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Case Report

Seven-year disease-free survival in a patient with osteoclast-like giant cell-containing pancreatic undifferentiated carcinoma: a case report and literature review

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Abstract: Background: Undifferentiated carcinoma with osteoclast-like giant cells (UCOGC) of the pancreas is a very rare variant of pancreatic malignant neoplasm. It is regarded as a highly aggressive tumor with a worse prognosis than conventional pancreatic ductal adenocarcinoma. Case presentation: A 54-year-old male patient presented with 3-month recurrent epigastric distress. Computed tomography of the abdomen showed a large cystic mass in the distal pancreas. On macroscopic examination, the lesion had numerous multiloculated cystic cavities. Microscopically, the tumor predominantly comprised a considerable number of evenly distributed non-neoplastic osteoclast-like giant cells and a few neoplastic pleomorphic cells. Although extensive histologic sampling was conducted, a classic ductal adenocarcinoma component was not identified. The patient received no further treatment after his surgery and has been doing well with no evidence of recurrence or metastasis for >7 years. Conclusions: Our results suggest that pure UCOGC has a significantly better prognosis and supports that pure UCOGC may represent a biologically distinct variant of pancreatic carcinoma and it should be separated from other undifferentiated pancreatic carcinomas.

Keywords: Undifferentiated carcinoma, pancreas, osteoclast-like giant cells, prognosis

Background

Giant cell tumors of the pancreas are rare neoplasms; they were originally described by Rosai [1]. Historically, they were classified into three histopathologic types: osteoclastic, pleomorphic and a mixture of the two [1-3]. At the benign end of the spectrum, osteoclast-type giant cell tumors (OGCTs) are characterised by osteoclast-like giant cells and mononuclear stromal cells identical to those observed in giant cell tumors of bone. At the malignant end of the spectrum, pleomorphic giant cell tumors of the pancreas are highly anaplastic neoplasms consisting of bizarre pleomorphic mononucleated and multinucleated giant cells. Further, a combination of these two cell types defines a third type.

The current World Health Organization (WHO) classification groups the three aforementioned types into a single category, undifferentiated carcinoma with osteoclast-like giant cells (UCOGC) [4]. UCOGC is different from plain undifferentiated carcinoma and is regarded as a highly aggressive tumor with an even worse prognosis than that of conventional pancreatic ductal adenocarcinoma [4]. Owing to the rarity of this tumor, its clinicopathologic features and prognosis remain elusive.

Here, we present a case of UCOGC in a 54-year-old male; the tumor did not harbor ductal adenocarcinoma despite extensive sampling. The patient received no adjuvant therapy after his surgery and has been well without disease recurrence or metastasis 7 years after his sur-

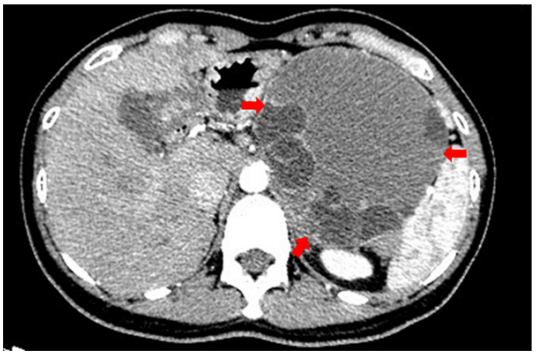

Figure 1. Abdominal computed tomography showing a large cystic lesion in the distal pancreas as indicated by the red arrows.

gery. Our results are consistent with recent studies that have reported a survival of ≥5 years for such patients [3, 5-7]. We hope, with more such cases are reported in the literature, the clinicopathologic features and prognosis of UCOGC will become clear so that patients will be treated accordingly.

Case presentation

A 54-year-old male was admitted to the department of gastroenterology in our hospital due to recurrent epigastric distress, nausea, and edema of the lower limbs for 3 months. He had no significant past medical history or family history. Physical examination revealed a vaguely palpable abdominal mass with mild and deep tenderness. A laboratory examination at the admission only revealed mild anemia with a hemoglobin level of 10.2 g/dL.

A computed tomography (CT) scan of the abdomen revealed a large cystic lesion measuring 20.4 × 15.5 × 9.0 cm in size in the tail of the pancreas (**Figure 1**). Laparotomy revealed that this large, distally located, pancreatic cystic lesion partially closely adhered to the transverse colon and the spleen. There was lymphadenopathy. The patient underwent subtotal pancreatectomy, splenectomy, and segmental resection of the transverse colon.

Macroscopically, the mass was encapsulated, multiloculated, and comprised numerous cysts. The capsule was thick and rough. The cysts contained bloody fluid and necrosis were observed on the cut surface. The mass was adherent to the transverse colon and the spleen. The tumor was extensively sampled for histology.

Histologic examination revealed that the tumor comprised numerous, evenly distributed, non-neoplastic osteoclast-like giant cells and few neoplastic pleomorphic cells (**Figure 2A**). Extensive hemorrhage was present. The osteoclast-like giant cells contained multiple, relatively uniform and bland nuclei and abundant eosinophilic cytoplasm. The neoplastic pleomorphic cells were medium-sized and contained round to spindle-shaped single nuclei. About 2 mitotic figures were observed per 10 high-power fields in the pleomorphic cells. Although extensive histologic sampling was performed, classic ductal adenocarcinoma components were not identified. In addition, the macroscopic impression of necrosis was confirmed to be old hemorrhage. Histologic examination confirmed that the tumor was confined in the pancreas, and had no invasion into the transverse colon and spleen. By immunohistochemistry, the osteoclast-like giant cells were positive for CD68 but negative for cytokeratin (**Figure 2B** and **2C**). The neoplastic pleomorphic cells were focally and weakly positive for cytokeratin (**Figure 2C**) and had a low Ki-67 labeling index (<5%) (**Figure 2D**). The final diagnosis was UCOGC according to the current WHO Blue Book series. All surgical resection margins were negative. Eleven lymph nodes retrieved from the resection specimen were negative for tumor. Appropriate imaging studies did not reveal metastases. The final pathologic stage of the tumor was Union for International Cancer Control T3N0M0 stage IIa.

The patient's postoperative course was uneventful. He was discharged home on postoperative day 10. He refused chemotherapy or radiotherapy. The patient has been doing well with no evidence of recurrence or metastasis for >7 years.

Discussion

Undifferentiated carcinoma with osteoclast-like giant cells (UCOGC) of the pancreas was not widely recognized until it was included in the current WHO classification; it is now regarded as a highly aggressive tumor [4]. Multiple terms have been used previously for UCOGC, such as pancreatic giant cell tumour, pancreatic osteoclastoma, mixed pleomorphic-osteoclast-like tumour of the pancreas, and osteoclastic and pleomorphic giant cell tumours of the pancreas [1-3, 8-11]. UCOGC comprises a wide spectrum

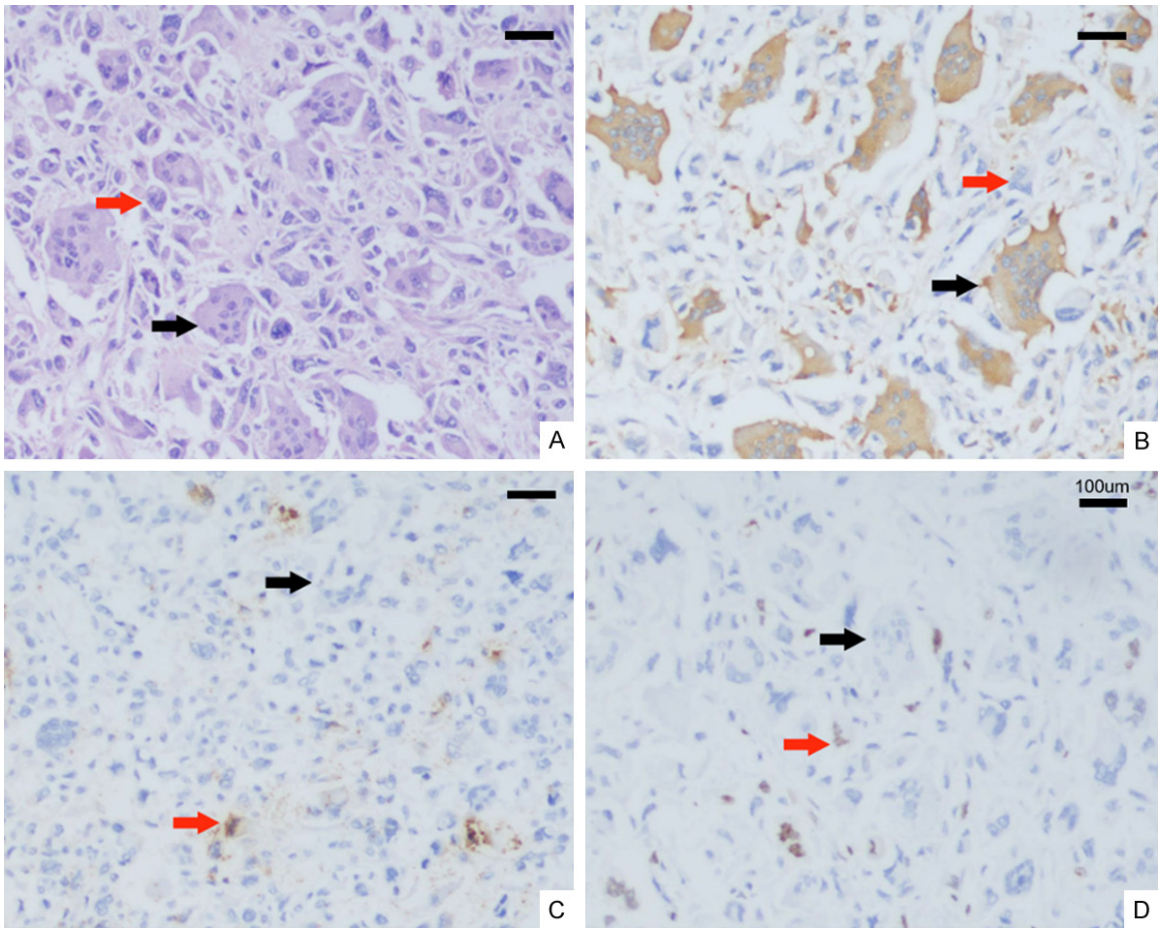

Figure 2. Hematoxylin-eosin and immunohistochemical findings of UCOGC. Red arrow: Neoplastic pleomorphic cells. Black arrow: Non-neoplastic osteoclast-like giant cells. A: A few neoplastic pleomorphic cells and considerable number of evenly distributed osteoclast-like giant cells in this microscopic field (×200). B: Strong CD68 expression in osteoclast-like giant cells (×200). C: Focally weak cytokeratin (CK) staining in neoplastic pleomorphic cells; negative CK staining in osteoclast-like giant cells (×200). D: Low Ki-67 staining (<5%) in neoplastic pleomorphic cells; negative Ki-67 staining in osteoclast-like giant cells (×200). Scale bars = 100 μm.

of tumors originating from cells ranging from mononuclear stromal cells to pleomorphic/anaplastic giant cells with osteoclast-like giant cells. Additionally, UCOGC often coexists with ductal adenocarcinomas or mucinous cystic neoplasms [3, 5, 12]. Currently, there are no criteria regarding the amount of the concomitant component, e.g. conventional ductal adenocarcinoma component, allowed in UCOGC [3].

Owing to the rarity of UCOGC, there are insufficient data on the clinicopathologic characteristics or prognosis of this tumor. The prognosis of UCOGC ranges from several months to >10 years [6]. Kobayashi *et al.* demonstrated that patients with UCOGC in the short-term survivor group had concomitant components of ductal adenocarcinoma, positive lymph node metastasis, and smaller tumor size [6]. The survival rates of patients with histologically pure UCOGC tend to be significantly higher than those of patients with an associated adenocarcinoma [3, 5]. This finding highlights the importance of extensive histologic sampling to exclude associated conventional ductal adenocarcinoma [11, 12]. The morphologic criteria of osteoclasts is important. For example, large, multinucleated, pleomorphic, giant cells that mimic osteoclasts with intracellular neutrophils or eosinophils are not in fact osteoclasts [3]. In addition, micropapillary carcinoma clusters can mimic osteoclastic cells and pose diagnostic challenges [3]. It has been speculated that the good prognosis in pure UCOGC may be due to the considerable chemotaxis of osteoclastic

Table 1. Characteristics and survival in patients with osteoclast-like giant cell-containing pancreatic undifferentiated carcinoma

Reference	Gender/ Age, years	Location	Maximal tumor dimension, cm	Associated with AC	IHC	Therapy	Survival, months	Invasion of other organ	lymph node	LVI	Resection margin
	F/82	tail	13	No	NA	NA	>4	NA	Neg	NA	NA
1	F/74	head	10	No	NA	NA	>10	NA	Neg	Yes	NA
2	M/60	body, tail	14	No	GC: vimentin(+), syn(+), CK(-), EMA(-)	NA	4	NA	Neg	NA	NA
6	F/37	head	4	Yes	GC: vimentin(+), p53(-), AC: p53(+)	Gemcitabine	>66	NA	Neg	NA	No
7	F/61	tail	10.4	NA	NA	Gemcitabine	>72	Left diaphragm	Neg	Yes	No
9	F/55	body	2.5	Yes	PC&MC: CK(+), viminetin(+), OGC: vimentin(-), AC: CA199(+), CK(+)	NA	3	Liver	Neg	NA	NA
9	F/71	head	4.5	NA	OGC&PGC: EMA(-), vimentin(-), CK(-) desmin(-), SMA(-)	NA	2	No	Neg	Yes	NA
9	M/50	body	7	NA	OGC: CK(-), CD68(+), PGC: CK(+), CD68(-)	NA	7	NA	NA	NA	NA
10	F/72	head	6.5	No	NA	NA	Dead 10 days after admission	Liver, adrenal gland	NA	NA	NA
11	F/56	tail	24	Yes (focal)	vimentin(+), EMA(-)	Radiation	>6	NA	NA	Yes	NA
12	F/68	neck, body	6	No	PC&MC: CK8/18(+), CK19(+), vimentin(+), ki-67(+, 30%); OGC: CD68(+), vimentin(+), CK8/18(-), CK19(-), ki-67(-)	Gemcitabine	10	No	Neg	No	No
13	M/49	head	2	Yes	OGC, MC: CD68(+), AE1/AE3(-)	NA	NA	No	NA	NA	NA
13	F/68	body, tail	14	No	OGC, MC: CD68(+), AE1/AE3(-)	NA	NA	Liver	NA	NA	NA
13	M/51	head	3.8	Yes	PC: CD68(-), AE1/AE3(-)	NA	NA	NA	Pos	NA	NA
Present case	M/54	tail	20.4	No	OGC: CD68(+), PC: focal weak CK(+), ki-67(+, <5%)	No	>84	No	Neg	No	Neg

Note: AC: adenocarcinoma; CK: cytokeratin; EMA: epithelial membrane antigen; F: female; GC: giant cell; IHC: immunohistochemistry; LVI: lymphovascular invasion; M: male; MC: mononuclear cell; NA: not available; Neg: negative; OGC: osteoclast-like giant cell; PC: pleomorphic cell; PGC: pleomorphic giant cell; Pos: positive; Ref: reference; SMA: smooth muscle actin; Syn: synaptophysin.

giant cells leading to a strong immune response [5]. The characteristics and treatment of UCOGC that have been described in the literature are summarized in **Table 1**.

The histogenesis of OGCT has been debated. Sakai *et al.* performed microscopic, immunohistochemical, and K-ras gene mutation analyses using a microdissection approach to clarify the origin of neoplastic pleomorphic cells and non-neoplastic osteoclast-like giant cells [13]. They observed that non-neoplastic osteoclast-like giant cells lacked K-ras gene mutations, suggesting that they were of mesenchymal origin, whereas neoplastic pleomorphic cells harboured K-ras gene mutations, probably because they were derived from epithelial cells [13]. Recent research has reported similar genetic alterations in UCOGC and conventional pancreatic ductal adenocarcinoma, including activating mutations of K-ras gene and inactivating mutations of CDKN2A, P53 and Smad4, respectively; however, the study did not specifically examine the molecular changes in the pleomorphic tumor cells and osteoclast-like giant cells [5].

Here, we report a case of pure UCOGC in a 54-year-old man with >7 year disease-free survival after curative surgery. Our current case, along with previously reported cases, suggests that UCOGC lacking a ductal adenocarcinoma component has a significantly better prognosis than what is implied in the current WHO blue book. Wide recognition and additional reports of this entity in the near future or a multicentric study using a more uniform definition for osteoclast-like giant cells, and precise molecular analysis of pleomorphic tumor cells and osteoclast-like giant cells may shed light on the characteristics, and confirm the good prognosis of a subset of UCOGCs.

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Disclosure of conflict of interest

None.

Abbreviations

CT, Computed tomography; OGCTs, Osteoclast-type giant cell tumors; UCOGC, Undifferentiated carcinoma with osteoclast-like giant cells; WHO, World Health Organization.

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