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DOI: 10.17235/reed.2021.8135/2021
Link: PubMed (Epub ahead of print)

Please cite this article as:
Shao Huijiang , Lu Baochun , Sun Xuezheng , Liu Fang. Clinical and pathological features of undifferentiated pancreatic carcinoma with osteoclastic giant cells: a rare case. Rev Esp Enferm Dig 2021. doi: 10.17235/reed.2021.8135/2021.

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OR 8135

Clinical and pathological features of undifferentiated pancreatic carcinoma with osteoclastic giant cells: a rare case

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Received: 07/06/2021

Accepted: 13/10/2021

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Conflict of interest: the authors declare no conflict of interest.

Authors' contributions: S.H.J wrote the manuscript; L.F revised the manuscript; L.B.C did the data analysis; S.X.Z did the data collection. All authors have read and approved the case.

Funding: this work was sponsored by the Science and Technology Planning Project of Shaoxing (no. 2018C30091)

Data sharing statement: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ABSTRACT

Introduction: undifferentiated pancreatic carcinoma with osteoclastic giant cells (UOC) is a rare pancreatic malignancy composed of three unique cell types. Currently, the histopathologic origin of UOCs remains unclear. Some studies considered that it was differentiated from epithelial tissues, while others favored a

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mesenchymal derivation.

Methods: we present the case of a 59-year-old UOC patient with a tumor (3.0 cm × 3.0 cm × 2.5 cm) in the pancreatic neck. He underwent an *en bloc* resection of the distal pancreas associated with the spleen.

Results: light microscopic examination revealed two typical types of UOC cells, with one type absent. The immunohistochemical staining was positive for pancytokeratin, epithelial membrane antigen, vimentin and cluster of differentiation 68, which indicated different derivations for these two kinds of cells.

Discussion: UOC is a rare condition with unique imaging and pathological features. Endoscopic ultrasonography and fine needle aspiration are dispensable preoperatively. Radical resection should be tried for UOC treatments. In our opinion, osteoclastic giant cells are reactive cells derived from histocytes. The case presented here will be of interest to the whole UOC cohort.

Keywords: Undifferentiated pancreatic carcinoma. Osteoclastic giant cells. Spindle cells.

INTRODUCTION

Undifferentiated pancreatic carcinoma with osteoclastic giant cells (UOC) is a rare pancreatic exocrine malignancy with an incidence of less than 1 % among patients with pancreatic tumors (1). Such a unique pancreatic carcinoma was first described by Sommers and Meissner in 1954 (2). There was no uniform nomenclature for this clinicopathological pattern until 2010 by the World Health Organization (WHO) (3). Generally, UOC is classified as a subtype or a variant of pancreatic ductal adenocarcinoma (PDAC). Nevertheless, there are still some disputes about its histogenesis. Most researchers consider it as an epithelial-derived tumor with mesenchymal differentiation (4,5), while others favor a mesenchymal origin (6).

It has been well acknowledged that UOC consists of three main cellular types, including osteoclastic giant cells (OGCs), pleomorphic mononuclear tumor giant cells (PGCs) and mononuclear tumor cells predominantly seen as spindle cells. In most cases, these cells could coexist with adenocarcinoma cells (7). The rarity of UOCs is

notable compared with the higher morbidity of PDAC, and there are no standards or unified guidelines for their diagnosis and treatment. In our study, we report an UOC patient with no PGCs throughout the specimen, which may serve as an interesting example for the whole cohort. In addition, we discuss the pathological origin of UOCs.

PATIENT AND METHODS

A 59-year-old male presented to our hospital due to epigastric pain for ten days. Physical examination revealed mild tenderness in the middle upper quadrant of the abdomen, with no rebound tenderness or palpable mass. He denied a history of smoking, alcohol abuse and pancreatitis. Laboratory investigations including routine blood tests, biochemical analysis, serum amylase and tumor markers were normal. The concentrations of carcinoembryonic antigen (CEA), CA199 and CA125 were 1.48 ng/ml (normal range: 0-5 ng/ml), 27.11 U/ml (normal range: 0-37 U/ml), and 18.3 U/ml (normal range: 0-35 U/ml), respectively. A computed tomography (CT) scan indicated a complex mass (3.0 cm × 3.0 cm) with hypodense areas in the center located in the pancreatic neck. There was mild dilation of the distal pancreatic duct. Furthermore, no enlarged lymph node and no vessel invasion were observed (Fig. 1A and B). Endoscopic ultrasonography (EUS) and fine needle aspiration (EUS-FNA) were performed of three passes without onsite evaluation. EUS confirmed a poorly-circumscribed lesion (2.5 cm × 3.0 cm) with hypoechoic areas in the center, which occupied the pancreatic neck (Fig. 1C). In addition, high-grade atypical cells were found in the FNA cytologic materials including smears, ThinPrep and cell blocks. Nevertheless, histopathologic diagnosis could not be given due to insufficiency of inspected tissues.

Fifty days after admission, the patient underwent an *en bloc* resection of the distal pancreas associated with the spleen. After surgery, a gray solid mass (3.0 cm × 3.0 cm × 2.5 cm) was observed to invade the pancreatic capsule. All the lymph nodes inspected were negative, and no adjacent vessels or organs were invaded by cancer tissues. For the hematoxylin-eosin (HE) staining, the samples were fixed using 4 % formalin and embedded in paraffin. HE staining based on sections (4 μm) indicated

polynuclear osteoclastic giant cells scattered within the background of spindle cells, combined with hemorrhage and erythrocyte infiltration in cell stroma (Fig. 2A). There was a transitional zone between UOC and PDAC cells (Fig. 2B). No pleomorphic mononuclear tumor giant cells were identified in this case. The Envision method was used for the immunohistochemical staining. The sections (4 μm) embedded in paraffin were incubated at 62 °C for 12 hours, followed by antigen recovery. Upon washing three times with PBS, the primary antibodies including pancytokeratin (CKpan), epithelial membrane antigen (EMA), vimentin, cluster of differentiation 68 (CD68) and Ki-67 (Dako) were added and incubated at room temperature for two hours. Then the second antibodies plus DAB chromogenic reagent (Dako) were used. The results were positive for CKpan, EMA and vimentin in spindle cells (Fig. 3A and C), together with CD68 in OGCs (Fig. 3D). The Ki-67 proliferation index was about 30 % (Fig. 3E). Taken together, this patient was diagnosed with undifferentiated pancreatic carcinoma with OGCs.

After surgery, the patient presented a grade A pancreatic fistula (biochemical leakage) and thrombocythemia. These symptoms did not persist after an intravenous injection of somatostatin (3 mg/day) for seven days and oral administration of aspirin enteric-coated tablets (100 mg/day) for ten days. Finally, he was discharged on day 15 after surgery. For personal reasons, the patient received no adjuvant treatments (e.g., chemotherapy or radiotherapy) and was lost during the follow-up.

DISCUSSION

UOC, a rare malignancy with an incidence of less than 1 % among pancreatic tumors (1), usually affects the elder population with no gender or regional disparities (8). According to the previous literature (9), the risk factors of UOC may be different from PDAC. In line with the previous study, there was no strong correlation between UOC and smoking or alcohol abuse in this case. Patients with UOC usually have a dismal prognosis with a mean survival of 12 months (3). For the cases not suitable for surgery, the median survival time is only 6.5 months (10). In addition, patients with tumors containing OGCs show a higher five-year survival rate than those with conventional PDAC cells (7). It is still a challenge to carry out the prospective studies

as it has a low morbidity.

The clinical symptoms of UOCs are usually non-specific and are mainly associated with the tumor size and location. The symptoms include jaundice with the mass involving the pancreatic head and penetrating the biliary duct system, abdominal pain in cases of a large mass invading the celiac plexus, as well as other tumor-related symptoms (e.g., anorexia, fatigue and loss of weight) (5,9,11). In a previous study, Rustagi et al. reported a UOC case with recurrent pancreatitis and persistent hyperamylasemia (8). For most UOC cases, there might be a moderate elevation in serum CEA and CA199 compared with the counterparts with PDAC, and some cases may maintain normal level. UOCs are usually manifested as a hypoecho or heterogeneous echotexture in ultrasound images (9), which present a hypodense or complex area in the CT scan that could be typically enhanced during the arterial phase (12). The dilation of distal pancreatic duct can also be detected upon invasion of the Wirsung duct by the mass. Many UOC patients, including our case, rarely showed lymphatic metastasis and vessel invasion regardless of tumor size, which were considered to be the typical imaging findings of PDAC (9). In clinical settings, EUS-FNA can offer cytologic assistance for preoperative diagnosis (5), but the histologic supports are limited due to the restriction to the aspirated cell blocks. In this case, FNA tissues were obtained, but the results were similar to those from smears and ThinPrep, except for some extra immunohistochemical results (e.g., CKpan+, EMA+, LCA-, and CD68-). Furthermore, preoperative FNA may increase the probability of postoperative complications and decrease the long-term survival in UOC patients (5). Therefore, we propose that preoperative FNA was dispensable in the presence of definite surgical indications for UOCs.

Generally, *en bloc* resection is considered as the first-line treatment option for UOC (13,14). The surgical modes usually refer to the guideline of PDAC in clinical practice. Although UOCs mostly present a large size and may involve adjacent organs, radical resections should be tried provided that tumors show an expansive growth and the existence of pseudo-capsules after CT scans (15). Currently, three-dimensional imaging system for tumors may be a good complementary evaluation for UOCs preoperatively. The effects of adjuvant therapy were not clear as there were only a

few isolated reports. Conventional gemcitabine-based chemotherapy regimens may be used for some patients referring to epithelial traits of UOCs and the combined component of PDAC cells (16). Radiotherapy is also recommended for treating UOCs as the giant cell tumors presented radio-sensitivity in bone (17) with some unresectable patients obtaining a relatively favorable prognosis (15).

Grossly, UOC tumors mostly involve the distal pancreas (13), presenting solid or solid-cystic well-circumscribed masses with a mean size of 9 cm (2-25 cm) (5,6). However, in our study, the tumor was poorly-circumscribed with a moderate size, which may be related to the high proportion of PDAC component and early diagnosis. There were three main types of tumor cells in UOCs including OGCs, PGCs and mononuclear tumor cells, which coexisted with PDAC cells in 75 % of patients (5). However, there were no PGCs in this case. The mononuclear tumor cells usually exhibited pleomorphism, such as mononuclear spindle cells or histiocytoid tumor cells (5) and they constituted the background within which OGCs and PGCs were diffused. Spindle cells can form pseudo-angiomatoid structures containing erythrocytes and OGCs can be seen in the peripheral region (Fig. 2C). The immunohistochemical results varied in different cases. In our study, CKpan and EMA in spindle cells were positive, which indicated the epithelial origin. Meanwhile, vimentin was also positive in the same cells indicating the mesenchymal origin. CD68 is positive in OGCs only, and the number of OGCs is very limited in our case. All these suggested that OGCs may derive from histocytes instead of tumor cells, which play a reactive role in tumorigenesis. P53 was negative in all cells.

To date, the histogenesis of UOCs is still not well defined. Most studies favored the epithelial origin based on the *K-ras* gene mutation identified in PDAC (18,19). On this basis, UOC is classified as a rare subtype of PDAC by the WHO (4). Nevertheless, some studies considered that UOCs were derived from mesenchymal tissues (6), after taking the mesenchymal immunohistochemical markers (e.g., vimentin+) and the similarities to bone giant cell tumors into consideration (20). According to our speculation, OGCs should not be classified as tumor cells, because they were CD68 positive and only classified as reactive cells derived from histocytes. As there were various types of tumor cells (e.g., PGCs, spindle cells, and PDAC cells) in one lesion,

we speculated that the origin of UOCs may be related to pancreatic tumor stem cells that can differentiate to heterogeneous tumor cells. Moreover, the transformations between different tumor cells can also play an important role in the polymorphism of UOCs due to the existence of transitional zones between PDAC and UOC cells. These conjectures should be further confirmed by accumulations of clinical data and basic studies. Perhaps, single cell sequencing can offer an appropriate approach.

In conclusion, UOC is a rare condition with unique imaging manifestations and pathological features. EUS-FNA is a promising diagnostic approach preoperatively, but not indispensable in the presence of definite indications of surgery. *En bloc* resection is considered to be the first-line option for treating UOC and radical resection should be tried on the basis of tumor growth characteristics. In our opinion, OGCs are reactive cells derived from histocytes.

ETHICAL STATEMENT

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient. The study protocols were approved by the Ethical Committee of the Shaoxing Hospital of Zhejiang University. Written informed consent was obtained from the participants for publication of this article and any accompanying tables/images. A copy of the written consent is available for review by the Editor of this journal.

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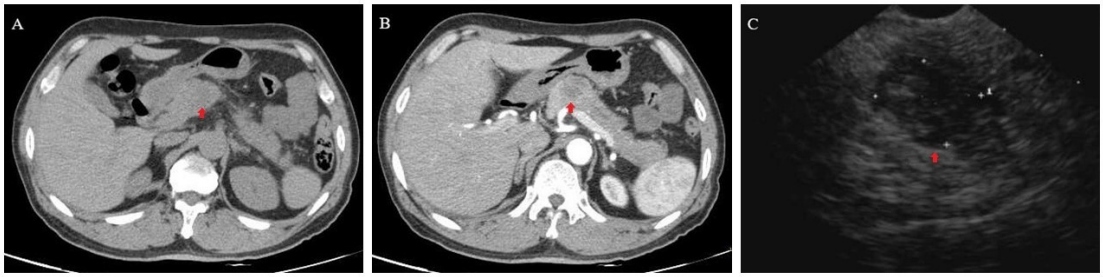

Fig. 1. Imaging findings of the UOC patient. A. Plain CT scan showed a hypodense mass in the neck of the pancreas. B. The hypodense mass was enhanced peripherally during the arterial phase. C. EUS showed a heterogeneous echotexture in the neck of the pancreas.

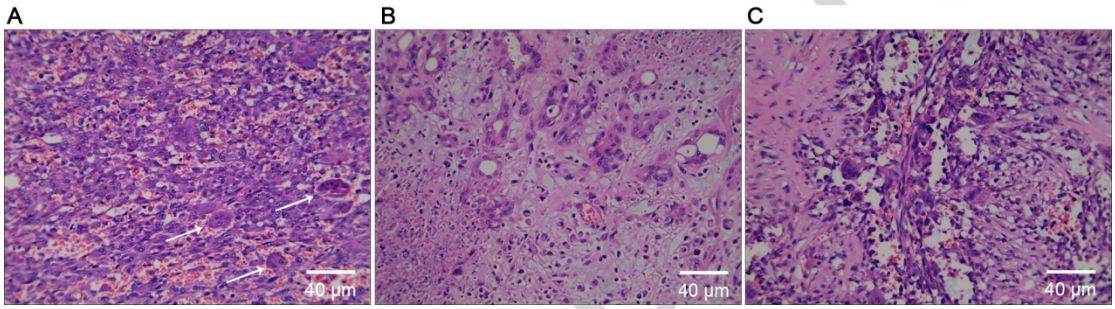

Fig. 2. HE staining images under a magnification of 200×. A. Polynuclear OGCs (white arrows) were scattered within the background of spindle cells, with hemorrhage and erythrocyte infiltration in the cell stroma. B. The transitional zone between UOC and PDAC cells. C. Spindle cells constituted pseudo-angiomatoid structures in which erythrocytes were diffused.

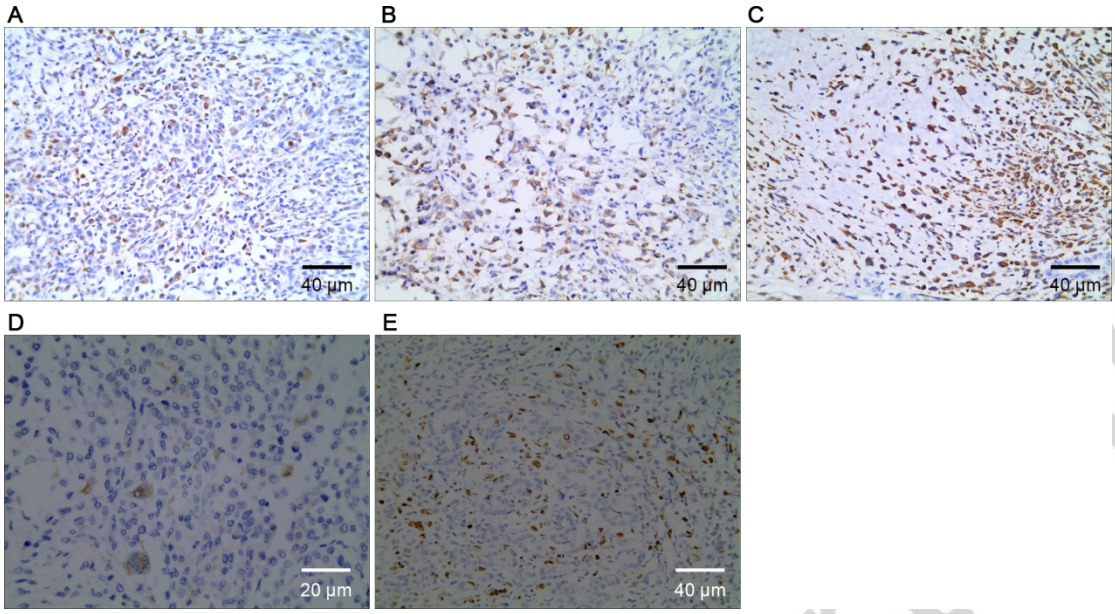

Fig. 3. Immunohistochemical staining images. A. CKpan was positive in spindle cells, which indicated the epithelial origin (under a magnification of 200×). B. EMA was positive in spindle cells, which indicated the epithelial origin (under a magnification of 200×). C. Vimentin was positive in spindle cells, which indicated the mesenchymal origin (under a magnification of 200×). D. CD68 was positive in OGCs only, which indicated the histiocytic origin (under a magnification of 400×). E. The Ki-67 proliferation index was about 30 % (under a magnification of 200×).