A Case Report Presenting an Undifferentiated Pancreatic Carcinoma with Osteoclastic-Like Giant Cells with an Unusual Indolent Course

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Patient: Male, 77
Final Diagnosis: Undifferentiated pancreatic carcinoma with osteoclastic giant cells like tumor
Symptoms: Severe abdominal pain
Medication: —
Clinical Procedure: —
Specialty: Surgery

Objective: Rare disease
Background: Undifferentiated pancreatic carcinoma with osteoclastic-like giant cells represents less than 1% of pancreatic cancers. Histogenesis and prognosis are still debated. Three subtypes are defined by the World Health Organization: osteoclastic, pleomorphic, and mixed. The differential diagnosis of a pancreatic tumor with giant cells varies from a benign osteoclastoma to an undifferentiated pancreatic carcinoma with osteoclastic-like cells. The specimen should be carefully examined to rule out conventional pancreatic adenocarcinoma even in the presence of the giant cells.

Case Report: A 77-year-old male was diagnosed with a pancreatic tail tumor with osteoclastic like cells revealed by a biopsy done by echo-endoscopy; the patient was lost to follow up for 24 months before he was admitted to our institute for severe abdominal pain. A computed tomography showed the same lesion without progression. He was operated on using laparoscopic distal pancreatectomy with splenectomy. Pathology analysis revealed the presence of osteoclast-like giant cells without pleomorphic cells. Mutated KRAS on molecular study confirmed the diagnosis of undifferentiated pancreatic carcinoma with osteoclast-like giant cells. The patient was in good performance status and disease-free 19 months after surgery without any sign of progression.

Conclusions: Undifferentiated pancreatic carcinoma with osteoclast-like cells has a challenging pathology diagnosis. Molecular and immunostaining are essential to diagnosis. The absence of pleomorphic cells in the present case has classified it into the osteoclastic subtype. Further cases and studies are needed to confirm the heterogeneity of the malignant course between subtypes.

MeSH Keywords: Carcinoma • Pancreatic Neoplasms • Pathology • Rare Diseases

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Background

Pancreatic neoplasms are the second most common tumor of the digestive system after colorectal tumors [1]. Adenocarcinoma is the most frequent type of pancreatic cancer [2]. The presence of osteoclast-like giant cells (OGC) defines the independent type of undifferentiated pancreatic carcinoma with osteoclast-like giant cells (UPC-OGC) which form less than 1% of pancreatic cancers [3,4]. According to the World Health Organization (WHO), UPC-OGC contains OGC and mononuclear spindle shaped cells and has a better prognosis than classical adenocarcinoma [5,6]. True histogenesis of UPC-OGC is controversial, both epithelial and mesenchymal origins are suggested. OGC are also seen in other benign pancreatic and extra pancreatic conditions [7]. It was first discovered in the pancreas in 1968 and was defined as giant cell pancreatic tumor (GCPT). This entity was divided in 3 subtypes: pleomorphic, osteoclast, and mixed [8]. However, since 2010 the WHO has grouped all subtypes under the name of UPC-OGC, even though differentiating between each subtype still is controversial in predicting prognosis [2]. We present a challenging diagnostic case of a 77-year-old male diagnosed since 43 months with an UPC-OGC, operated since 19 months, and still alive and clinically disease-free without any adjuvant treatment.

Case Report

Our case was a 77-year-old Caucasian male known to have controlled diabetes, hyperlipidemia, and coronary artery disease. After episodes of hematochezia, the patient underwent gas- troscopy, colonoscopy, and abdominal computed tomography (CT) scan without injection due to an elevated creatinine level in August 2015. Both endoscopic explorations were normal. A mass in the tail of the pancreas was observed on CT scan. An echo endoscopy showed a mass on the tail of the pancreas of 2.5 cm. The biopsy specimen revealed the presence of OGC. The patient was lost to follow up until August 2017 when he presented to the emergency department with severe abdominal pain without any fever, jaundice, nausea, vomiting, or other clinical sign. He had soft abdomen with generalized tenderness. The patient had normal white blood cell count, with normal liver functional test, normal pancreatic enzymes, and his C-reactive protein was not elevated. An abdominal pelvic CT scan with intravenous (IV) contrast was conducted. A nodular exophytic lesion of 2.7 cm was discovered on the anterior side of the pancreatic tail. The tumor had heterogeneous aspect after injection of contrast, with a clear center and a powerful enhancement of the periphery. No suspicious masses were reported.

Figure 1. Computed tomography with intravenous injection. (A) Axial view; (B) Coronal view. Arrow shows the tumor in the tail of the pancreas. The tumor density enhanced after contrast injection with a size of 3×3 cm.

Figure 2. Macroscopic view of the tumor with the spleen separated of it. Big arrow: the tumor is in the tail of the pancreas with a size of 3×3 cm. Small arrow: the body of the pancreas.
lymph nodes were found. The liver was free of disease, and there was no ascites (Figure 1). Ca 19-9 and CEA was in normal range. We conducted a laparoscopic distal pancreatectomy with splenectomy. The procedure took about one hour and a half without any complication. The patient was discharged at day 7 after surgery, with good functional status.

Gross examination revealed a 2.8 cm mixed solid and cystic tumor of the pancreatic tail, without any communication with the pancreatic duct (Figure 2). On microscopic examination the tumor was densely cellular composed of mononuclear, oval and spindle shaped cells mixed with multinucleated OGC (Figures 3, 4). The mononuclear cells showed mild atypia and no suspicious mitotic activity. Immunostaining was negative with cytokeratin (figure 5). P-53 was not overexpressed.

Figure 3. Microscopic examination. Staining: hematoxylin and eosin; scale 200×. Large arrows show osteoclast like giant cells and small arrows show mononuclear cells without atypia.

Figure 4. Immunostaining for cytokeratin is negative. Scale 400×. The tumor cells are counter stained with hematoxylin eosin (blue color). The brown staining indicate hemosiderin depot.

Figure 5. Immunostaining for cytokeratin is negative. Scale 400×. Staining is negative for cytokeratin. The blue color means a negative staining for cytokeratin. A positive staining is present in most conventional ductal pancreatic carcinoma. Note that the colored points are due to hemosiderin.

Figure 6. Few cystic cavities were identified in the tumor area lined by mildly dystrophic epithelium without significant atypia (arrow). Adjacent pancreatic tissue showed atrophic chronic pancreatitis. Arrow shows the epithelium.

Proliferation index Ki-67 was mild to moderate. Few cystic cavities were identified in the tumor area lined by mildly dystrophic epithelium without significant atypia. Adjacent pancreatic tissue showed atrophic chronic pancreatitis (Figure 6). Fifteen lymph nodes were found and they were free of metastasis. The diagnosis of GCPT was considered. However, UPC-OGC could not be ruled out. Subsequent molecular studies were performed and revealed a mutation in the KRAS gene. This finding favored the diagnosis of UPC-OGC.

After 19 months of surgery the patient is clinically disease free, without any abdominal pain, digestive symptoms and...
without any sign of progression like significant weight loss or fatigue. Unfortunately, the patient refused a suggested follow-up based on CT scan with IV contrast.

Discussion

Few reports have discussed the histological, cytological, and survival characteristics of GCPT due to the tumor rarity [9]. Our case presented a single but important proof of the low malignant potential of UPC-OGC with dominant OGC. The stable lesion size for 43 months and the disease-free survival without any adjuvant treatment of our patient since more than 19 months are the key elements of that low malignant potential.

True histogenesis of UPC-OGC is still controversial. Researchers using immunohistochemistry and molecular biology have concluded the possibility of mesenchymal and epithelial origins [10]. Positivity to CD68, vimentin, and the negativity of cytokeratin favors the mesenchymal origins. Otherwise, the positivity of keratin and high CEA favors epithelial derivation [11]. The unknown origin theory has been generated by the variety of cells that can form the tumor [12]. The multinuclear osteoclastic like giant cells found in the UPC-OGC are considered benign histiocytic origin that lack atypia. Their presence is related to the positivity of CD68 and vimentin [9]. The multinuclear spindle atypical cells with inconsistent positivity to epithelial markers like keratin are linked to the potential malignant aspect of the UPC-OGC tumors [13].

Some authors have divided the UPC-OGC tumors in 2 distinct tumors. The first is dominated by OGC, with the possibility to lack mononuclear cells atypia and thought resemble benign giant cell tumors of bone and be called “osteoclastoma” [9]. The second is dominated by pleomorphic mononucleated and multinucleated giant cells and lack the OGC described in the first type and is called pleomorphic giant cell tumor with an aggressive malignant course [14]. Mixed osteoclast/pleomorphic tumors are also described in the literature [1]. Authors suggested that in mixed tumors, both cell types might represent 2 different ends of the same biological spectrum [15]. The giant cells in our case were OGC with no atypia. No pleomorphic cells were found. We had difficulties ruling out the presence of malignant cells. The negativity of epithelial markers as found in our case cannot rule out malignancy because many UPC-OGC had the same result in the literature [16].

Molecular analysis in our case showed a mutated KRAS gene. Luchini et al. analyzed the molecular aspect of UPC-OGC and in their series all tumors shared K-RAS gene mutation like conventional pancreatic ductal carcinoma [17]. Westra et al. also showed a positive KRAS mutation in osteoclastic giant cell tumors of the pancreas with negative epithelial markers. They concluded that those tumors were UPC-OGC, and that the positivity of the KRAS mutation in the GCPT may reflect the phagocytized malignant cell by the giant cells [18]. The search for an underlying conventional pancreatic ductal carcinoma or an intraductal papillary mucinous neoplasms of the pancreas is mandatory because OGC can be associated to those tumors and in that case the diagnosis of UPC-OGC is declined [17].

Published data on PGCT survival rate varies from 4 months to 15 years. This variation is probably due to the variability of the tumor constitution [14]. Patients with positive epithelial markers tend to live less than those with pure mesenchymal origin [19]. In comparison with conventional ductal pancreatic carcinoma, Muraki et al. concluded that the mean survival rate over 5 years for UPC-OGC was around 60% versus 15% for the conventional adenocarcinoma [6].

Experience is lacking in adjuvant treatment concerning UPC-OGC. There is no available data to differ adjuvant treatment from conventional ductal adenocarcinoma. The benefit of radiotherapy in bone GCT could extrapolate some benefit in PGCT. This is questioned especially due to the morbidity of small bowel irradiation. In a case with a complete surgical resection, with negative margins and negative nodal metastasis, a simple program of surveillance based on CT scan with IV contrast is recommended after an adequate adjuvant chemotherapy treatment like the conventional ductal adenocarcinoma modalities [2].

Conclusions

UPC-OGC still is a controversial subject in the literature. Little is known about these tumors, and published data is confusing concerning histogenesis and prognosis. We presented an example of a slow progression subtype represented by a stable size in a period around 2 years from the diagnosis until surgery. Differential diagnosis can oscillate from a benign osteoclastoma to an aggressive undifferentiated pleomorphic giant cell tumor. The presence of giant cells alone as in this case cannot rule out malignancy. Negative immunostaining for cytokeratin as in this patient’s lesion cannot confirm a benign nature. The expression of a mutated KRAS confirmed the diagnosis of UPC-OGC. The absence of pleomorphic cells classified the tumor in the osteoclastic subtype and might be responsible for the slow progression character. Further publication with cases that share the same pathology characteristics are needed to confirm or to deny the unusual indolent course rate of this subtype as presented in our case.
Department and Institution where work was done

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Conflict of interest

None.

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