Pathol. Oncol. Res. (2009) 15:129–131
DOI 10.1007/s12253-008-9053-9

ORIGINAL PAPER

A Case of Osteoclast-like Giant Cell Tumor of the Pancreas Associated with Borderline Mucinous Cystic Neoplasm

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Received: 20 March 2007 / Accepted: 10 April 2008 / Published online: 21 May 2008

Abstract A 34-year-old, previously healthy female presented with severe acute upper quadrant abdominal pain and an 11-cm cystic mass in the tail of the pancreas. The patient underwent distal pancreatectomy with total gross excision of the mass. Grossly, the mass consisted of a multiloculated cystic lesion measuring 11.7 cm in its greatest dimension. An irregular solid lobulation at the lateral aspect of the cyst was visible, measuring 3 cm in the largest dimension. Histologically, there were two distinct components: a mucinous, neoplastic epithelial cyst with few foci of moderate atypia, and nodular spindle cell areas containing multinucleated tumor giant cells. Immunohistochemically, the multinucleated giant cells were positive for vimentin, CD68 and CD45, and negative for cytokeratin and epithelial membrane antigen (EMA). The spindle cells of hypercellular stroma were stained for vimentin, but not for EMA or carcinoembryonic antigen (CEA). Neuron-specific enolase (NSE), S100 and Ki-67 showed no reactivity. The histological diagnosis "osteoclast-like giant cell tumor of the pancreas associated with borderline mucinous cystic neoplasm" was made. The patient recovered and is free of disease 4 years after the diagnosis.

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Keywords Osteoclast-like giant cell tumor · Mucinous cystic neoplasm · Immunohistochemistry · Pancreas

Abbreviations

CEA	carcinoembryonic antigen
EMA	epithelial membrane antigen
LSAB	labeled streptavidin-biotin
NSE	neuron-specific enolase
OGCT	osteoclast-like giant cell tumor
α-SMA	α-smooth muscle actin

Introduction

Osteoclast-like giant cell tumor (OGCT) of the pancreas is a rare entity, with a frequency of only 0.2% of the total reported pancreatic carcinomas [9]. There have been about 30 papers since 1977, representing more than 40 patients [3, 4, 6]. Alguacil-Garcia and Weiland [1] were first to describe a malignant giant-cell tumor of the pancreas with osteoclast-like giant cells. During the past three decades, reports have described this neoplasm uniformly with respect to clinical and pathologic characteristics. Osteoclast-like giant-cell tumors have been noted to occur in the parotid gland, thyroid gland, skin, orbit, kidney, and breast [2, 7, 16]. However, the pancreas seems to have the highest predilection for these lesions. They most commonly present as large cystic neoplasms, 5–10 cm in diameter [19]. OGCTs are typically well circumscribed, yellow-pink, and fleshy. By light microscopy, they are composed of multinucleated, benign appearing giant cells dispersed among infiltrating mononuclear tumor cells. The multinu-

cleated giant cells closely resemble the osteoclasts of resorbing bone. OGCTs are frequently associated with mucinous cystic neoplasms and in situ or infiltrating adenocarcinomas [14, 19].

Clinical History

A 34-year-old previously healthy female has developed severe acute upper quadrant abdominal pain in spring of 2003. She was seen in a local emergency department. An ultrasound and computed tomography scan of the abdomen revealed an 11-cm cystic mass in the tail of the pancreas. At laparotomy, a large cystic mass was found which was dissected from the retroperitoneum, left adrenal gland, and left colon. Local extension in adjacent organs was not seen. The patient underwent distal pancreatectomy with total gross excision of the mass. Grossly, the mass consisted of a multiloculated cystic lesion measuring 11.7 cm in its greatest dimension. An irregular solid lobulation at the lateral aspect of the cyst was visible, measuring 3 cm in the largest dimension.

Materials and Methods

The surgical specimen was fixed in 10% buffered formalin, embedded in paraffin and cut in 4-μm sections. Hematoxylin and eosin-stained sections were prepared for histological evaluation, and the clinical history was reviewed. Immunohistochemical stainings were performed using the LSAB methodology (substrate: DAB) with mouse anti-human primary antibodies against vimentin (clone V9), CD68 (clone PG-M1), CD45 (clone T29/33), epithelial membrane antigen (EMA, clone E29), cytokeratin (clone MNF116), carcinoembryonic antigen (CEA, clone II-7), neuron-specific enolase (NSE, clone BBS/NC/VI-H14), α-smooth muscle actin (α-SMA, clone 1A4), S100 (rabbit polyclonal) and Ki-67 antigen (clone MIB-1) (all from Dako, Glostrup, Denmark).

Results

Microscopically, the neoplasm was composed of two distinct components: a mucinous, neoplastic epithelial cyst and nodular areas of atypical mononuclear infiltrate with osteoclast-like multinucleated giant cells (Fig. 1A,B). The mucinous epithelium showed few areas of moderate atypia, pseudostratification without the suggestion of invasion into the stroma (Fig. 1C), intraluminal papillary formations, goblet cells, with ovarian-like hypercellular stroma. The multinucleated giant cells resembled bone osteoclasts with no signs of atypia (Fig. 1D). The small areas of pancreatic tissue were also seen with fibrosis and intense lymphocytic infiltration.

Immunohistochemically, the mucinous epithelial cells stained for EMA and cytokeratin, but not for CEA. The multinucleated giant cells were positive for vimentin (Fig. 1E) and cell surface proteins CD68 and CD45 (Fig. 1F,G), and negative for cytokeratin and EMA. Thus, the immunohistochemical profile of multinucleated giant cells was consistent with a mesenchymal phenotype. The spindle cells of hypercellular stroma were stained for vimentin (Fig. 1E), but not

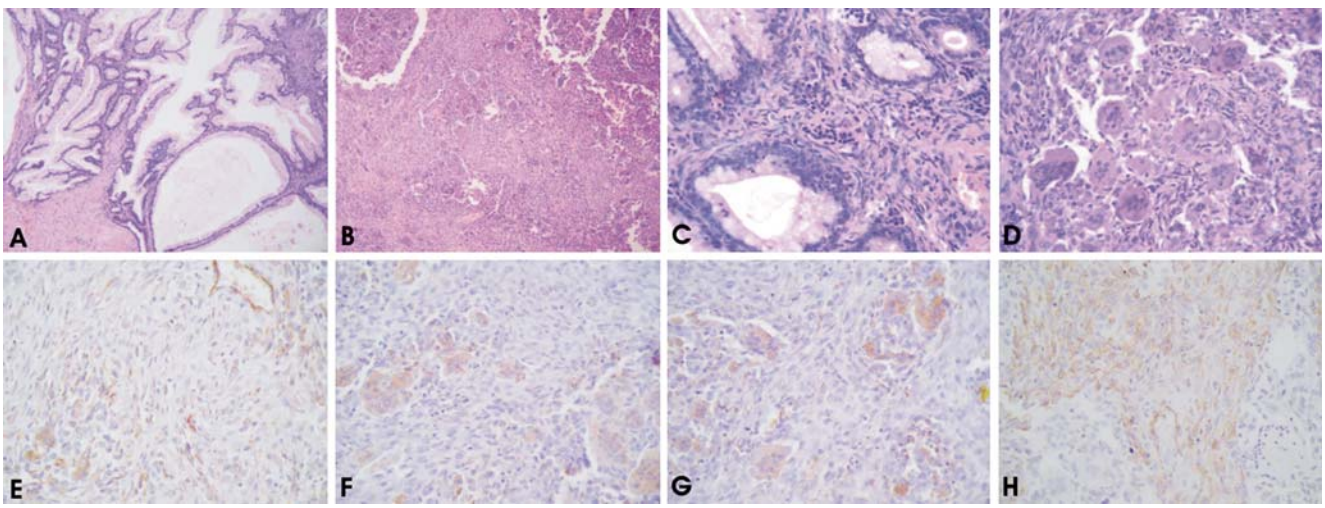

Fig. 1 **A** Areas of mucinous cystic neoplasm; **B** multinucleated giant cells in the atypical mononuclear cell component; **C** mucinous epithelium with moderate atypia and pseudostratification; **D** multinucleated giant cells resembling bone osteoclasts with no signs of atypia. **A** and **B** **H&E**, ×100, **C** and **D**: **H&E**, ×400. **E** Vimentin immunoreactivity in osteoclast-like multinucleated giant cells and mononuclear cell component; **F** CD68 positivity in osteoclast-like multinucleated giant cells; **G** CD45 positivity in osteoclast-like multinucleated giant cells; **H** α-smooth muscle actin (α-SMA) immunoreactivity in the atypical mononuclear cell component. **E** and **H**: immunohistochemistry, LSAB, DAB, ×400

for EMA or CEA. The mononuclear stromal cells expressed α-smooth muscle actin focally (Fig. 1H). CEA, NSE, S100 and Ki-67 showed no reactivity. The final histopathological diagnosis was made as follows: "osteoclast-like giant cell tumor of the pancreas associated with borderline mucinous cystic neoplasm".

Discussion

Two histologically and clinically distinct types of giant cell tumors of the pancreas have been described [15]. Anaplastic carcinoma is considered a variant of ductal adenocarcinoma with distinctive appearance and extremely poor prognosis. Microscopically, it is a pleomorphic tumor with discohesive, bizarre, multinucleated giant cells (not osteoclast-like), which resembles giant cell carcinomas of lung, adrenal gland or liver [11]. The other type histologically resembles giant cell tumor of bone and has better prognosis. Osteoclast-like giant cells, pleomorphic large cells, histiocyte-like mononuclear cells, atypical mononuclear cells and ductal carcinoma cells can be seen in this lesion [10].

In anaplastic giant cell carcinoma, immunohistochemical analysis by immunostaining for EMA and cytokeratin demonstrates an epithelial origin for the mononuclear cell population [13, 19]. In this case stromal cells showed no atypia and immunoreactivity with EMA and cytokeratin, and thereby their epithelial origin could be excluded. In contrast, the positive staining for vimentin suggested the mesenchymal origin of these cells. In addition, CEA and MIB-1 antibodies did not react with epithelial cells, but focal pseudostratification and papillary formations were evident, which was consistent with the diagnosis of a borderline mucinous cystic neoplasm.

Osteoclastic giant cells rarely express epithelial markers but show staining for histiomonocytic markers (CD68) [12, 13]. As reported in this patient, OGCT cells possessed cell-surface markers: CD68, CD45, as well as vimentin. In this instance, the osteoclast-like giant cell tumor appeared to arise in association with a mucinous epithelial component. OGCT may also contain abundant osteoid [19]. In our case the osteoid meteplasia was not seen. Only small areas of pancreatic tissue were detected with fibrosis and intense lymphocytic infiltration. Several pathologic evaluations have distinguished osteoclastic tumor giant cells of uncertain lineage [8, 13, 15]. Sun et al. in 1998 [18] have proposed that the neoplastic component may produce chemotactic and growth factors that stimulate the proliferation of circulating precursors cells to differentiate into osteoclastic giant cells. The question of whether the giant cell component is neoplastic or reactive is controversial.

In most OGCTs metastasis is slow and lymph node spread is rare but survival is very short in some patients. Mean survival is 20.4 months after diagnosis or surgery [17]. Our patient recovered and is free of disease 4 years after the diagnosis.

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