Cytologic Features and Clinical Implications of Undifferentiated Carcinoma with Osteoclastic Giant Cells of Pancreas; An Analysis of 15 Cases

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Running title: Undifferentiated pancreatic carcinoma with osteoclastic giant cells

Summary Statement: Undifferentiated pancreatic carcinoma with osteoclastic giant cells is a rare malignant tumor that is typically large, frequently has a ductal component and shows three classical cell types including benign osteoclastic giant cells, and malignant pleomorphic giant cells and spindled/histiocytoid tumor cells, making cytologic diagnosis possible in most cases.

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Abstract

Background: The cytologic features of undifferentiated pancreatic carcinoma with osteoclastic giant cells (UOC) are rarely described.

Methods: Cytologic and clinicopathologic characteristics in 15 UOC FNAs were analyzed.

Results: 6 males, 8 females, mean age 65, had UOCs [head (7), body (3) and tail (4)] of mean radiologic size 7.3 cm with cystic component (9). Three cell types [osteoclastic giant cells (OGC), pleomorphic giant cells (TGC) and spindled/histiocytoid cells (SHC)] were seen in 12/15 (80%). Pancreatic ductal adenocarcinoma (PDAC) was present in 11. FNA diagnoses were: UOC (6), PDAC (5), poorly-differentiated carcinoma (2), "suspicious for neoplasm" (1) and "negative" (1). OGCs were CD68+ in 5/5. Pancytokeratin (6/7), CAM5.2 (2/3), and EMA (2/2) highlighted TGCs and SHCs. INI-1 was retained in 3/3 cases. Ki-67 index was performed in 3 cases and was 12, 18, and 40%; 4/12 resected UOCs were pure and 8 were mixed with PDAC; 1 resection had intraductal papillary mucinous neoplasm and 2 had mucinous cystic neoplasms. Median overall survival (OS) of FNA'ed UOCs was 8 mths [6 died (OS 8 mths; 2 -22) and 8 were alive (OS 3 mths; 1 – 27)], which was similar to 74 FNA'ed PDACs (OS 15 mths; p=0.279) but worse than 27non-FNA'ed UOCs (OS 92 mths; p=0.0135).

Conclusion: The 3 classical UOC cell types are identifiable on FNA, making cytologic diagnosis possible if considered in the differential. A PDAC component is also often seen. The survival advantage of UOC over pure PDACs appears to be negated by FNA and requires further investigation.

Key words: Undifferentiated carcinoma with osteoclastic giant cells of pancreas; osteoclast-like giant cell carcinoma; pancreas; cytology; FNA

Introduction

The vast majority of pancreatic masses represent ductal adenocarcinoma (PDAC), which has a dismal 5-year survival of less than 8%, and is currently the third leading cause of cancer-related deaths in the United States.[1] Undifferentiated pancreatic carcinoma with osteoclastic giant cells (UOC) is an extremely rare pancreatic cancer that has a preponderance of osteoclastic giant cells showing all the characteristics of osteoclasts of bone. It was first described by Sommers *et al* in 1954 as "unusual carcinoma of pancreas".[2] In 1968 Rosai named these tumors "carcinomas of pancreas simulating giant cell tumor of bone".[3] Its' true incidence remains unknown because of the plethora of names by which it has been described including "pleomorphic carcinoma of pancreas", "giant cell carcinoma", "osteoclastic giant-cell tumor or carcinoma", "sarcomatoid carcinoma" and "carcinosarcoma" to name a few. In the 2010-World Health Organization book these tumors were classified as "variants" of pancreatic ductal adenocarcinoma under the heading "undifferentiated carcinoma with osteoclastic giant cells", [4] and are fundamentally epithelial derived tumors with mesenchymal differentiation.[3, 5]

The average patient age is 62 years but age varies widely from 32 – 93 years.[4, 6-8] Tumors are typically large and circumscribed, and are defined by non-neoplastic, phagocytic, osteoclastic giant cells containing over 20 bland nuclei, in a background of "sarcomatoid" carcinoma, which may produce osteoid.[6, 8-10] Some tumors show polypoid intraductal or intra-ampullary growth or cystic degeneration, [8, 11, 12] while others arise in neoplastic mucinous cysts (mucinous cystic neoplasm (MCN) or intraductal papillary mucinous neoplasm (IPMN)).[8, 13-15]

Other than the macrophage-like osteoclastic giant cells that are typical of this tumor,[9] two other distinct tumor cell types, including large, highly pleomorphic mononuclear tumor giant cells as well as small spindled or histiocytoid tumor cells sometimes resembling stromal cells may be seen. Osteoclastic giant cells have been shown by morphologic, immunohistochemical, molecular and ultrastructural studies to represent benign histiocytic cells likely recruited by the tumor's sarcomatoid component.[9, 16] Elevated chemoattractants noted in oral squamous and inflammatory breast cancers have been postulated to play a similar chemotactic role in some pancreatic and ampullary cancers, including UOC.[8, 17, 18]

Osteoclastic giant cells express CD68, vimentin, leukocyte common antigen, and are negative for keratin and p53; however, the truly malignant cells in this tumor, i.e. the pleomorphic tumor giant cells and spindled or histiocytoid cells (that are often overlooked in the background), strongly express vimentin, and variably, but typically, express keratin, show mutant p53 staining pattern (with diffuse positivity) and elevated Ki-67 proliferation index.[4, 8-10, 19, 20] UOCs frequently show an associated component of conventional PDAC.[4, 8] While some studies suggest an overall poor prognosis for UOC, with mean survival of 12 months,[4, 7] more recent studies have shown these tumors to have a more protracted clinical course relative to conventional PDAC.[8, 21-23]

While the histologic features of UOC (a.k.a. "osteoclastic giant cell carcinoma") are well known its cytologic features are only rarely described and mostly as isolated reports or small series.[12, 24-38] We herein present the cytologic findings in 15 fine needle aspirations (FNAs) defined by the

presence of osteoclastic giant cells, and highlight useful diagnostic cytologic characteristics as well as pertinent clinicopathologic features and associations. To date, this is the largest cytologic series in the English literature.

Materials and Methods

A multi-institutional pathology database search yielded 15 FNAs from 14 patients, including 6 from Emory University's archives and consultation files, 2 each from Thomas Jefferson University, Philadelphia, PA, University of Michigan, Ann Arbor, MI and University of British Columbia, Vancouver, BC and 1 each from Northside Hospital, Atlanta, GA, Mayo Clinic, Rochester, MN, and Cleveland Clinic, Cleveland, OH. Resected pure undifferentiated carcinoma lacking osteoclastic giant cells were excluded from analysis.

All patients had image-guided (endoscopic ultrasound (n=11) or computerized tomography (n=3)) FNAs, with or without on-site evaluation, with 1 – 7 passes per patient (mean 3.9). Cyst fluid analysis and molecular studies were not performed on the specimens. Cytologic material including smears, ThinPrep®, cellblocks and immunocytochemical stains (when available) were reviewed. On average, 7 slides were available per case (range 2 – 19), including both Papanicolaou and Diff Quik. Core biopsies were also available for review in 1 patient (# 14).

Twelve of 14 patients (86%) had follow-up resections and the tumors' clinicopathologic characteristics were documented. Additionally, cytologic samples were analyzed for the presence and frequency (focal (1), moderate (2) or extensive (3)) of four cell types: (1)

osteoclastic giant cells (OGCs), (2) spindled or histiocytoid tumor cells (SHCs), (3) mononuclear pleomorphic tumor giant cells (TGCs), (4) PDAC component. Necrosis and acute inflammation was also documented.

Comparison of Survival Differences between Aspirated UOCs, UOCs with No Prior FNA and Conventional PDAC with Prior FNA

The survival of the FNA'ed UOC patients (n=14) was contrasted with a cohort of unaspirated, resected UOCs in the authors' database (n=27), the detailed analysis of which was already published,[8] as well as a cohort of conventional PDACs that had been subjected to FNA (n=74).

Results

Clinical Characteristics

The 15 specimens were from 14 patients including 6 males and 8 females, ranging in age from 35-77 years (mean, 65.3 years). Seven were in the pancreatic head, 3 the body and 4 in the tail. Clinicopathologic findings are summarized in Table 1.

Radiologic Findings

On imaging tumors ranged in size from 2.0 – 15 cm (mean, 7.3 cm) and were either purely cystic (n=2, one was suspicious for a pseudocyst), purely solid (n=3, with radiologic diagnoses of PDAC in 2 and sarcoma in 1), or mixed cystic and solid masses (n=9). Other radiologic diagnoses included IPMN and cystic pancreatic neuroendocrine tumor (PanNET), among others (Table 1). Interestingly, only one tumor, a 9.0 cm solid pancreatic mass, was called sarcoma on imaging.

Cytologic Findings

Diff Quik, Papanicolaou smears and ThinPrep® slides ranged from moderately cellular (14/15 cases, 93%) to hypocellular (1/15; 7%). There were three distinct types of tumor cells: (1) multinucleated osteoclastic giant cells, (2) large pleomorphic tumor giant cells and (3) smaller spindled or histiocytoid cells (Figure 1 -5). Malignant pleomorphic giant and spindled/histiocytoid cells were in clusters, syncytial groups and singly dispersed, with high nuclear to cytoplasmic ratio and nuclear irregularity (both present in 12/15, 80%) (Figure 1-5). Additionally, variable numbers of multinucleated osteoclast-like giant cells, ranging in size from 50 – 500 microns, were seen in 12/15 (80%) FNAs (Figure 1 - 2). Of the 3 FNAs that lacked all three cell types one represented a 25cm MCN with a 2.0 cm UOC focus that was likely not sampled by FNA, another (case # 15) was almost exclusively PDAC with only scattered small patches of UOC component (of overall estimated size < 0.5 cm) identified only on the resection specimen, and the third case (case # 6) had acellular smears, with rare atypical glandular cells on cellblock but was called “negative” on initial cytologic diagnosis. Mitotic figures were identified in rare tumor nuclei (Figure 3). Background necrotic debris (12/15, 80%) and a neutrophilic inflammatory infiltrate (6/15, 40%) were seen in several (Figure 2).

On Papanicolaou-stained slides (smears and ThinPrep® slides), cellblocks and cores the osteoclastic giant cells were easily identifiable, with multiple (10 or more) centrally clustered oval or raisinoid nuclei, indistinct nucleoli and abundant pale blue- grey or eosinophilic cytoplasm (Figure 1 and 2). The spindled/histiocytoid cells ranged from long, slender and

atypical to round and bland (Figure 1). Pleomorphic tumor cells had large bizarre hyper- to hypochromatic nuclei, and were single-lobed or polylobated, some with mummified features, and macronucleoli (Figure 1 and 3). In all cases, tumor giant cells were the most frequent, followed by spindled or histiocytoid cells then osteoclastic giant cells.

An adenocarcinoma component was notable on smears in 11/15 (73%) cases. These were represented by sheets, clusters or singly dispersed malignant epithelial cells, with or without cytoplasmic mucin vacuoles or overt gland formation (Figure 4). The corresponding resections in these 11 cases also showed a PDAC component.

Cell blocks were available for review in 13/15 (87%) specimens and were very helpful in supporting the diagnosis as they often showed the osteoclastic giant cells (Figure 1 and 2). Single cell necrosis and confluent necrosis were present in 12/15 (80%) cases. A core biopsy had also been performed in case #14 and showed the 3 classical cell types of UOC (Figure 5). Cytologic findings are summarized in Table 2.

The final diagnoses in associated cytopathology reports were UOC (6/15; 40%), poorly differentiated carcinoma (2/15; 13%), “suspicious for neoplasm” (1/15; 7%), “negative for malignant cells”(1/15; 7%) and PDAC (5/15; 33%), one (case #7) arising in a neoplastic mucinous cyst which on FNA showed mucinous epithelium with high-grade atypia and necrosis. Interestingly, on re-review the “negative” case (case # 6) in hindsight would best have been interpreted as “atypical cells present or suspicious for adenocarcinoma” since the cell block

showed a single highly atypical gland, while the smears were mostly acellular.

Immunocytochemical Findings

Immunocytochemical stains were performed in several cases and showed the following pertinent results: CD68 (a histiocytic marker) was diffusely and strongly positive in osteoclastic giant cells (5/5 cases) and focally positive in rare isolated histiocytoid cells. Epithelial markers were frequently positive, albeit focally, in tumor giant cells and spindled or histiocytoid tumor cells; pancytokeratin was positive in 6/7 cases tested and was stronger in tumor giant cells; CAM 5.2 and epithelial membrane antigen (EMA) were focally positive in tumor giant cells and spindled or histiocytoid tumor cells in 2/3 and 2/2 cases respectively; 1 showed a mutant p53 pattern (diffuse, strong positivity) while p53 was negative in 2 cases (Figure 5). INI-1 which has recently been shown to be a marker of a specific subset of undifferentiated carcinoma of pancreas (typically without OGCs),[39] was retained in all 3 tested tumors. Additional pertinent negative stains include S100 in 3/3 cases. Interestingly Ki-67 immunostain was performed in 3 tumors and the proliferation index was 12, 18, and 40% respectively.

Histologic Findings in the 12 Resected Cases

Tumors were located in the pancreatic head (n=6), body (n=2) and tail (n=4) and resections included 6 pancreatoduodenectomies and 6 distal pancreatectomies. Two tumors were not resected. Tumors ranged in size from 0.6 – 13.0 cm (mean, 6.9 cm) and were mostly demarcated and solid, with a cystic component in 11 cases; 3/11 cystic tumors had associated neoplastic mucinous cysts (IPMN with high-grade dysplasia (n=1) and MCN with high grade

dysplasia (n=2)). Of the 12 resections, 4 (33%) were pure UOC and 8 (67%) had admixed PDAC, ranging from focal (10% in 5) to extensive (30-90% in 3) (Figure 1). One unresected tumor was a pure UOC on FNA and core biopsy, while the other was "mixed". The 12 resections had lymph node sampling (15 – 33 lymph nodes) and four patients had lymph node metastasis. One patient (case # 8) had liver metastasis at the time of pancreatectomy. Lymph-vascular and perineural invasion were seen in 5 (42%) and 6 (50%) cases respectively and tumor margins were positive in 1/12 (8%). Regarding pathologic(p) TNM stage (per American Joint Committee on Cancer; Cancer Staging Manual 7th edition),[40] one (8%) was pT1N0MX, four (33%) were pT2N0MX, five (42%) were pT3N0MX, one (8%) was pT3N1MX and one (8%) was pT3N1M1. One unresected tumor was staged as T3N1M1 (case #14) based on markedly enlarged peripancreatic lymph nodes and a large liver mass on imaging.

Follow-up Information

At an overall median follow-up period of 5 months (range 1-27), one patient died of peri-operative complications, 8 were alive (6 with no evidence of disease, and 2 with liver metastasis; median survival, 3 months (range 1-27)), 6 were dead of disease (1 – 21 months), and one was lost to follow up at 3 months (Table 3). Chemotherapy was given to 5 patients (survival 1 – 27 months), 3 of whom were alive at last follow-up, one was dead (survival 10 months) and the fifth was lost to follow-up after chemotherapy. See Table 1 for detailed length of survival of each patient.

Comparison of Survival between Aspirated UOCs, UOCs without Prior FNA and Conventional PDACs with Prior FNA

When the FNA'ed UOC cohort (n=14) was compared to a cohort of UOCs that had not been previously aspirated but was not stage-matched (n=27), there was a statistically significant difference in survival between the two, with the FNA'ed UOCs showing significantly shorter median overall survival (8 months versus 92.4 months, p = 0.0135) than the UOCs that had not been aspirated before resection (Table 3, Figure 6). When the same FNA'ed UOCs (n = 14) were compared to an FNA'ed conventional PDAC cohort (also not stage-matched) (n=74), FNA'ed UOCs continued to trend toward shorter overall survival than the PDAC group (median survival 8 versus 15 months), but this failed to reach statistical significance (p = 0.279). Meanwhile, there was a more striking survival advantage of the non-FNA'ed UOCs (n=27) compared to the 74 FNA'ed PDACs, but this fell short of statistical significance (p=0.058).

Discussion

Unique cytologic features of UOCs include a mixture of large, bland, multinucleated, osteoclastic giant cells as well as highly pleomorphic malignant tumor giant cells and small spindled or histiocytoid tumor cells. These are often present in a background of necrosis and variable neutrophilia, and may be associated with a conventional PDAC component, a frequent finding on FNA of UOCs.[34]

The three classical cell types of UOC are identifiable on FNA in the majority of cases, making cytologic distinction possible if this entity is considered in the differential. This was not just

evident in our cohort but others'.[31, 34, 37, 38] UOC is not only recognizable on FNA but also on brushings of its intraductal counterpart.[12] The osteoclastic giant cells are perhaps easiest to recognize, and once identified, should prompt a search for the other two cell types. Interestingly, although only 40% of cases were correctly called UOC on cytology, review of the original cytology material of the remainder revealed that 60% of cases initially called PDAC, both "poorly differentiated carcinomas" and the "suspicious for neoplasm" case all had the three distinct tumor cell types typical of UOC, particularly osteoclastic giant cells. Thus, 80% of specimens could have been accurately identified as having a UOC component on FNA. Only three cases lacked all three cell types on FNA. One case showed features of a neoplastic mucinous cyst with high-grade atypia and was diagnosed on cytology as "(at least) adenocarcinoma in situ arising in a neoplastic mucinous cyst with high-grade atypia; suspicious for invasion". On resection, this case turned out to be a 25.0 cm MCN with extensive high-grade dysplasia and a 2.0 cm focus of mixed UOC and PDAC, which was unlikely to have been sampled during FNA. Despite generous sampling in one case, only PDAC was identified on FNA, while the corresponding resection showed 90% PDAC and a very limited UOC component.

In mixed cases the UOC component may be focal, emphasizing the importance of careful cytologic examination and histologic sampling. Additionally, for those with an extensive cystic component (whether due to degeneration or concomitant neoplastic mucinous cyst), the UOC component may be overlooked. Tumors may also exhibit extensive fibrosis, hemorrhage and even osteoid formation, which can lead to non-diagnostic samples.

Tumors are known by names such as “osteoclastic giant-cell tumor of pancreas” and “pleomorphic (giant cell) carcinomas of pancreas”. [36,34] Some have suggested differences in behavior based on the amount of osteoclastic giant cells, with less aggressive behavior in tumors more rich in osteoclastic giant cells. It is important to note that all UOCs have similar behavior, despite the quantity of the three distinct cell types, including osteoclastic giant cells.

The significance of a UOC component cannot be overstated as we showed in a recent histologic study of 38 UOCs that (whether pure or combined with PDAC), tumors with a UOC component have a more protracted clinical course with significantly longer 5-year survival than conventional PDAC (59.1 versus 15.7% in poorly differentiated PDACs).[8] This suggests that UOCs should be resected once identified, if patients are good surgical candidates. However, an interesting observation in our limited FNA cohort was the shorter survival of FNA’ed UOCs which was very similar to, if not worse than that of PDACs, while UOCs without an FNA prior to resection had a much better prognosis than both groups. This may be attributable to selection bias where patients with more aggressive UOCs were more likely to have diagnostic procedures perhaps because of symptoms. Additionally, the PDACs and non-FNA’ed UOCs were not stage-matched with our cohort, which may also account for survival differences. Nevertheless, the shorter survival of FNA’ed UOCs relative to our previously studied UOC group raises concern for “whether FNA negatively impacts these tumors’ prognosis”. The FNA procedure is safe for the majority of tumors, including pancreatic ones. In fact, we recently analyzed our PDAC database comparing FNA’ed tail PDACs with those that had not been FNA’ed before resection and found survival to be identical in both groups (unpublished data). But it is possible that some tumors

(pancreatic colloid carcinoma and mixed salivary gland tumors) may spread after manipulation, and may require removal of the needle tract, similar to mixed salivary glands tumors.[41,42] If this observation is ultimately confirmed by other studies, then UOC may prove to be one of those rare tumors with unique biological properties that create vulnerability to iatrogenic spread.

The clinicopathologic characteristics in our cohort are similar to previous reports, in that our patients were predominantly female, of mean age 65 years, [4, 6, 7, 10] with large tumors (mean 6.9 cm), many with a PDAC component and tumoral intraepithelial neoplasms (MCN and IPMN) in 20%.[8, 13] The coexistence of UOC with MCN and IPMN is well documented.[8, 13-15] A cystic component (mostly cystic degeneration) was seen in most UOCs in our cohort. This can cause radiologic misdiagnosis as neoplastic mucinous cyst or pseudocyst, or limit sampling of the tumor's solid component. Knowledge of the association between UOC and neoplastic mucinous cysts is critical in ensuring that resected mucinous cysts are extensively sampled, so as not to miss a UOC component. UOCs may also protrude as polyps into the pancreatic or bile duct, duodenum or ampulla, leading to radiologic misdiagnosis as IPMN, intra-ampullary tubulo-papillary neoplasm or intraductal papillary neoplasm of bile duct.[8, 11, 12]

Immunohistochemistry can be especially helpful in the cyto-histologic diagnosis of UOC as osteoclastic giant cells consistently express the histiocytic marker CD68 and are typically negative for epithelial markers and Ki-67.[8, 9] Additionally, malignant pleomorphic tumor cells and spindled/histiocytoid tumor cells variably express pancytokeratin, CAM5.2 and EMA, which are typically negative in osteoclastic giant cells. Ki67 proliferation index is also high in these

cells. p53 may be expressed by malignant tumor giant cells and spindled or histiocytoid tumor cells but is negative in osteoclastic giant cells.[4, 8] Only one of four UOCs in our cohort showed a mutant p53 staining pattern.

The significance of the presence and amount of PDAC in these tumors has been previously studied, including by our group.[8] In our prior study we found a PDAC component in 75% of cases however it had no effect on overall survival, when PDAC percentages were examined.

Differential Diagnosis

Multinucleated (reactive or neoplastic) giant cells can be seen in benign and malignant processes in the pancreas including chronic pancreatitis, PanNET and solid-pseudopapillary neoplasm (SPN).[35, 43, 44] The highly atypical, hyperchromatic multinucleated giant cells in PanNETs represent neuroendocrine "atypia" of a symplastic nature, a well-known degenerative phenomenon with no clinical significance.[44] Degenerating "cercariform" giant cells have also been described in SPN.[43] In both PanNETs and SPN background tumor cells show the other cytologic characteristics that typify these neoplasms (such as plasmacytoid cells with salt and pepper chromatin in PanNETs and open chromatin and longitudinal nuclear grooves in SPN), facilitating distinction.

A major differential of UOC is undifferentiated PDAC, NOS type. On cytology these tumors are highly pleomorphic with clustered or singly dispersed highly malignant cells with or without cytoplasmic mucin vacuoles but with high nuclear to cytoplasmic ratio, necrosis and brisk

mitotic activity. These tumors however lack osteoclastic giant cells which distinguishes them from UOC. Additionally tumor cells in undifferentiated PDAC are keratin positive and do not express histiocytic markers. Their prognosis however is typically much worse than UOC.

Another "undifferentiated" pancreatic primary, undifferentiated rhabdoid carcinoma with *KRAS* alterations and SMARCB1 (INI-1) loss which was recently described by Agaimy *et al*, is an important differential.[39] This tumor typically shows eosinophilic rhabdoid cells with pleomorphic nuclei and prominent nucleoli that may mimic the pleomorphic tumor giant cells of UOC. However, they either exhibit loss of INI-1 or show *KRAS* mutations, unlike UOC which to date has not been shown to have INI-1 loss. Undifferentiated rhabdoid pancreatic carcinomas do not contain osteoclastic giant cells.[39] We performed INI-1 testing in three UOCs and it was retained in all three.

Malignant melanoma frequently metastasizes to the pancreas and be confused with UOC.[45, 46] Melanoma tumor cells may be spindled or epithelioid and single, with prominent nucleoli that mimic UOC. Additionally, multinucleated tumor giant cells may be confused with the osteoclastic giant cells of UOC. However, melanoma is negative for histiocytic and epithelial markers and positive for melanoma markers S100, melan-A and HMB-45, which would be negative in UOC.

While primary pancreatic sarcoma is uncommon, sarcoma metastasizing to pancreas (including leiomyosarcoma and rhabdomyosarcoma) is a known phenomenon.[45-47] Such tumors are

unlikely to show the bland osteoclastic giant cells of UOC, are typically more cellular and mitotically active than UOC, and are negative or only focally positive for epithelial markers.

Another key differential is chronic pancreatitis with exuberant granulation tissue formation. When one of our cases (case # 3, a consult from an outside institution) was initially reviewed by five experienced pathologists at our intradepartmental conference, it was interpreted as chronic pancreatitis with exuberant granulation tissue formation, because it contained numerous foamy looking histiocytoid cells, giant cells and capillaries. Immunohistochemical stains had been performed by the submitting institution including pancytokeratin, CAM5.2, vascular markers (ERG and CD31), S100, CD45, ALK and CD35 (all of them negative). Despite strong CD68 and CD163 positivity in the osteoclastic giant cells a definitive diagnosis was not reached at the outside institution. EMA was performed at our institution and its positivity in the spindled and histiocytoid cells was helpful in leading to an accurate cytologic diagnosis of UOC. Additionally, ki-67 index was high in malignant cells.

Conclusion

In conclusion, undifferentiated pancreatic carcinoma with osteoclastic giant cells is a rare distinctive malignant pancreatic tumor that is typically large, frequently has a PDAC component and shows three classical cell types (osteoclastic giant cells, pleomorphic tumor giant cells and spindled or histiocytoid tumor cells), which make cytologic diagnosis possible in the majority of cases. Tumors show a strong association with mucinous tumoral intraepithelial neoplasms and have a propensity for cystic degeneration. While UOCs have been recently shown to have a better prognosis than that historically thought, the prognosis in our small cohort was poor,

raising the possibility of selection bias in subjecting more aggressive UOCs to FNA, versus a negative link between FNA and survival. Larger studies are needed to explore this association.

Table 1. Clinicopathologic Characteristics of Undifferentiated Pancreatic Carcinoma with Osteoclastic giant Cells (n=15)

FNA #	Age	Sex	Location	Imaging Modality	Size on Imaging (cm)	Additional Radiologic Findings	Radiologic Diagnosis	Cytologic Diagnosis	Histologic Diagnosis	Size of Invasion (cm)	Follow-up (mths)
1	71	F	Head	MRI	7.2	Clustered cysts w/ septal enhancement; No large solid component	IPMN	Poorly differentiated carcinoma	Mixed UOC and PDAC	3.0	10 mths, LTF/U after chemo
2								Poorly differentiated carcinoma			
3	54	F	Body	N/A	N/A	N/A	N/A	UOC	UOC	2.1	2.2 mths, ALIVE, NED
4	66	F	Tail	MRI	6.8	Solid and cystic mass	PDAC	UOC	Mixed UOC and PDAC	7.1	10.2 mths, DEAD w/ liver mets (PDAC component)
5	51	F	Head	CT	3.4	Cystic mass w/ peripheral nodular components	Cystic NET	Suspicious for neoplasm	Mixed UOC and PDAC	5.4	4.1 mths, Alive, NED, Received radiation
6	75	F	Head	MRI	N/A	Pancreatic neck stricture, severe pancreatic duct dilatation; no measurable mass	Chronic pancreatitis vs Tumor	Negative for malignant cells	Mixed UOC and PDAC	0.6	12.9 mths, DEAD
7	35	F	Tail	MRI	25.0	Complex solid and cystic mass	PDAC	PDAC possibly arising in NMC	Mixed UOC and PDAC, MCN w/ HGD	2.5	27 mths, ALIVE, NED
8	49	F	Tail	MRI	5.6	Cystic and solid mass	Possible cystic NET	PDAC	UOC, PDAC and MCN	1.0	1.2 mths, ALIVE w/ UOC liver mets
9	43	M	Head	CT	6.0	Cystic lesion	Pseudocyst	UOC	UOC	6.5	21.18 mths, DEAD
10	77	F	Head	CT	9.0	Solid mass	Sarcoma	UOC	N/A	N/A	1.7 mths, DEAD
11	65	M	Head	EUS	2.0	Solid mass	PDAC vs lymphoma	PDAC	UOC and PDAC	2.5	6.13 mths, DEAD
12	67	M	Tail	EUS	4.9	Solid and cystic body and tail mass	PDAC	UOC	UOC and IPMN w/ HGD	11.0	3.17 mths, ALIVE
13	59	M	Head	EUS	2.2	Mass in head	PDAC	PDAC	UOC and PDAC	4.1	5.1 mths, DEAD w/ liver mets
14	65	M	Body	MRI	13.0	Solid and cystic mass in body	PDAC	UOC	N/A	N/A	3.15 mths, ALIVE w/ liver mets
15	75	M	Body	EUS	5.4	Solid mass with 1.3 cm cyst	PDAC	PDAC	UOC and PDAC	7.3	22 mths, ALIVE,NED post chemo

FNA, fine needle aspiration; MRI, magnetic resonance imaging; PDAC, pancreatic ductal adenocarcinoma; UOC, undifferentiated pancreatic carcinoma with osteoclastic giant cells; CT, computerized tomography; NET, neuroendocrine tumor; EUS, endoscopic ultrasound; NMC, neoplastic mucinous cyst; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; NED, no evidence of disease; LTF/U, lost to follow-up; Mets, metastasis; Chemo, chemotherapy; N/A, not available.

Table 2. Cytologic Findings in Undifferentiated Pancreatic Carcinoma with Osteoclastic Giant Cells (n=15)

Case #	Cytologic Diagnosis	Osteoclastic Giant Cells	Pleomorphic Giant Cells	Spindled or Histiocytoid Cells	PDAC Component	Neutrophils	Necrosis
1	PDCA	1	3	1	1	2	Yes
2	PDCA	1	3	1	1	2	Yes
3	UOC	2	3	3	0	2	Yes
4	UOC	3	3	3	1	2	Yes
5	Suspicious for neoplasm	2	2	1	2	2	Yes
6	Negative	0	0	0	1	0	No
7	PDAC possibly arising in NMC	0	0	0	1	0	Yes
8	PDAC	1	3	3	1	0	Yes
9	UOC	2	2	1	0	0	No
10	UOC	1	1	3	2	0	No
11	PDAC	2	1	2	3	0	Yes
12	UOC	3	3	3	0	0	Yes
13	PDAC	3	3	2	1	0	Yes
14	UOC	3	3	3	0	0	Yes
15	PDAC	0	0	0	3	0	Yes
TOTAL (n=15)		**12/15 (80%)**	**12/15 (80%)**	**12/15 (80%)**	**11/15 (73%)**	**5/15 (33%)**	**Yes =12/15 (80%)**
Frequency (n=45)		**24/45 (56%)**	**30/45 (67%)**	**26/45 (57%)**	**17/45 (38%)**	**10/45 (22%)**	

0, absent; 1, present focally; 2, moderate amount; 3, extensive; PDCA, poorly differentiated carcinoma; UOC, undifferentiated carcinoma with osteoclastic giant cells, NMC, neoplastic mucinous cyst; PDAC, pancreatic ductal adenocarcinoma.

Table 3. Overall Patient Survival Based on Diagnosis and History of Previous FNA

	UOC with Prior FNA (n=14)	UOC without Prior FNA (n=27)	PDAC with Prior FNA (n=74)	p-value
Median survival (mths)	8	92.4	15.6	0.0578
1-year survival (%)	39.3	87.4	60.7	
3-year survival (%)	-	57.5	31.6	
5-year survival (%)	-	57.5	23	

FNA, fine needle aspiration; UOC, undifferentiated pancreatic carcinoma with osteoclastic giant cells; FNA, fine needle aspiration; PDAC, pancreatic ductal adenocarcinoma.

Legends to Figures

Figure 1: Case # 4. (**A**) Hypercellular smear composed of 3 distinct cell types including a centrally located multinucleated osteoclastic giant cell surrounded by pleomorphic tumor giant cells and spindled and histiocytoid tumor cells (Diff Quik stain, magnification x200). (**B**) Tumor cells in a syncytial cluster including pleomorphic tumor giant cells and spindled cells with a multinucleated osteoclastic giant cell on the right (Papanicolaou stain, magnification x200). (**C**) Tumor giant cells are markedly pleomorphic, with nuclear irregularity and hypochromasia (Papanicolaou stain, magnification x400). (**D**) Corresponding resection in same patient showed a mixed conventional pancreatic ductal adenocarcinoma (upper half) and circumscribed undifferentiated carcinoma with osteoclastic giant cells (lower half) (Hematoxylin and eosin stain, magnification x40).

Figure 2: **Morphologic spectrum of osteoclastic giant cells**: (**A**) Numerous multinucleated giant cells ranging in size from 50-500 μ are present in this example (Papanicolaou stain, magnification x100). (**B**) Osteoclastic giant cells are noted in a background of necrotic debris, neutrophils and rare pleomorphic tumor giant cells (Papanicolaou stain, magnification x200). (**C**) Osteoclastic giant cells have centrally clustered, bland nuclei with fine chromatin (Papanicolaou stain, magnification x400). (**D**) In this example (case # 11) Osteoclastic giant cells were infrequent and best seen on cell block where they had more atypical nuclei with washed out chromatin and large prominent nucleoli admixed with spindled tumor cells (Hematoxylin and eosin stain, magnification x400).

Figure 3: **Morphologic spectrum of pleomorphic tumor giant cells**. (**A**) Numerous singly dispersed epithelioid tumor cells with high nuclear to cytoplasmic ratio, irregular nuclei and numerous abnormal mitotic figures are seen in case # 3 (Diff Quik stain, magnification x200). (**B**) On ThinPrep these pleomorphic tumor giant cells (case # 1) have a high nuclear to cytoplasmic ratio with coarse chromatin and marked nuclear irregularity (Papanicolaou stain, magnification x400).

Figure 4: **Morphologic spectrum of pancreatic ductal adenocarcinoma component**. (**A**) In this example (case # 11) a sheet of malignant ductal cells with nuclear hypochromasia and prominent nucleoli is seen with background pleomorphic tumor giant cells (Papanicolaou stain, magnification x200). (**B**) ThinPrep smear (case # 13) shows cluster of slightly pleomorphic ductal cells with high nuclear to cytoplasmic ratio and mild pleomorphism in a background of necrosis and rare single pleomorphic tumor giant cells (Papanicolaou stain, magnification x200). (**C**) In this example (case # 4) the adenocarcinoma component was more difficult to identify and was present as rare isolated clusters of epithelial cells with prominent cytoplasmic vacuoles containing targetoid mucin droplets (Papanicolaou stain, magnification x400). (**D**) This cell cluster in case # 11 is recognizable as adenocarcinoma because of the central mucin vacuole (Papanicolaou stain, magnification x400).

Figure 5: **Case # 14**: (**A**) Core biopsy shows sheets of pleomorphic tumor giant cells, histiocytoid tumor cells and osteoclastic giant cells (Hematoxylin and eosin stain, magnification x400). (**B**) Osteoclastic giant cells and scattered histiocytoid tumor cells show strong positivity for CD68

(magnification x200). Strong diffuse positivity for p53 (**C**) and Ki-67 (**D**) is seen in pleomorphic and histiocytoid tumor cells but is negative in osteoclastic giant cells (magnification x200).

Figure 6: Kaplan Meier survival curves show that patients with previously aspirated UOCs had a significantly shorter survival than their non-aspirated counterparts (8 vs 92 months; p=0.0135) and a comparable if not worse survival than aspirated conventional PDACs (8 vs 15 months; p=0.2791). This is in contrast to non-aspirated UOCs which have a longer survival (92 vs 15 months; p=0.058) than aspirated PDACs.

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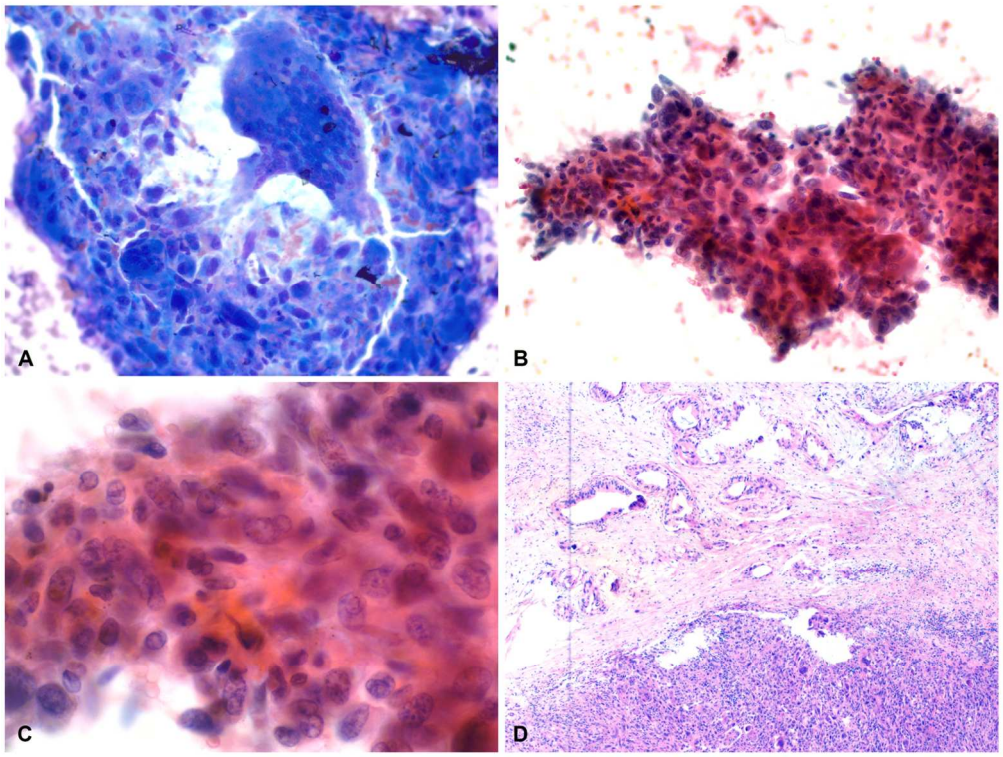

Figure 1: Case # 4. (A) Hypercellular smear composed of 3 distinct cell types including a centrally located multinucleated osteoclastic giant cell surrounded by pleomorphic tumor giant cells and spindled and histiocytoid tumor cells (Diff Quik stain, magnification x200). (B) Tumor cells in a syncytial cluster including pleomorphic tumor giant cells and spindled cells with a multinucleated osteoclastic giant cell on the right (Papanicolaou stain, magnification x200). (C) Tumor giant cells are markedly pleomorphic, with nuclear irregularity and hypochromasia (Papanicolaou stain, magnification x400). (D) Corresponding resection in same patient showed a mixed conventional pancreatic ductal adenocarcinoma (upper half) and circumscribed undifferentiated carcinoma with osteoclastic giant cells (lower half) (Hematoxylin and eosin stain, magnification x40).

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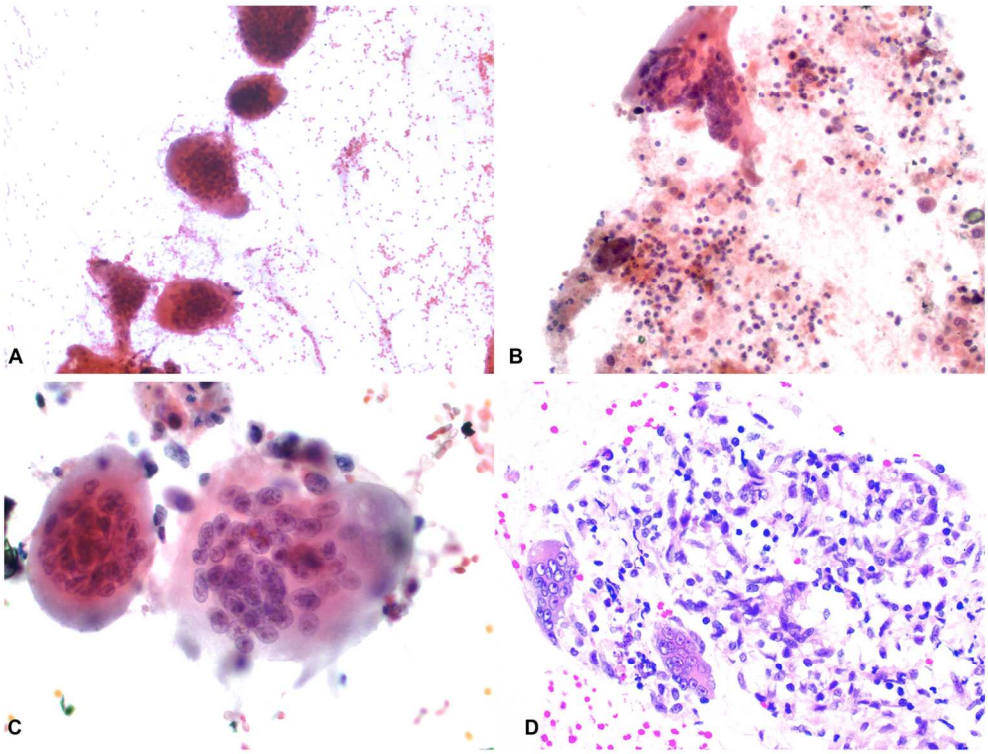

Figure 2: Morphologic spectrum of osteoclastic giant cells: (A) Numerous multinucleated giant cells ranging in size from 50-500 μ are present in this example (Papanicolaou stain, magnification x100). (B) Osteoclastic giant cells are noted in a background of necrotic debris, neutrophils and rare pleomorphic tumor giant cells (Papanicolaou stain, magnification x200). (C) Osteoclastic giant cells have centrally clustered, bland nuclei with fine chromatin (Papanicolaou stain, magnification x400). (D) In this example (case # 11) Osteoclastic giant cells were infrequent and best seen on cell block where they had more atypical nuclei with washed out chromatin and large prominent nucleoli admixed with spindled tumor cells (Hematoxylin and eosin stain, magnification x400).

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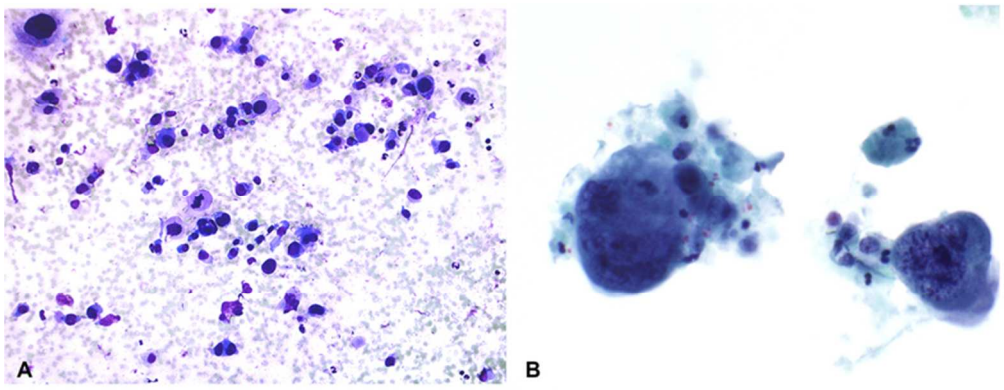

Figure 3: Morphologic spectrum of pleomorphic tumor giant cells. (A) Numerous singly dispersed epithelioid tumor cells with high nuclear to cytoplasmic ratio, irregular nuclei and numerous abnormal mitotic figures are seen in case # 3 (Diff Quik stain, magnification x200). (B) On ThinPrep these pleomorphic tumor giant cells (case # 1) have a high nuclear to cytoplasmic ratio with coarse chromatin and marked nuclear irregularity (Papanicolaou stain, magnification x400).

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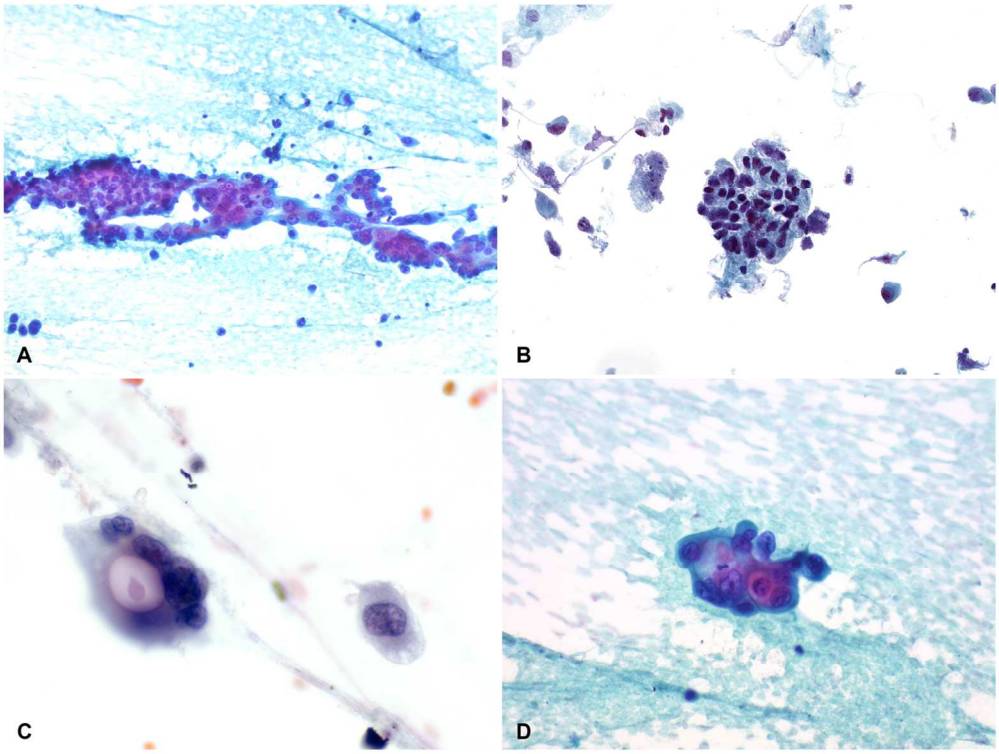

Figure 4: Morphologic spectrum of pancreatic ductal adenocarcinoma component. (A) In this example (case # 11) a sheet of malignant ductal cells with nuclear hypochromasia and prominent nucleoli is seen with background pleomorphic tumor giant cells (Papanicolaou stain, magnification x200). (B) ThinPrep smear (case # 13) shows cluster of slightly pleomorphic ductal cells with high nuclear to cytoplasmic ratio and mild pleomorphism in a background of necrosis and rare single pleomorphic tumor giant cells (Papanicolaou stain, magnification x200). (C) In this example (case # 4) the adenocarcinoma component was more difficult to identify and was present as rare isolated clusters of epithelial cells with prominent cytoplasmic vacuoles containing targetoid mucin droplets (Papanicolaou stain, magnification x400). (D) This cell cluster in case # 11 is recognizable as adenocarcinoma because of the central mucin vacuole (Papanicolaou stain, magnification x400).

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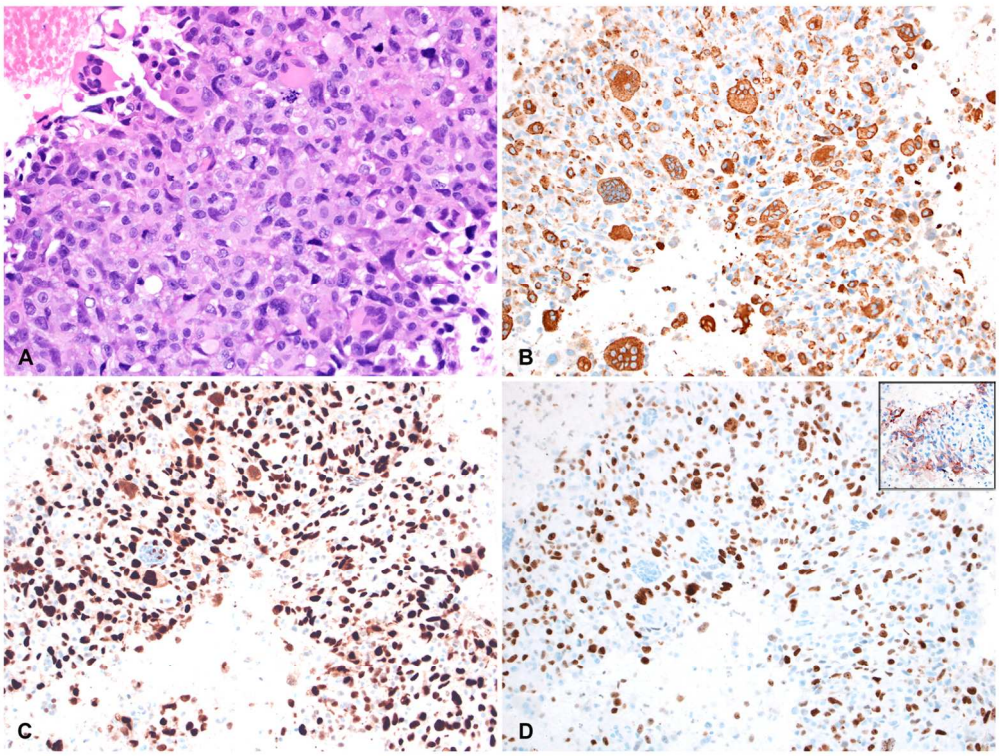

Figure 5: Case # 14: (A) Core biopsy shows sheets of pleomorphic tumor giant cells, histiocytoid tumor cells and osteoclastic giant cells (Hematoxylin and eosin stain, magnification x400). (B) Osteoclastic giant cells and scattered histiocytoid tumor cells show strong positivity for CD68 (magnification x200). Strong diffuse positivity for p53 (C) and Ki-67 (D) is seen in pleomorphic and histiocytoid tumor cells but is negative in osteoclastic giant cells (magnification x200).

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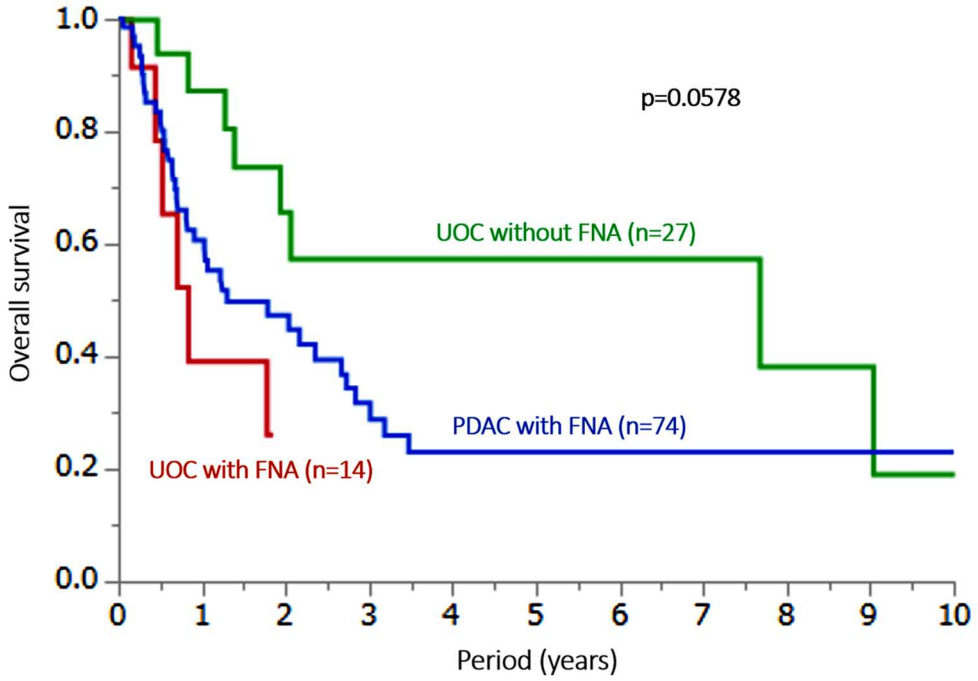

Figure 6: Kaplan Meier survival curves show that patients with previously aspirated UOCs had a significantly shorter survival than their non-aspirated counterparts (8 vs 92 months; p=0.0135) and a comparable if not worse survival than aspirated conventional PDACs (8 vs 15 months; p=0.2791). This is in contrast to non-aspirated UOCs which have a longer survival (92 vs 15 months; p=0.058) than aspirated PDACs.

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Table 1. Clinicopathologic Characteristics of Undifferentiated Pancreatic Carcinoma with Osteoclastic giant Cells (n=15)

FNA #	Age	Sex	Location	Imaging Modality	Size on Imaging (cm)	Additional Radiologic Findings	Radiologic Diagnosis	Cytologic Diagnosis	Histologic Diagnosis	Size of Invasion (cm)	Follow-up (mths)
1	71	F	Head	MRI	7.2	Clustered cysts w/ septal enhancement; No large solid component	IPMN	Poorly differentiated carcinoma	Mixed UOC and PDAC	3.0	10 mths, LTF/U after chemo
2								Poorly differentiated carcinoma			
3	54	F	Body	N/A	N/A	N/A	N/A	UOC	UOC	2.1	2.2 mths, ALIVE, NED
4	66	F	Tail	MRI	6.8	Solid and cystic mass	PDAC	UOC	Mixed UOC and PDAC	7.1	10.2 mths, DEAD w/ liver mets (PDAC component)
5	51	F	Head	CT	3.4	Cystic mass w/ peripheral nodular components	Cystic NET	Suspicious for neoplasm	Mixed UOC and PDAC	5.4	4.1 mths, Alive, NED, Received radiation
6	75	F	Head	MRI	N/A	Pancreatic neck stricture, severe pancreatic duct dilatation; no measurable mass	Chronic pancreatitis vs Tumor	Negative for malignant cells	Mixed UOC and PDAC	0.6	12.9 mths, DEAD
7	35	F	Tail	MRI	25.0	Complex solid and cystic mass	PDAC	PDAC possibly arising in NMC	Mixed UOC and PDAC, MCN w/ HGD	2.5	27 mths, ALIVE, NED
8	49	F	Tail	MRI	5.6	Cystic and solid mass	Possible cystic NET	PDAC	UOC, PDAC and MCN	1.0	1.2 mths, ALIVE w/ UOC liver mets
9	43	M	Head	CT	6.0	Cystic lesion	Pseudocyst	UOC	UOC	6.5	21.18 mths, DEAD
10	77	F	Head	CT	9.0	Solid mass	Sarcoma	UOC	N/A	N/A	1.7 mths, DEAD
11	65	M	Head	EUS	2.0	Solid mass	PDAC vs lymphoma	PDAC	UOC and PDAC	2.5	6.13 mths, DEAD
12	67	M	Tail	EUS	4.9	Solid and cystic body and tail mass	PDAC	UOC	UOC and IPMN w/ HGD	11.0	3.17 mths, ALIVE
13	59	M	Head	EUS	2.2	Mass in head	PDAC	PDAC	UOC and PDAC	4.1	5.1 mths, DEAD w/ liver mets
14	65	M	Body	MRI	13.0	Solid and cystic mass in body	PDAC	UOC	N/A	N/A	3.15 mths, ALIVE w/ liver mets
15	75	M	Body	EUS	5.4	Solid mass with 1.3 cm cyst	PDAC	PDAC	UOC and PDAC	7.3	22 mths, ALIVE,NED post chemo

FNA, fine needle aspiration; MRI, magnetic resonance imaging; PDAC, pancreatic ductal adenocarcinoma; UOC, undifferentiated pancreatic carcinoma with osteoclastic giant cells; CT, computerized tomography; NET, neuroendocrine tumor; EUS, endoscopic ultrasound; NMC, neoplastic mucinous cyst; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; NED, no evidence of disease; LTF/U, lost to follow-up; Mets, metastasis; Chemo, chemotherapy; N/A, not available.

Table 2. Cytologic Findings in Undifferentiated Pancreatic Carcinoma with Osteoclastic Giant Cells (n=15)

Case #	Cytologic Diagnosis	Osteoclastic Giant Cells	Pleomorphic Giant Cells	Spindled or Histiocytoid Cells	PDAC Component	Neutrophils	Necrosis
1	PDCA	1	3	1	1	2	Yes
2	PDCA	1	3	1	1	2	Yes
3	UOC	2	3	3	0	2	Yes
4	UOC	3	3	3	1	2	Yes
5	Suspicious for neoplasm	2	2	1	2	2	Yes
6	Negative	0	0	0	1	0	No
7	PDAC possibly arising in NMC	0	0	0	1	0	Yes
8	PDAC	1	3	3	1	0	Yes
9	UOC	2	2	1	0	0	No
10	UOC	1	1	3	2	0	No
11	PDAC	2	1	2	3	0	Yes
12	UOC	3	3	3	0	0	Yes
13	PDAC	3	3	2	1	0	Yes
14	UOC	3	3	3	0	0	Yes
15	PDAC	0	0	0	3	0	Yes
TOTAL (n=15)		**12/15 (80%)**	**12/15 (80%)**	**12/15 (80%)**	**11/15 (73%)**	**5/15 (33%)**	**Yes =12/15 (80%)**
Frequency (n=45)		**24/45 (56%)**	**30/45 (67%)**	**26/45 (57%)**	**17/45 (38%)**	**10/45 (22%)**	

0, absent; 1, present focally; 2, moderate amount; 3, extensive; PDCA, poorly differentiated carcinoma; UOC, undifferentiated carcinoma with osteoclastic giant cells, NMC, neoplastic mucinous cyst; PDAC, pancreatic ductal adenocarcinoma.

Table 3. Overall Patient Survival Based on Diagnosis and History of Previous FNA

	UOC with Prior FNA (n=14)	UOC without Prior FNA (n=27)	PDAC with Prior FNA (n=74)	p-value
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