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CASE REPORT

EUS-guided fine needle biopsy is able to provide diagnosis in rare osteoclast-like giant cells undifferentiated carcinoma of the pancreas: report of two cases

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Undifferentiated carcinoma of the pancreas with osteoclast-like giant cells (UC-OGC) is a rare subtype of pancreatic cancer, accounting for less than 1% of all pancreatic tumors. Preoperative diagnosis is cumbersome as cross-sectional imaging is often not capable to distinguish between UC-OGC and other pancreatic tumors such as pancreatic adenocarcinoma, mucinous carcinoma or neuroendocrine tumors and specific tumor markers seem to be lacking. Endoscopic ultrasound r `m(EUS) with tissue acquisition via fine-needle aspiration (FNA) or biopsy (FNB) with microscopic HE staining and immunohistochemistry allows for an accurate diagnosis, thus influencing further treatment. We present herein the cases of two patients with osteoclast-like giant cells tumors of the pancreas diagnosed by EUS-guided fine needle biopsy and perform a literature review on the role of EUS-guided biopsy for diagnosis.

Key words: endoscopic ultrasound-guided fine needle aspiration, endoscopic ultrasound-guided fine needle biopsy, immunohistochemistry, osteoclast-like giant cell, pancreatic cancer, tumor markers.

INTRODUCTION

Amongst all pancreatic tumors, undifferentiated carcinoma with osteoclast-like giant cells (UC-OGC) is an extremely rare entity, accounting for less than 1% of all pancreatic malignancies [1]. Histopathological, UC-OGC is characterized by coexistence of osteoclastic giant cells (OGC) and neoplastic and non-neoplastic mononuclear cells, mimicking benign bone proliferation, such as giant cell tumors of the bone. The origin of osteoclast-like cells is still debated, with studies showing epithelial or mesenchymal provenance [2,3]. Although similar, UC-OGC is a malignant tumor, being recognized as a clinically and morphologically distinct form of pancreatic ductal adenocarcinoma (PDAC) in the most recent WHO Classification. Earlier studies suggested UC-OGC to be an extremely aggressive tumor with a prognosis similar to pancreatic ductal adenocarcinoma (PDAC), but recent studies have differentiated true UC-OGC from undifferentiated pancreatic carcinoma and support a more favorable prognosis of the former, especially if amenable to surgical resection [4][5]. Because of likely differences in prognosis and treatment plan, distinguishing UC-OGC from other types of pancreatic adenocarcinomas is important. Due to preferential localization of these tumors in the body and tail of the pancreas, symptoms are unspecific and often present when the tumor is large. On imaging, UC-OGC typically appear as an inhomogeneous lesions sometimes with a cystic component, similar to pancreatic adenocarcinoma, apart from having slightly larger dimensions. Histological or cytological examination is, therefore, paramount to a correct diagnosis, and tumor sampling via endoscopic ultrasound (EUS) has allowed for correct preoperative diagnosis. There are few reports in the literature describing the clinical course, histopathology, and treatment of this neoplasm, but specific criteria for the management of UC-OCG are still lacking. Surgical resection is the recommended treatment for local disease, but oncologic treatment is not yet standardized due to limited numbers of reported cases.

We present herein two cases of UC-OGC, both diagnosed by endoscopic ultrasound (EUS)-guided fine needle biopsy (FNB) and perform a literature review regarding EUS-guided diagnosis of this rare entity.

CASE REPORTS

A 66-year-old Caucasian female, with no history of smoking or alcoholism, presented to her primary care physician after three months history of unintentional weight loss, loss of appetite and fatigue. Past medical history was significant for type 2 diabetes mellitus and cholecystectomy performed years before due to gallstone disease, but she had no other major conditions. The initial abdominal ultrasound examination revealed bilateral hypoechoic intrahepatic lesions, the largest one measuring 6 cm in diameter, and a 6.5 x 5.2 cm hypoechoic lesion, with poor vascularization, at the level of the pancreatic tail. No other lesions were visible. Percutaneous liver biopsy of the intrahepatic lesions was initially performed in other department, but the results were inconclusive as the tissue sample was insufficient. She was referred to our clinic for further investigations. A contrast enhanced computed tomography (CT) scan was performed showing a 6 x 5 cm inhomogeneous soft tissue mass with multiple fluid areas and an area of necrosis in the pancreatic tail, in close contact with the spleen (Fig. 1). Numerous hypodense lesions in both hepatic lobes were also described, suggestive of liver metastases.

Endoscopic ultrasound was performed as a diagnostic method of choice, with a linear array echoendoscope showing the above-described 6 × 5.8 cm pancreatic tail mass that was largely solid with mixed echo structure and small cystic areas, along with multiple secondary lesions in the liver; splenic vein thrombosis was also seen. EUS-guided fine needle biopsy (EUS-FNB) was performed using a 22-gauge Franseen needle (Acquire™ EUS FNB Needle, Boston Scientific Co., Natick, MA, USA) (Fig. 2). Four passes were performed; the resulted material was expressed in formalin and processed as standard endoscopic biopsies. The smears showed numerous giant cells with over 10 clustered nuclei and prominent nucleoli, consistent with osteoclast-like giant cells, and mononucleated and highly atypical tumor cells (Fig. 3).

After histopathological analysis, a diagnosis of osteoclast-like giant cell pancreatic tumor was rendered. Immunohistochemistry studies showed the tumor cells to be positive for cytokeratin (CKs) 8/18 and p53, confirming the diagnosis.



Fig. 1. Contrast enhanced computer tomography showing a heterogenous lesion of the pancreatic tail, in close contact with the spleen. No vascular invasion is apparent.

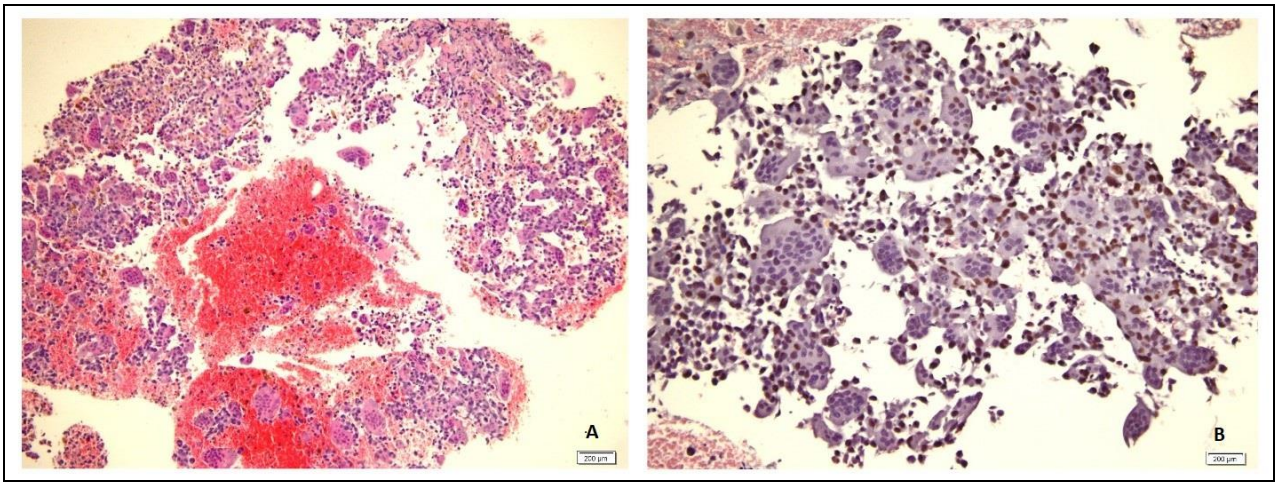


Fig. 2. Cell block preparation: **Panel A**. Dual proliferation composed of some round, pleomorphic, mononuclear, highly atypical tumoral cells and numerous large, non-neoplastic, osteoclast-like multinucleated cells with over 10 small nuclei (Hematoxylin-eosin 100x); **Panel B**. p53 immunohistochemical stain only positive on the tumoral nuclei (dark brown, 200x).

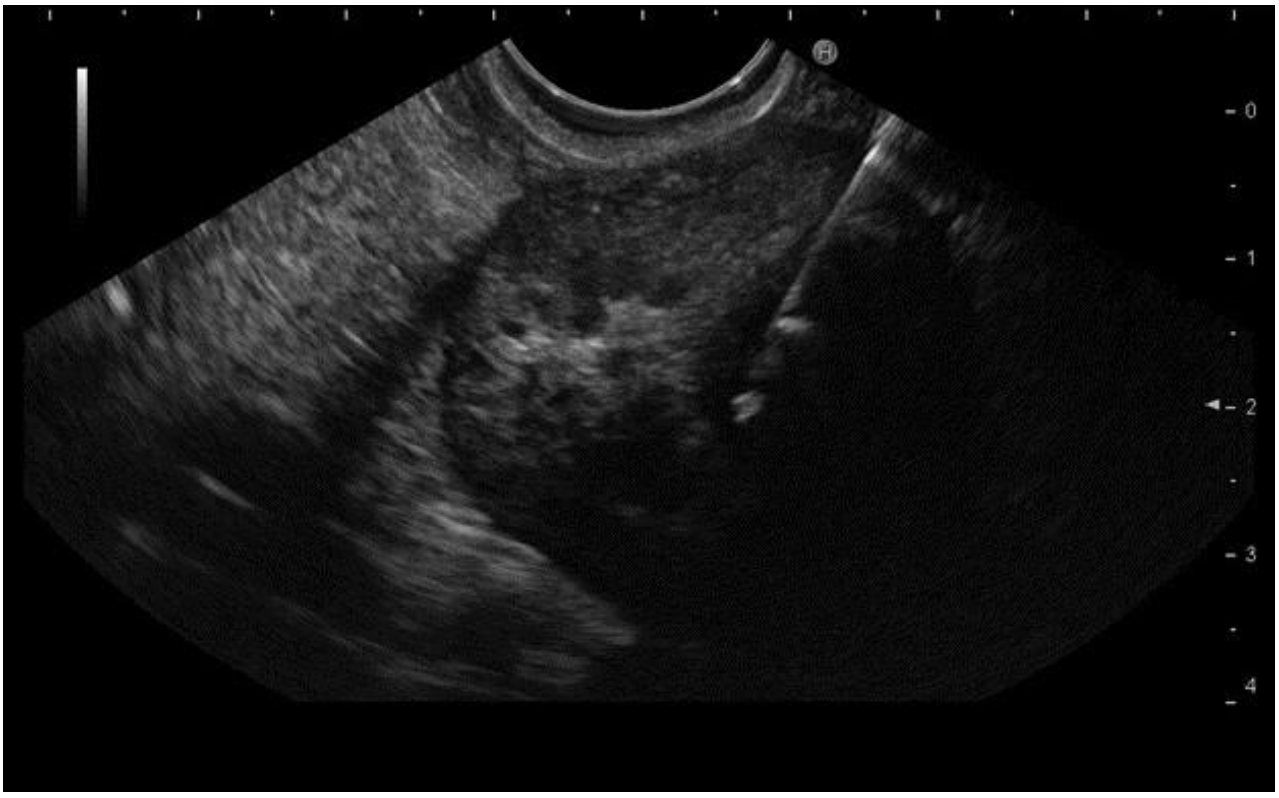


Fig. 3. Endoscopic ultrasound showing a heterogenous lesion with irregular margins in the uncinate process of the pancreas. EUS-FNB needle is visible within the tumor (EUS-FNB was performed with a 22G SharkCore™ needle.

The patient was then referred to an oncologist for continuation of palliative treatment and underwent 2 courses of chemotherapy before passing away 6 months later due to disease progression. No details about the specific chemotherapy used could be obtained.

The second case is that of a 75-year-old male, with no known comorbidities and no significant history of alcohol consumption or smoking. He underwent a routine abdominal ultrasound examination after an abdominal trauma which detected a 41 mm lesion in the uncinate process of the pancreas, with central necrosis and smooth, well-defined margins. Computed tomography (CT) described the same lesion (Fig. 4), with a good enhancement in the arterial phase. No other lesions suggestive of metastases were described. EUS-FNB (Fig. 5) was performed using a fork-type EUS-FNB needle (SharkCore™, Medtronic Inc., Sunnyvale, CA), and the histological exam revealed

poorly differentiated carcinoma with a rich component of osteoclast-like giant cells. After diagnosis, the patient underwent a pylorus-preserving pancreaticoduodenectomy, also bringing the confirmation of UC-OGC on the resection specimen. He was referred for oncological treatment and received adjuvant chemotherapy, with initial good response. The patient succumbed 34 months later due to disease progression.

DISCUSSION

Pancreatic cancer is the second most common gastrointestinal malignancy, most diagnosed tumor being PDAC [6]. Amongst all pancreatic tumors, UC-OGC is an uncommon subtype, with an incidence of less than 1% of all pancreatic tumors [7] (Table 1). This type of tumor consists of undifferentiated monocellular cell population as well as non-neoplastic osteoclastic-like cells. The exact origin of osteoclastic-like cells is still controversial, reports in literature suggesting them being either epithelial or mesenchymal. UC-OGC's common origin with PDAC is supported by the presence of shared mutation in the KRAS gene as well as other tumor suppressor genes commonly associated with pancreatic cancer such as TP53, CDKN2A and SMAD4 [8].

It is more commonly diagnosed in middle-aged and elderly patients, within the 6th and 7th decade of life, and seems to be equally encountered in females and males [1,7]. The presenting symptoms are usually atypical, mostly consisting of upper abdominal pain and/or unintentional weight loss. Other reported presenting symptoms are nausea, loss of appetite, steatorrhea, while anemia and jaundice have been rarely reported [10]. In some cases, patients may be asymptomatic, especially in the earlier phases when the tumor is smaller in size, and the diagnosis is incidental. Most commonly UC-OGCs are located in the body or tail of the pancreas [5], and are usually large in size, averaging around 8 cm in diameter [11].

Scant data are available on the CT or MRI appearance of these tumors, these lesions mimicking the more common PDAC, except for a tendency to be much larger at diagnosis [6]. Contrast-enhanced CT scanning usually shows an inhomogeneous lesion with arterial enhancement of the peripheral rim as well as heterogenous contrast uptake of the tumor, present also in the delayed venous phases. Tumors located in the head and neck of the pancreas can lead to obstructive jaundice and dilatation of the pancreatic duct, making a differential diagnosis from PDAC difficult [7]. Despite the tumors being large in volume, local invasion and lymph node metastases are not common findings at cross-sectional imaging although advanced tumors can present with an aggressive clinical evolution [6,7]. MRI features of UC-OGC include low-signal intensity in T1W1 and high-intensity central cystic part in T2W1, with low-intensity interval and solid surrounding tissue. In some cases, the tumors can exhibit patchy signals due to hemosiderin deposits [12].

These tumors' EUS appearance differs from the typical pancreatic adenocarcinomas, by having a markedly heterogeneous echotexture and well demarcated hypo and hyperechoic areas within the same lesion, in contrast with PDAC which tends to be more uniformly hypoechoic [6]. However, diagnostic EUS is not sufficient for differentiating the two entities and tissue acquisition is necessary for an accurate diagnosis.

EUS – fine needle aspiration (FNA) – is an invaluable tool for diagnosis of solid and cystic pancreatic lesions, with a sensitivity for detecting malignancy ranging from 80–90% [13]. However, accurate diagnosis also depends on tissue volume, with larger samples offering better results. The demand to acquire larger samples with better preserved tissue architecture has increased the use of EUS fine needle biopsy (FNB) in sampling pancreatic tumors. Although the diagnostic yield was thought to be similar between FNA and FNB techniques, the greater capability of the FNB needle to obtain a core tissue biopsy reduces the number of needle passes needed for establishing a pathological diagnosis [14], with 2–3 passes being sufficient to ensure a sensitivity for detecting malignancy of 90% [15]. Newer models of FNB needles, such as fork-tip and crown-tip needles were shown to have an even better diagnostic accuracy for pancreatic solid lesions (96%), with no significant differences between the needle types [16]. A recent meta-analysis compared these third generation FNB needle tissue acquisition to standard FNA technique in establishing malignancy of pancreatic solid lesions, and discovered that EUS-FNB outperformed EUS-FNA in both histological yield (77 vs 44%, $p<0.001$) and diagnostic accuracy (87 vs 78%, $p=0.002$) [17].

So far, EUS-guided diagnosis of UC-OGC has been reported in a few case reports and case series. We conducted an extended literature research and summarized cases in Table 2. Importantly, as proven in a study with 38 resected UC-OGCs, 76% percent of them had an invasive ductal or tubular adenocarcinoma component [5,18]. Thus, a good quality of tissue specimens is needed to provide a clear diagnosis and not misdiagnose it as a standard PDAC.

Tissue acquisition allows for histological evidence of OCG and other neoplastic and non-neoplastic mononuclear cells and helps differentiate UC-OGC from other pancreatic malignancies. OGCs show a lack of mitoses and proliferative activity, as detected by Ki-67, and do not express epithelial markers (CKAE1/AE3) but have positive staining for histiocytic markers (CD68). Strong cytoplasmic p53 staining was also observed in the cytoplasm of the neoplastic mononuclear cells, suggesting a mix of epithelial and mesenchymal lineage of UC-OGCs [19]. To allow for a better characterization of this distinct behavior of epithelial to mesenchymal transition, further molecular analysis is needed.

Table 1

WHO classification of malignant epithelial tumors [9]

Malignant epithelial tumors (WHO classification 2021)
Ductal adenocarcinoma
Colloid carcinoma
Poorly cohesive carcinoma
Signet ring cell carcinoma
Medullary carcinoma
Adenosquamous carcinoma
Epidermoid carcinoma
Large cell carcinoma with rhabdoid phenotype
Carcinoma, undifferentiated
Undifferentiated carcinoma with osteoclast-like giant cells
Acinar cell carcinoma
Acinar cell cystadenocarcinoma
Mixed acinar-neuroendocrine carcinoma
Mixed acinar-endocrine-ductal carcinoma
Mixed acinar-ductal carcinoma
Pancreatoblastoma
Solid pseudopapillary neoplasm of the pancreas
Solid pseudopapillary neoplasm with high grade dysplasia

Table 2

Summary of cases reported so far on the use of EUS-guided tissue acquisition for diagnosis of osteoclast-like giant cell pancreatic carcinoma

Author, year	**Type of study**	**No. of patients**	**Type of needle used**	**Tumor location**	**Mean tumor size**	**Final diagnosis in cytopathology reports**	**Adverse events**
Silverman *et al*. [20], 1988	Case Report	1	EUS-FNA	Head	NA	UC-OGC	NR
Ezenekwe *et al*. [21], 2005	Case Report	1	EUS-FNA	Head	NA	UC-OCG	NR
Chopra *et al*. [22], 2007	Case series	2	EUS-FNA	Neck (1) Head (1)	2.5 cm	UC-OGC (1, 50%) Non-diagnostic sample (1, 50%)	NR
Layfield *et al*. [23], 2008	Case series	6	EUS-FNA	Head (5) Body (1)	NR	UC-OGC (1, 16,6%) Pleomorphic Giant Cell Carcinoma (5, 83.3%)	NR
Moore *et al*. [24], 2009	Case Series	5	EUS-FNA	Head (4) Body (1)	Mean size 4.7 cm (2–7 cm)	UC-OGC (1, 20%) Pleomorphic Giant Cell Carcinoma (3, 60%) Mixed Type (1, 20%)	NR
Woohyeon *et al*. [25], 2016	Case Report	1	EUS-FNA	Body	5 cm	UC-OGC	NR
Sakhi *et al*. [26], 2017	Case Report	1	EUS-FNA	Body	3.5 cm	UC-OGC	NR
Reid *et al*. [27], 2017	Retrospective analysis of pathology reports	14 (15 samples)	EUS-FNA	Head (7) Body (3) Tail (4)	9.0 cm	UC-OGC (6, 40%) Poorly differentiated carcinoma (2, 13%) Suspicious for neoplasm (1, 7%) Negative for malignant cells (1, 15%) PDAC (5, 33%)	NR

Table 2 (continued)

Author, year	Type of study	No. of patients	Type of needle used	Tumor location	Mean tumor size	Final diagnosis in cytopathology reports	Adverse events
Yepuri *et al.* [28], 2018	Case Report	1	EUS-FNA	Head	2.1 cm	UC-OGC	NR
Hanayneh *et al.* [29], 2019	Case Report	1	EUS-FNA	Head	2.3 cm	OC-OGC + MCN	NR
Nehmeh *et al.* [30], 2019	Case Report	1	NR	Tail	2.5 cm	UC-OGC	NR
Speisky *et al.* [31], 2020	Case report	1	EUS-FNB	Head	5.0 cm	UC-OGC	NR
Kalogeraki *et al.* [32], 2021	Case Report	1	EUS-FNA	Head	1.2 cm	UC-OGC	NR
Gao *et al.* [33], 2021	Case Report	1	EUS-FNA	Head	0.7 cm	UC-OGC + NET	NR
Ashfaq *et al.* [34], 2022	Case Report	1	EUS-FNB	Head	2 cm	UC-OGC	NR
Igarashi *et al.* [35], 2022	Case Report	1	EUS-FNA	Head + Body	7.5 cm	UC-OGC	NR

Abbreviations: UC-OGC, undifferentiated pancreatic carcinoma with giant osteoclastic-like cells; PDAC, pancreatic ductal adenocarcinoma; NR, notreported; EUS-FNA, endoscopic ultrasound guided fine needle aspiration; EUS-FNB, endoscopic ultrasound guided fine needle biopsy; NET, neuroendocrine tumor; MCN, mucinous cystic neoplasm

In a first report of EUS-FNA for the diagnosis of UC-OGC, from the two cases, the probability diagnosis was made in only one of the cases, in which immunohistochemical stains performed on the cell block were unsuccessful [22]. In another retrospective analysis of pathology reports study, from 15 samples, EUS-FNA was able to correctly diagnose UC-OGC in only 6 (40%) of cases [27]. Interestingly, the same retrospective analysis showed a shorter survival of the patients with UC-OGC that underwent EUS-FNA prior to resection compared to the cohort without preoperative diagnosis confirmation. This may be partly attributed to selection bias, with larger and more aggressive tumors being subjected to pre-operative diagnosis via EUS-FNA. Although EUS-FNA is a safe procedure in sampling pancreatic tumors, there are some tumors, such as pancreatic colloid tumors or mixed salivary gland tumors that are susceptible to seeding and might require needle tract removal. Weather UC-OGC are vulnerable to iatrogenic spread is still debatable, and studies addressing this concern are needed.

In the first EUS-FNB report, the available sampling material allowed immunohistochemical techniques to be carried out, and a clear diagnosis of UC-OGC was established [31]. The data is too limited so far to be able to evaluate the role of EUS-FNB in correctly diagnosis UC-OGC. As mentioned earlier, it has been however proven that for pancreatic cancer, the last generation EUS-FNB needles are superior to standard FNA needles in providing neoplastic tissue, as well as desmoplastic stroma thus allowing for a correct histopathological diagnosis [17]. Immunocytochemical studies could be performed on the EUS-FNB specimens demonstrating positive staining of the malignant cells for cytokeratin (CKs) 8/18, structural proteic markers specific for epithelial cells, and for p53, whose detection has been strongly correlated with mutations in the p53 tumor suppressor gene [36], thus providing support for the correct diagnosis. Indeed, in a randomized study including 129 patients, samples collected using last-generation Franseen or fork-tip needles had significantly higher cellularity than samples collected using other types of FNB reverse-bevels or Menghini-tip needles.

Early diagnosis seems also important, as in a retrospective study, the mean survival rate of these patients was of 12 months, compared to 3 months for standard PDAC cases [5]. In this study performed on surgically resected UC-OGC, 7 out of 38 cases (18%) were alive over 5 years after surgery with no evidence of tumor recurrence, including 3 patients who were alive after more than 10 years, thus supporting other available case reports [11,37], where UC-OGC was more indolent than other types of pancreatic tumors.

Thus, EUS-FNB can be a better option allowing diagnosis of these types of tumors from the pre-surgical stages or in non-surgical candidates. Early diagnosis and subsequent resection could be the only chance to

cure this rare tumor, while once diagnosis provided, different treatment options could be available with the advent of personalized oncologic treatment approach.

The prognosis of UC-OGC is unclear due to the rarity of this entity and few available cases in the literature. The evolution tends to be unpredictable with survival rates ranging from a few months to years [3, 7], according to the stage at diagnosis and availability of treatment.

Because of the scarcity of cases, treatment guidelines for the management of UC-OGC are not available, and treatment recommendation are based mostly on case reports. Radical surgical resection is advocated as the first line of treatment, but reported cases show a high recurrence rate after complete resection and rapid progression afterwards, with a more protracted course being present in cases of tumors with greater osteoclast component [5]. Surgical treatment options are similar to those recommended for PDAC. Depending on the tumor location, a Whipple procedure or distal pancreatectomy can be performed, with lymph node dissection. The role of adjuvant treatment in UC-OGC is not clearly established due to the limited experience. The suggestion of epithelial lineage of UC-OGC can explain the positive results of cisplatin and gemcitabine-based chemotherapy regimens used in some literature reports [38], while radiotherapy has been proposed as a potential treatment based on the radiosensitivity of giant cell tumors of the bone [39].

Molecular tumor profiling was shown to aid in targeted therapy in patients with pancreatic ductal adenocarcinoma, resulting in prolonged survival [40]. Applying the same molecular profiling to UC-OGC might reveal particular sensitivity of this tumor type to specific oncologic regimens, but further studies are necessary to establish targeted therapies.

CONCLUSION

Undifferentiated carcinoma with osteoclast-like giant cells is a rare neoplasm of the pancreas, with unique clinical and pathological features. Clear preoperative diagnosis is possible by using the last generation of EUS-guided FNB needles, as proven by the two presented cases, allowing for personalized treatment decisions. However, after integrating these advancements into current clinical practice, allowing for an improved diagnosis, long-term follow-up dedicated studies are needed to establish better prognostic factors and best treatment options for these patients.

Carcinomul pancreatic nediferenţiat cu celule "osteoclast-like" reprezintă un subtip rar de tumoră pancreatică, reprezentând mai puţin de 1% din patologie. Diagnosticul preoperator poate fi dificil, tehnicile de imagistică medicală reuşind rareori să facă diferenţa între diverse tipuri de formaţiuni tumorale pancreatice, precum tumorile nediferenţiate cu cellule mari "osteoclast-like", adenocarcinomul pancreatic, carcinomul mucinos sau tumori neuroendocrine, iar markerii specifici tumorali tind să lipsească. Ecoendoscopia (EUS) cu achiziţie de ţesut prin tehnici de aspiraţie (FNA) sau biopsiere (FNB) împreună cu examinarea microscopică şi imunohistochimică a probelor obţinute permit un diagnostic clar şi influenţează astfel deciziile terapeutice ulterioare. Prezentăm două cazuri de tumori pancreatice nediferenţiate cu celule mari "osteoclast-like" diagnosticate prin EUS-FNB şi efectuăm un review al literaturii de specialitate.

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