Undifferentiated Pancreatic Carcinoma With Osteoclast-Like Giant Cells: What Do We Know So Far?

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Undifferentiated carcinoma of the pancreas is an aggressive but rare tumor for which several other terms have been used to describe its histological appearance: anaplastic carcinoma, pleomorphic carcinoma, pleomorphic large cell carcinoma, pleomorphic giant cell carcinoma, spindle cell carcinoma, sarcomatoid carcinoma and carcinosarcoma. In the current WHO Classification, all these terms are lumped together into one single category designated as undifferentiated carcinoma of the pancreas despite their histological differences (1). In addition, as osteoclast-like giant cells may accompany undifferentiated carcinoma of the pancreas, the WHO Classification distinguishes undifferentiated carcinoma with osteoclast-like giant cells (UC-OGC) from plain undifferentiated carcinoma since there are a few histopathological and clinical differences. UC-OGC was initially thought to be associated with worse prognosis compared to invasive ductal pancreatic adenocarcinoma, since it is often unresectable at diagnosis and tends to recur rapidly even if completely resected. When true UC-OGGs are carefully dissected out from other anaplastic carcinomas, it becomes, however, clear that UC-OGCs do have more indolent behavior, especially the pure UC-OGCs. This mini-review summarizes the current knowledge on UC-OGC.

Keywords: undifferentiated (anaplastic) carcinoma, pancreas, osteoclast-like giant cells, pancreatic ductal adenocarcinoma, adenocarcinoma

INTRODUCTION

Undifferentiated carcinoma of the pancreas is an aggressive but rare tumor for which several other terms have been used to describe its histological appearance: anaplastic carcinoma, pleomorphic carcinoma, pleomorphic large cell carcinoma, pleomorphic giant cell carcinoma, spindle cell carcinoma, sarcomatoid carcinoma and carcinosarcoma. In the current WHO Classification, all these terms are lumped together into one single category designated as undifferentiated carcinoma of the pancreas despite their histological differences (1). In addition, as osteoclast-like giant cells may accompany undifferentiated carcinoma of the pancreas, the WHO Classification distinguishes undifferentiated carcinoma with osteoclast-like giant cells (UC-OGCs) from plain undifferentiated carcinoma since there are a few histopathological and clinical differences.
Undifferentiated carcinoma of the pancreas is a rare tumor (2) and UC-OGC is a very rare tumor accounting for less than 1% of all pancreatic malignancies (3, 4). Sommers and Meissner published a first description of this tumor in 1954 (5) as an “unusual carcinoma of the pancreas”; in 1968, Juan Rosai published two cases and notified that they simulated giant cell tumors of bone (6). UC-OGC was initially thought to show worse prognosis than that of invasive ductal adenocarcinoma of the pancreas (7–9), because it is frequently found to be unresectable at diagnosis due to advanced stages (10) and tends to recur early even after complete surgical resection (11, 12). Correspondingly, median or average survival of patients with UC-OGC has been reported less than 1 year with few exceptions (9, 13–15). Another series reveals, however, a significantly better prognosis (5-year survival >50%) than conventional ductal adenocarcinoma (16). When true UC-OGGs are carefully dissected out from other anaplastic carcinomas, it becomes indeed clear that UC-OGCs do have more indolent behavior (4, 17, 18), especially the pure UC-OGCs (19).

Literature on UC-OGC is relatively scarce and largely based on case reports. In this review we mainly focus on the histological and molecular aspects of UC-OGC.

HISTOPATHOLOGICAL FEATURES

Tumors with osteoclast-like giant cells have been reported within a variety of organs including the skin (20), breast (21), thyroid gland (22), heart (23), lung (24), and uterus (25). Within the pancreas they are usually greater than conventional pancreatic ductal adenocarcinoma with a size reaching more than 5 cm in 80% of UC-OGC at the time of diagnosis and with more than 10 cm in 50% of UC-OGC (14). UC-OGC can present an intraductal growth leading to the formation of a polypoid mass in the periampullary area, causing occlusion of the orifice of the common bile duct with jaundice and jaundice-associated symptoms (4, 16).

According to the 5th edition of WHO classification, UC-OGC contains three cell types: osteoclast-like multinucleated giant cells that are non-neoplastic, mononuclear histiocytes, and neoplastic mononuclear cells (1). The former usually contain >20 uniform and small nuclei, and are often found in areas adjacent to hemorrhage or necrosis (1). Osteochondroid differentiation, osteoid and bone formation can be observed (19, 26, 27). Immunohistochemically, most of the neoplastic mononuclear cells express vimentin, some express keratin, and some label with antibodies to p53. On the other hand, osteoclast-like giant cells and a subset of the mononuclear histiocytic cells, express CD68, vimentin and leukocyte common antigen, but are negative for keratin and do not label with antibodies to p53 (8, 27–29) (Figure 1). The mononuclear histiocytic cells strongly and diffusely express the tumor-associated macrophages (TAM) 2 marker CD163 (30).

UC-OGC can be pure or associated with another pancreatic neoplasm like intraductal papillary mucinous neoplasm, pancreatic mucinous cystic neoplasm, adenosquamous carcinoma, cystadenocarcinoma, and conventional ductal adenocarcinoma (12, 31–38).

![Figure 1](image-url) | Microscopy of UC-OGC. (A) At low magnification, UC-OGC presenting an intraductal growth (black arrows) with few hemorrhagic foci (asterisks); intraductal part extending to small duct distant to the main lesion (red arrow). (B) UC-OGC can also present a periductal growth (black arrows); overlying epithelium exhibiting high-grade dysplasia. (C) UC-OGC is composed of non-neoplastic multinucleated osteoclastic-like giant cells admixed with neoplastic pleiomorphic mononuclear cells.
MOLECULAR ASPECTS

Using whole exome sequencing of eight UC-OGCs, a recent study demonstrated that genetic alterations observed in UC-OGC are closely similar to those identified in carcinogenesis of pancreatic ductal adenocarcinoma and include activating mutations in the oncogene KRAS and inactivating mutations in the tumor suppressor genes CDKN2A, TP53 and SMAD4 (19). This finding supports current WHO classification as variant of pancreatic ductal adenocarcinoma (1, 28). The study also revealed mutations in SERPINA3 in two cases; the presence of non-synonymous missense mutations at the same amino residue suggests an oncogene (19). SERPINA3 encodes alpha 1-antichymotrypsin, the most abundant component of a family of serine protease inhibitors (also known as serpins) (39). Interestingly, high SERPINA3 expression is strongly associated with worse overall and disease specific survival at 5 years in melanoma patients (40). Moreover, the protein promotes endometrial cancer cell growth (41) and SERPINA3 expression shows a rising trend in low, intermediate, and high metastatic potential colon cancer cells (42).

The detection of GLI3 mutations in two cases suggests that GLI3 is also a driver of UC-OGC (19). The transcription factor GLI3 is a member of the Hedgehog (Hh/HH) signaling pathway and regulates various biological processes that are important for cancer cell growth and progression (43). Mutations in TTN, MAGEB4, and MEGF8 have also been detected. Since these mutations all are non-synonymous missense mutations that are not clustered in any specific hotspot, the functional importance of them is, however, difficult to interpret (19).

The multinucleated histiocytic giant cells are considered as non-neoplastic because microdissected histiocytic giant cells positive for CD68 didn’t harbor KRAS mutations while highly neoplastic pleomorphic mononuclear cells negative for CD68 did, bearing the hypothesis of common ductal lineage (44). However, some authors detected KRAS mutations in histiocytic giant cells suggesting the ability of these cells to phagocytize tumoral cells (29).

With regard to carcinogenesis of pancreatic ductal adenocarcinoma, well-known molecular alterations occur like telomere shortening, activating mutations in KRAS, inactivating mutations or epigenetic silencing of p16/CDKN2A and inactivating mutations in TP53 and SMAD4 leading to invasive ductal adenocarcinoma (45). As mentioned above, UC-OGC shares with pancreatic ductal adenocarcinoma the same genetic background and derives from ductal tumoral clones; however, molecular events determining the pleomorphic phenotype of tumoral cells forming UC-OGC are currently unknown. Some authors suggest that such pleomorphic phenotype similar to a mesenchymal phenotype is the result of epithelial-to-mesenchymal transition (EMT): Yonemasu et al. report a loss of E-cadherin in seven undifferentiated carcinomas (46), Sano et al. demonstrate a deregulation of the β-catenin pathway in anaplastic carcinoma (47) and, more recently, Naito et al. highlight that these cells are negative for E-cadherin and strongly positive for vimentin and ZEB1 (48) which is a pivotal element of the EMT process (49). A recent report described, however, that EMT activation is more frequent in undifferentiated carcinoma than in UC-OGC (50). Evidence of EMT activation was found in 50% of UC-OGC cases, and the frequency was higher in UC-OGC with an associated pancreatic ductal adenocarcinoma. The most strongly and frequently expressed marker in both tumor types was Snail2; this was also the most important in determining the observed differences between UC-OGC and plain undifferentiated carcinoma (50). EMT activation in UC-OGC seemed more frequent after neoadjuvant chemotherapy (50); another recent report described frequent expression of EMT-related markers in neoadjuvant-treated pancreatic ductal adenocarcinoma (51).

The pleomorphic tumoral cells can produce granulocyte colony-stimulating factor (G-CSF) allowing recruitment of non-neoplastic OGCs (52), and high serum level of G-CSF was found in a patient with anaplastic carcinoma (53).

Figure 2 summarizes the potential pathways leading to pancreatic ductal adenocarcinoma, anaplastic carcinoma, carcinosarcoma, pure UC-OGC and mixed UC-OGC.

DIAGNOSIS

Pancreatic ductal adenocarcinoma has been well described in terms of computed tomography (CT) and magnetic resonance imaging (MRI) characteristics. The CT and MRI characteristics of undifferentiated carcinoma of the pancreas are, however, not well known. On imaging work-up, UC-OGC appears larger than pancreatic ductal adenocarcinoma and generally displays a cystic component (14). Bile duct dilatation, pancreatic duct dilatation and necrotic areas are common findings (54, 55). Calcification (56), hemorrhage (56, 57), and venous tumor thrombus (57) have also been described. At abdominal MRI UC-OGC usually presents a low to dark signal intensity on T1- and T2-weighted images. This low-intensity appearance likely results from hemosiderin deposits in the abundant histiocytic cells of the tumor. Relatively high signal intensity in the central area may reflect the necrotic part of the tumor. Recognition that UC-OGC has a well-defined hypovascular appearance with a decreased signal on MRI may be helpful in differentiating it from other pancreatic solid lesions (54, 58). Larger studies should, however, reveal to which extent these findings are characteristic of UC-OGC.

Elevated serum levels of CEA and CA19.9 are less commonly observed than in pancreatic ductal adenocarcinoma (14). Endoscopic ultrasonography with fine-needle aspiration or biopsy provides cytological or histological material and allows immunohistochemistry (59–61). Components of UC-OGC can be identified on cytologic material. Giant cells can, however, also be detected in case of pancreatitis, representing an important differential diagnosis with UC-OGC, especially at cytology (61).

PROGNOSIS AND TREATMENT

The survival of UC-OGC varies from 4 months to 10 years (27). Shiozawa et al. who summarized the prognosis of cases published
until 1997, observed only two long-term survivors in a group of 32 patients (62), while Strobel et al. reported that 80% of the patients who underwent curative surgery survived for at least 2 years (63). In a more recent meta-analysis, the authors highlight that older age, male gender, small tumor, lymph node metastases, and a concomitant component of pancreatic ductal carcinoma are characteristics associated with short-term survival (64). Discordant prognosis data in the literature is probably due to the use of wrong terminology, as mentioned before.

Luchini et al. demonstrated that the most important criterion for prognosis is the presence of an associated pancreatic ductal adenocarcinoma; they showed that median overall survival for pure UC-OGC was 36 months, compared with 15 months for UC-OGC with associated pancreatic ductal adenocarcinoma (19). This study underlines the importance of extensive sampling for histopathological examination.

Due to the rarity of UC-OGC, treatment options have never been standardized. Surgery is the first-choice treatment. The efficacy of radio- and/or chemotherapy in UC-OGC remains to be evaluated (14); since UC-OGC is considered a variant of ductal adenocarcinoma of the pancreas, standard chemotherapeutic regimens can, however, be used. FOLFIRINOX is currently preferred to gemcitabine since this results in better overall survival (65). Since patients with undifferentiated carcinoma are often in poor condition, paclitaxel-containing regimens can, however, be considered a reasonable choice; this would offer relatively long survival, as has been shown in a recent retrospective multicenter cohort study (66).

PD-1 or PD-L1 monoclonal antibody therapy has demonstrated promising therapeutic effects in clinical studies of several cancer types. This therapy has been successful in multiple prospective randomized clinical trials on non-small cell lung cancer, renal cell carcinoma, melanoma, Hodgkin lymphoma, breast carcinoma, head and neck squamous cell carcinoma and a subset of urothelial carcinoma (67–72). It has been demonstrated that PD-L1 is expressed in neoplastic cells of about 60–80% of UC-OGC cases, and particularly in cases with an associated pancreatic ductal adenocarcinoma. Expression of PD-L1 is associated with poor

![FIGURE 2](https://example.com/figure2.png) Schematic representation of pancreatic carcinogenesis. (A) Telomere shortening and KRAS, p53, CDKN2A and SMAD4 mutations lead to development of preneoplastic lesions like Panin. (B, C, D) Invasive tumoral cells of ductal origin break through the basal membrane and invade surrounding tissue; such tumoral cells (positive for keratins and negative for vimentin and CD68) will form pancreatic ductal carcinoma. (E) After EMT process (loss of E-cadherin and gain of vimentin and ZEB1), tumoral cells of ductal origin will develop a mesenchymal/pliomial phenotype; such tumoral cells are associated with anaplastic carcinoma and, if a classical pancreatic ductal adenocarcinoma is present, with a carcinosarcoma. (F) Mesenchymal/pliomial tumoral cells produce G-CSF recruiting multinucleated non-neoplastic OGCs; admixed pleiomorphic tumoral cells with multinucleated non-neoplastic OGCs form pure UC-OGC or, if a classical pancreatic ductal adenocarcinoma component is present, form a mixed UC-OGC. Panin, pancreatic intraepithelial neoplasia; UC-OGC, undifferentiated carcinoma with osteoclast-like giant cells; EMT, epithelial-to-mesenchymal transition; K, keratin; V, vimentin.
prognosis (30, 73, 74). The possible mechanism underlying the aggressive behavior of PD-L1 positive UC-OGC might be the inhibition of anti-tumor immunity by PD-L1, allowing neoplastic cells to escape the cytotoxic activity of T-lymphocytes (73). This hypothesis is supported by the fact that UC-OGC contains numerous inflammatory cells (1); UC-OGC contains significantly more CD3+ and CD8+ tumor-infiltrating lymphocytes/mm² than conventional pancreatic ductal adenocarcinoma (73). These insights might have potential impact for therapeutic strategies and suggest a strong need for a clinical trial of immune checkpoint immunotherapy in patients with advanced PD-L1 positive UC-OGC. Such immunotherapy may also exert antitumor effects on distant metastases of UC-OGC, as recently shown (75).

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

The identification of UC-OGC is important since this tumor has a better prognosis than conventional pancreatic ductal adenocarcinoma and than undifferentiated carcinoma without giant cells. This especially holds true for pure UC-OGC, i.e. UC-OGC without associated ductal adenocarcinoma. The improved survival of patients with pure UC-OGC might suggest that the unique morphology is a result of the immune response to an otherwise classical ductal pancreatic adenocarcinoma: elimination of the pancreatic ductal adenocarcinoma component by a strong immune response could result in improved prognosis (19). Proof for this hypothesis is, however, lacking.

Recent studies have given important new insights into the clinical and molecular features of UC-OGC. Available data suggest that UC-OGC shares genetical similarities with conventional ductal adenocarcinoma, but is clinically distinct from it. Future studies should compare molecular alterations in UC-OGC and associated pancreatic ductal adenocarcinomas from the same patient to further define what is unique or typical for UC-OGC. The histopathological and clinical characteristics of this tumor type are, however, unlikely to be due to specific genetic alterations but are probably the result of gene expression or other molecular processes not related to somatic mutations (19).

Currently surgery is the first-choice treatment whereas the efficacy of radio- and/or chemotherapy remains to be evaluated. Since expression of PD-L1 is associated with poor prognosis, a clinical trial with immune checkpoint immunotherapy seems warranted. Moreover, since the neoplastic cells and osteoclast-like giant cells are surrounded by CD163+ TAM2 that promote survival and proliferation of neoplastic cells (30), UC-OGC may be investigated as a model for testing therapies that block or “re-educate” that macrophage population (76, 77). Whole exome sequencing might further provide potential treatment strategies for UC-OGC. Since high-quality data on this tumor type are rare, an international registry of UC-OGC would be ideal to study its pathogenesis and treatment regimen.

AUTHOR CONTRIBUTIONS

PD and LV contributed equally to this work, generated the figures, and wrote the manuscript. RM, FP, MD, SD, FC, MG, and JLVL contributed to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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