of the pancreas with pancreatic ducts with severe intra-epithelial dysplasia, which was declared as direct evidence for ductal evolution [14].

There are also noted similarities between the presented case and that recently described by Tezuka K *et al*. [24]. In the latter case, the lumen of the main pancreatic duct was also occupied by a polypoid (intraluminal) tumor, comprised of sheets of spindle cells intermingled with scattered osteoclast-like giant cells and pleomorphic giant cells. These findings were consistent with undifferentiated carcinoma of the pancreas with osteoclast-like giant cells and extra-ductal invasion was not found. In Tezuka *et al*.'s [24] opinion, this was the first reported case of undifferentiated carcinoma of the pancreas in situ within the main pancreatic duct, without the evidence of invasion beyond the pancreatic duct. Interestingly, the patient described by Tezuka *et al*. was alive, without recurrence after 22 months. Additional reports since published also support the assertion that undifferentiated carcinoma of the pancreas with osteoclast-like giant cells is associated with long term survival [25]. As noted, our patient remains clinically and radiologically disease free after 36 months. It will therefore be interesting to follow patients with undifferentiated carcinoma of the pancreas with osteoclast-like giant cells and intraductal growth pattern for longer periods, to ascertain its correlation with survival benefit.

In summary, the patient described here has a diagnosis of pancreatic undifferentiated carcinoma (anaplastic) with osteoclast-like giant cells, showing an intraductal growth pattern with various degree of pancreas duct involvement. Our findings support the epithelial origin of undifferentiated carcinoma of the pancreas. Distinctive immunoprofile (CK 5/6, p63 and p53 positive) of the epithelial neoplastic component and p63 and p53 positivity of the nonepithelial neoplastic component should be explained and further investigated in the similar cases. Our findings support prior assertions [24] that undifferentiated carcinoma of the pancreas with osteoclast-like giant cells may develop from carcinoma in situ within the main pancreatic duct or its branches. In addition, it may confer some survival benefit compared to undifferentiated carcinoma of the pancreas without osteoclast-like giant cells based on limited studies in the available literature.

Acknowledgement No financial support received

Conflict of interest The authors have no potential conflicts of interest

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