Case report & Review

Cephalic undifferentiated carcinoma with osteoclast-like giant cells arising from the main pancreatic duct: case report and literature review

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Abstract

Undifferentiated carcinoma with osteoclast-like giant cell (UCOGC) is a ductal carcinoma variant with a recently reported more protracted survival and pathognomonic histology comprising two cell populations: the mononuclear tumoral cells and nontumoral multinucleated giant cells. It usually presents as a large heterogenic tumor with mixed solid-cystic components. The tumor develops from the ductal epithelium but the sequence of epithelial changes is often not identified due to the rapid tumoral growth and associated necrotic changes. We report a case of a 76-year-old patient diagnosed with cephalic UCOGC originating in the epithelium of the main pancreatic duct with endoluminal growth and foci of other ductal neoplasms (high-grade pancreatic intraepithelial neoplasia (PanIN) and conventional ductal carcinoma). The particularity of our case consists in the identification of the columnar epithelium conversion, through high-grade PanIN, into UCOGC specific malignant features, in a large size tumor – aspect usually reported in small tumors. Alongside our case we also present a brief literature review of cephalic UCOGC case reports and case series.

Keywords: *pancreatic UCOGC; ductal carcinoma; high-grade PanIN*

Introduction

Undifferentiated carcinoma with osteoclast-like giant cell is a rare entity, firstly described in 1968 by Rosai [1]. This pathologic entity is reported in the mainstream under various terms: metaplastic/anaplastic carcinoma, osteoclastoma, or osteoclastic giant cell tumor [2-5].

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The key element for diagnosis consists in the association of tumoral mononuclear cells with a variable number of non-tumoral multinucleated cells, osteoclast-like [6]. Summing less than 1% among malignant epithelial pancreatic proliferations [7], the tumor has origin in the pancreatic ductal epithelium and a similar genic signature with ductal carcinoma [8], but very different morphology and variable prognosis [9, 10]. Even if data about UCOGC are accumulating, there are still unexplained events in the tumor biology. Recent research addresses the role of osteoclast-like giant cells [5, 11], the involvement of different pancreatic intraductal

lesions, presumed as origin point [3, 12-14], and the identification of the morphological alterations sequence leading from ductal epithelium to UCOGC [15].

Therefore, we present a case of UCOGC associated with conventional ductal carcinoma, arising from the main pancreatic duct epithelium. By highlighting the main clinicopathological features, our report complements data already published on this topic and contributes to a better characterization of the tumor behavior.

Case report

We describe the case of a 76-year-old female presented at the Surgical Department of "Sf. Spiridon" County Emergency Hospital with a large palpable upper abdominal tumor. The patient reported right upper abdominal pain, nausea, vomiting, asthenia and weight loss during the last month. She also had a history of ischemic heart disease and chronic cardiac failure NYHA II. Physical examination revealed pale, not jaundiced, dehydrated skin, cachexia (BMI=16.5 kg/m), and a 12/10 cm mass located in epigastrium and right hypochondrium, mobile, firm and well-circumscribed. Laboratory tests revealed moderate anemia (Hb=9.9 g/dL, Ht=31%), high levels of carbohydrate antigen 19-9 (CA_{19-9} =194 U/mL; normal <33 U/mL) and C reactive protein (CRP=3.59 mg/L; normal <0.5 mg/L). Abdominal computed tomography (Figure 1) revealed a heterogeneous tumor of 83/130/100 mm, predominantly cystic, belonging to the head of the pancreas, in close contact with the superior mesenteric vein and spleno-mesenteric vein (on a length of over 55 mm), narrowing the vessels without thrombosis; Wirsung duct was dilated (10 mm in diameter); peritumoral lymphadenopathies were noted. Due to the close contact of the tumor with the vascular components, and the patient's anaesthetic risk (ASA III), an exploratory laparotomy was first performed. This procedure showed a cephalic pancreatic tumor invasive into the antro-pyloric region of the stomach, without liver involvement; the lymph nodes were negative for tumoral cells on frozen section. The surgical team decided to continue the surgery with the Whipple procedure, removing the entire expansive process (Figure 2).

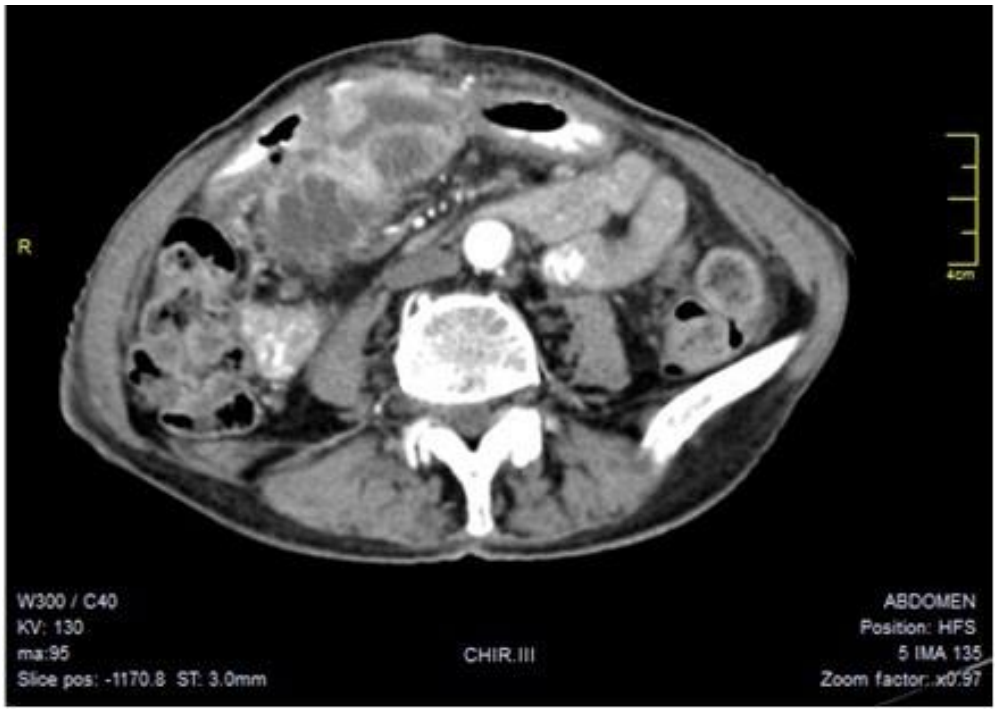

Fig. 1. Cephalic pancreatic tumour predominantly cystic in tight contact with the superior mesenteric vein.

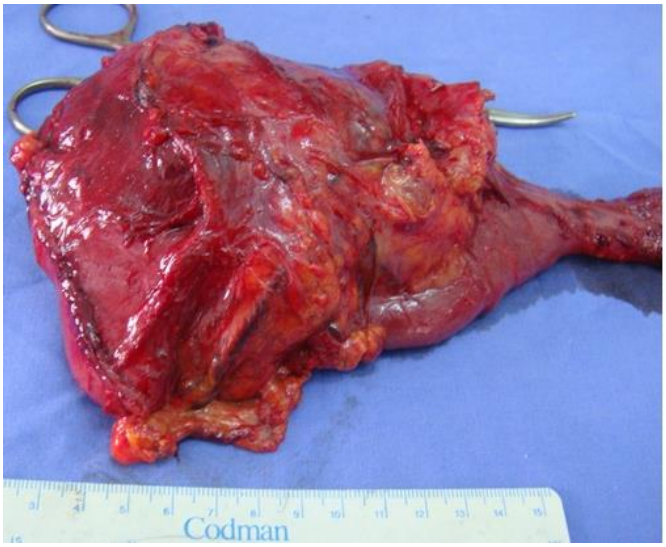

Fig. 2. Surgical specimen: antrum, duodenum, first jejunal loop, head of the pancreas presenting tumor mass and distal commone bile duct.

Gross examination of the surgical specimen revealed a 115/70 mm pancreatic mass, firm, relatively well-circumscribed, located in the cephalic zone with intraluminal extension into the dilated main pancreatic duct towards ampullary region; thus, the major duodenal papilla was still permeable. On cut section, the tumor appeared heterogeneous, with solid tan areas, low density brown-reddish areas and microcystic lesions.

Tissue samples were fixed in 10% formalin, embedded in paraffin blocks, sectioned at 4-µm thickness, and stained with Hematoxylin–eosin for light microscopy evaluation.

The pancreatic tissue samples presented a diffuse tumor proliferation composed mainly of large mononuclear pleomorphic cells, from round-ovoid to spindle-shaped, discohesive, with inconspicuous mitotic activity (1-2 mitosis/HPF), associated with numerous, diffusely spread multinucleated osteoclast-like giant cells, phagocitically active, and moderate desmoplastic stroma. The tumor growth patterns were pushing border, endoluminal/polypoid and infiltrative into the stroma (Figures 3-5). Areas of tumor necrosis and hemorrhage were also identified.

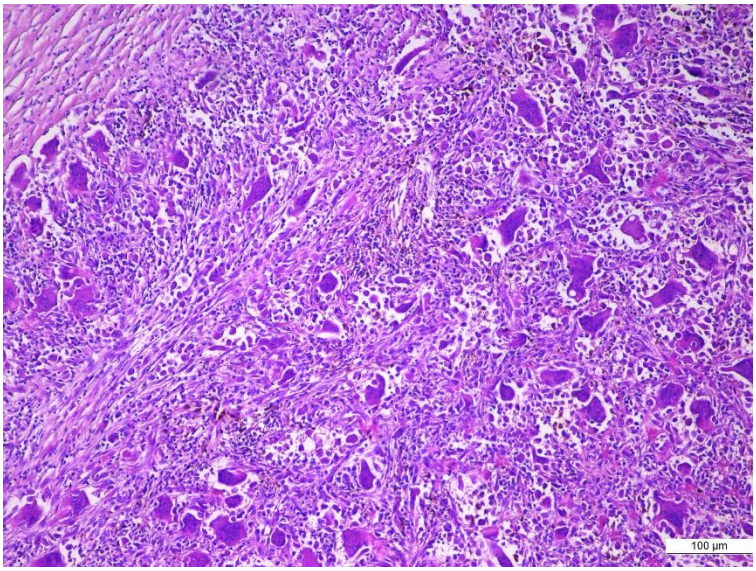

Fig. 3. UCOCG - solid area with 'pushing border' margin composed of pleomorphic mononuclear cells, ovoid or spindlle, and numerous diffusely spread large cells with eosinophilic cytoplasm and 5-20 centrally located blunt nuclei (HE, x100).

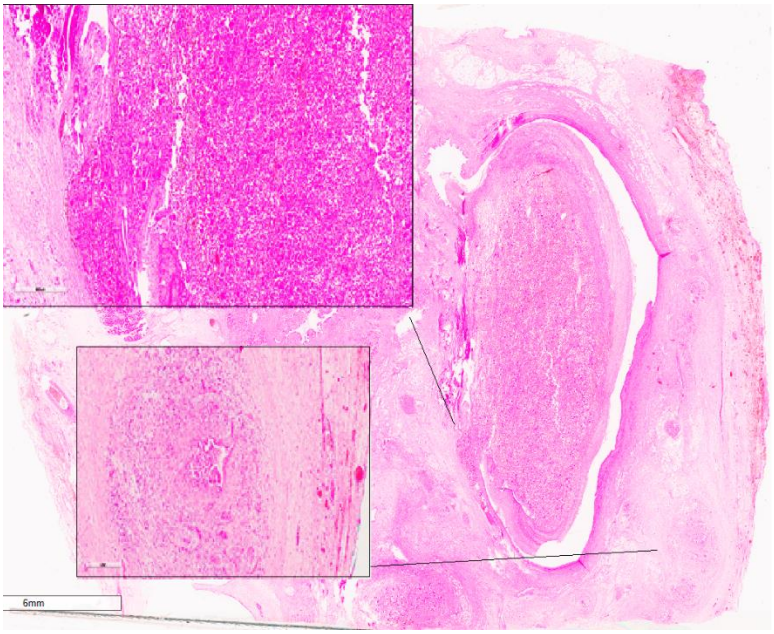

Fig. 4. Dilated pancreatic duct mostly covered with columnar epithelium and endoluminal tumor growth (HE, scanned specimen). *Large insert* - stratified ductal epithelium with citological atypia (at the polipoid tumor stalk) with a sudden morphology switch to UCOGC (pleomorhic mononuclear cells with abundant large multinucleated cells). *Small insert* - "Incomplete" duct asociated with micropapillary features mimicking giant cells (highly sugestive for invasive ductal carcinoma).

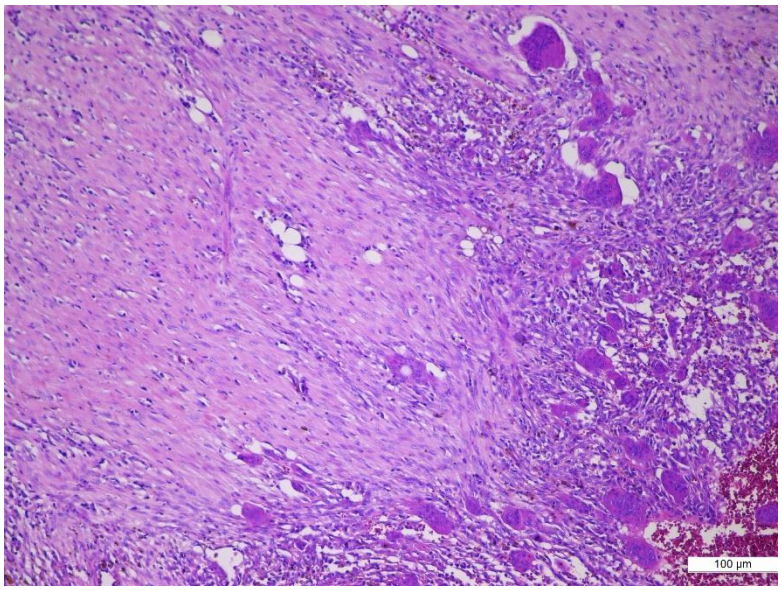

Fig. 5. Invasive front of UCOGC with desmoplastic stroma, small recent hemorrhagic area and entraped adipocites (HE, x100).

Areas of tumor necrosis and hemorrhage were also identified. The tumor proliferation originated into the main pancreatic duct and extended focally into the duodenal wall without muscular layer or gastric antrum involvement. The main pancreatic duct was dilated, focally with high grade dysplasia, associating foci of invasive ductal adenocarcinoma (Figure 6).

The adjacent pancreatic parenchyma presented pancreatic intraepithelial neoplasia (PanIN low-grade and high-grade) and chronic pancreatitis foci (Figure 7).

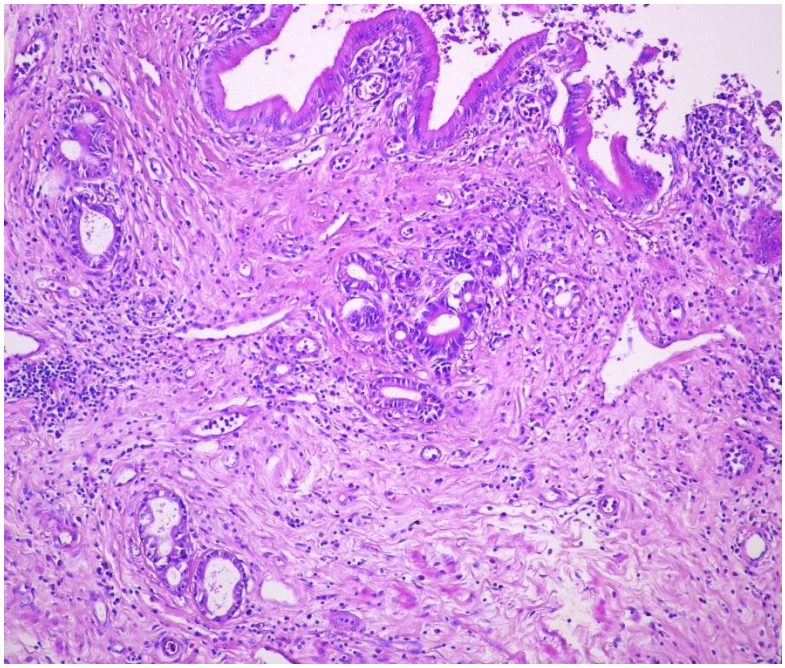

Fig. 6a. Main pancreatic duct with dysplastic epithelium and isolated duct-like structures with pleomorphic nuclei and mild desmoplastic response (ductal carcinoma foci) (HE, x100).

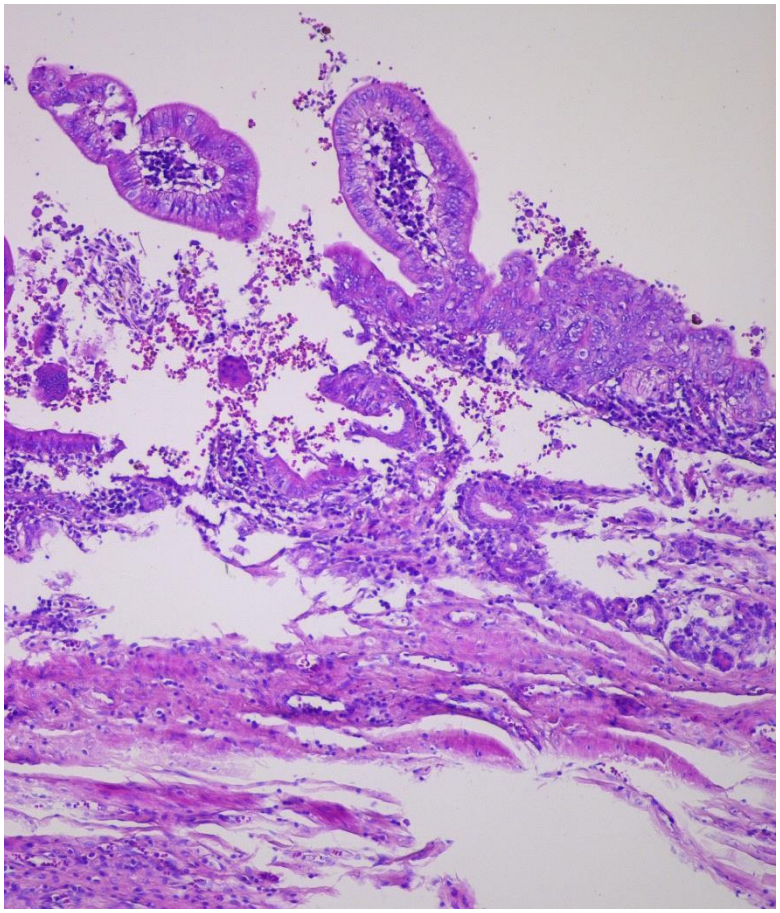

Fig. 6b. Main pancreatic duct towards apullary zone with high grade dysplasia (HE, x100).

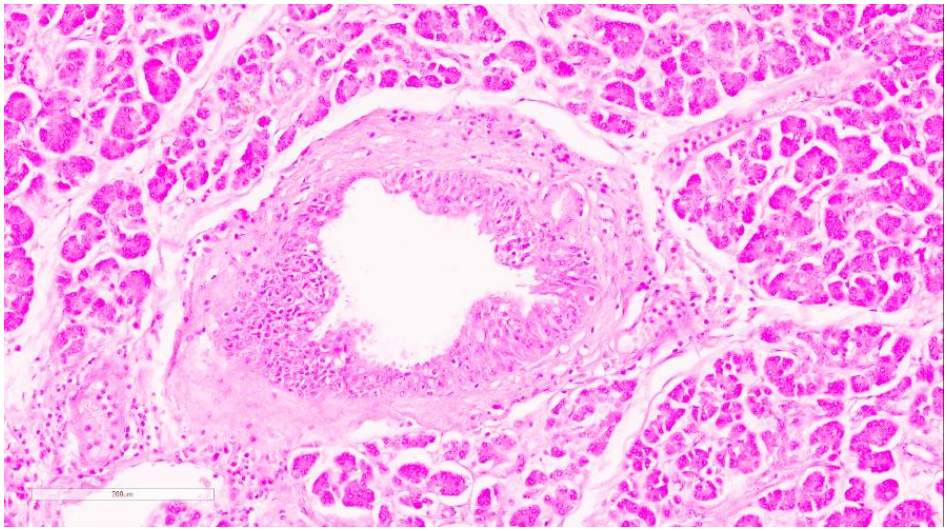

Fig. 7a. High grade PanIN *versus* immature squamos metaplasia (HE, scanned specimen).

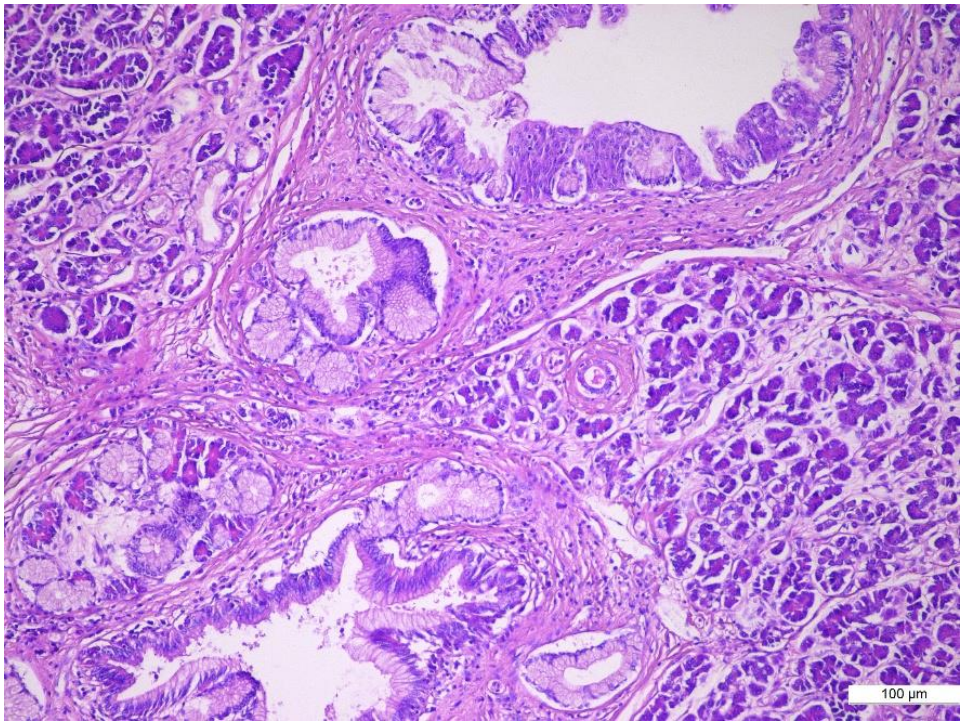

Fig. 7b. Small main pancreatic duct branches with low and high grade intraepithelial neoplasia (HE, x100).

The surgical resection margins and 16 lymph nodes were negative for tumor cells.

The histological aspects oriented towards an UCOGC associated with conventional pancreatic ductal carcinoma.

Further immunohistochemistry examination using monoclonal antibodies against cytokeratin (Dako, clone AE1/AE3, dilution 1:50), CD68 (Novocastra, clone 514H12, dilution 1:100) and Vimentin (Novocastra, clone V8, dilution 1:150) confirmed the diagnosis of UCOGC.

The multinucleated osteoclastic giant cells were strongly positive for CD68 and Vimentin, and negative for CK AE1/AE3, and the pleomorphic tumoral cells were positive for CK AE1/AE3 and Vimentin (Figures 8-10).

Due to favorable uneventful post-operatory evolution the patient was discharged on 9th day with the diagnosis of stage IIA UCOGC (pT3N0M0 LV0Pn0), associated with invasive conventional pancreatic ductal carcinoma (5%). Unfortunately, the patient died 4 months after surgery, without any documented recurrent or metastatic neoplastic process.

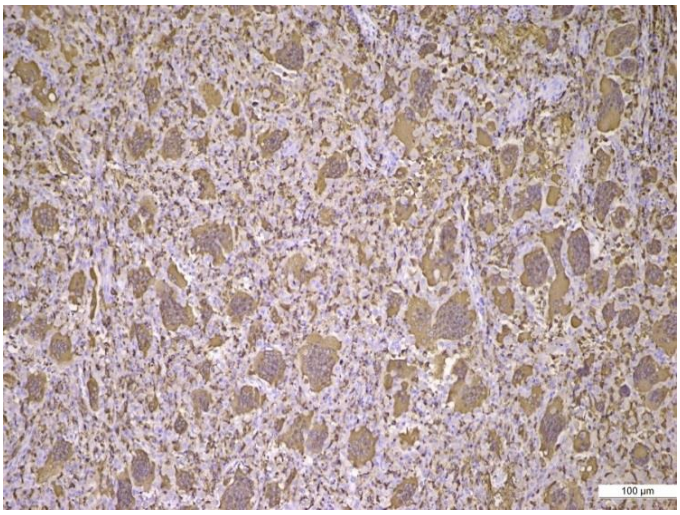

Fig. 8. CD 68 positive mononuclear inflamatory cells (hystiocyte) and large round benign-looking cells with centrally numerous nuclei (osteoclast-like giant cells) (IHC, anti-CD68, x100).

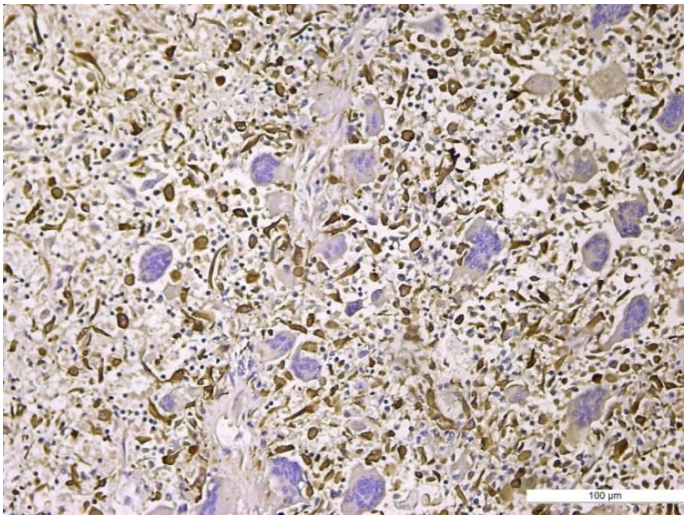

Fig. 9. CK AE1/AE3 positive on round-ovoid and spindlle mononuclear proliferation alongside negative multinucleated large cells with 5-15 nuclei centrally located (IHC, anti-CK AE1/AE3, x200).

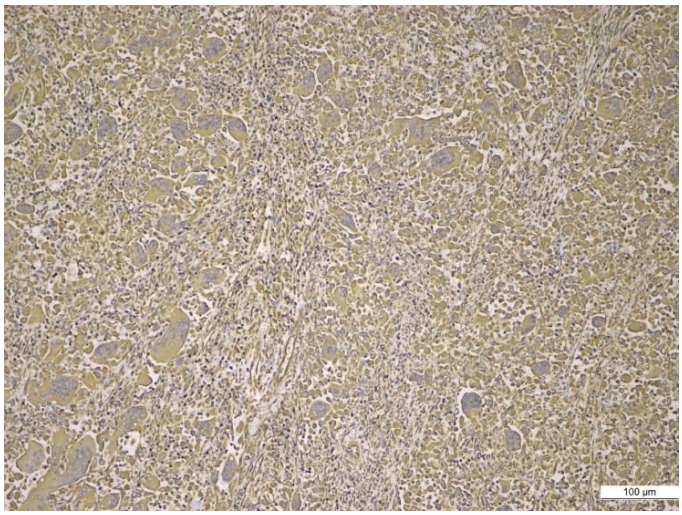

Fig. 10. Vimentin marking both mononuclear tumoral cells and non-tumoral multinucleated osteoclast-like giant cells (IHC, anti-vimentin, x100).

Discussions

WHO 2010 sets undifferentiated carcinoma with osteoclast-like giant cell and pleomorphic giant cell as a pancreatic ductal adenocarcinoma variant, although UCOGC is a tumor with a much better prognosis [16].

The awareness regarding UCOGC led to an increase of the number of published papers: from less than 50 cases between 1968 – 2011 [11] to over 150 nowadays, including several studies performed on larger groups that also associate ultrastructural, molecular and genetic data.

However, the lack of consensus concerning the histopathological assessment, clinical course or surgical management is due to the relative rarity of this type of tumor [8, 9]. One of the main issues regards the origin – the precise lineage of tumor components being a matter of debate. Three different hypotheses were formulated, sustaining either an epithelial origin, a mesenchymal origin or a common pluripotent progenitor which undergoes both epithelial and mesenchymal dedifferentiation [6, 17, 18]. Nowadays, the epithelial origin is the most widely accepted, based on the K-*ras* codon 12 mutation identified in the mononuclear tumor cells – that is one of the driver mutation also present in conventional pancreatic duct adenocarcinoma, and on the retained expression of epithelial markers (CK, EMA) – at least focally [19]. On the other hand, the vimentin expression in the mononuclear cells of this epithelial tumor sustains the epithelial-mesenchymal transition within the carcinogenic process [20]. However, the positive mesenchymal and epithelial markers could support the interconnection of these three theories.

Despite all this evidence, it is still unknown how the same genetic driver mutations and the same preneoplastic lesions as ductal carcinoma can lead to such different histological features. Most probably, the UCOGC pathogenic mechanism involves not only somatic mutations, but also other molecular events [8].

The common clinical presentation of UCOGC is nonspecific and includes symptoms such as upper abdominal pain, jaundice, anorexia, steatorrhea, weight loss, anemia, elevated CA 19-9, CEA and CRP levels [21, 22]. Unusual presentation includes diabetes exacerbation, melena, impaired liver function or fatigue.

Gross evaluation usually reveals a cystic tumor with solid component, with large areas of necrosis commonly confined to the head of the pancreas. This situation can be associated with dilated main pancreatic duct, especially if the polypoid endoluminal growth pattern is present. It appears that 60% of the cases have intracystic/ductal prominent growth. The described nodular pushing border could represent ducts filled in by the tumoral process [9, 11, 13].

Although the tumor grows rapidly - more than half of reported cases measuring over 10 cm at the time of the diagnosis, incidental small sized tumors or “in situ” lesion are documented [10, 15, 23, 24].

The gold standard in diagnosis consists in the identification of the two cell populations, the pathognomonic element being the benign-looking multinucleated giant cells associated with mononuclear pleomorphic tumor cells. The appearance of osteoclast-like giant cells, beside tumor mononuclear histiocyte-like cells, is considered as an early event in tumor progression [15]. The different pancreatic neoplastic components/patterns should be assessed as percentages [25]. Recent data underline the value of a preoperative diagnosis by using fine needle aspiration, that could be decisive in adequate therapy and prognostic stratification [10, 21, 26].

Differential diagnosis should always include all the pancreatic cystic lesions: mucinous cystic neoplasm, intraductal papillary mucinous neoplasm (IPMN), neuroendocrine tumors, pancreatic ductal adenocarcinoma, pseudocyst, due to the most frequently gross appearance of a mixed cystic-solid lesions. It should also include ductal carcinoma with micropapillary features, “groove” pancreatitis due to cells resembling osteoclast-like giant cells or gastrointestinal stromal tumors [9, 10, 12, 27].

Classically, UCOGC was considered a tumor with dismal prognosis, but recently published case series reporting long-term survivors has shown the opposite [2, 10, 28, 29]. Consequently, UCOGC can be

considered a “good” type of pancreatic cancer compared to conventional pancreatic ductal adenocarcinoma, with a 5-years survival of around 60%. The variability of survival results available in the mainstream, from 4 months to 7 years, could be explained by individual tumor biology, uneven pathological evaluation of such large tumors, differences in surgical protocol, histological heterogeneity of the tumor (see grading), or different protocols of chemotherapy or radiotherapy [9, 30].

The pure forms of UCOGC, even in locally advanced stages, have a better prognosis than the cases associated with ductal adenocarcinoma [10]. The recurrent tumor process in residual pancreatic tissue or the development of metastases were most frequently composed of conventional pancreatobiliary carcinoma [2, 28], followed by the spindle-shaped component [30], with or without osteoclast-like giant cells. Our case had undifferentiated carcinoma predominance, which represented around 95% of the tumor. Foci of ductal carcinoma (5%) were identified on careful examination. The importance of thorough extensive examination is relevant because of the likelihood of metastases or recurrences of the ductal component, regardless its dominant or focal appearance [2, 9, 26, 28].

The only treatment with curative intention remains the surgical resection [10, 22], similar to classic pancreatic cancer: duodeno-pancreatectomy for cephalic localization and splenopancreatectomy for body/tail localization [13]. The use of radio- or chemotherapy has been reported in sporadic cases using gemcitabine, 5-fluorouracil, paclitaxel but the small number of patients who received adjuvant therapy can not lead to safe conclusions [29-32].

The particularity of our case consists in capturing the morphological alteration sequence on a large cephalic UCOGC arising from the main pancreatic duct. This evidence complements previously reported data regarding the evident ductal involvement in UCOGC, but on smaller size tumors [15, 24, 33]. In our case, extensive sampling allowed us to identify various epithelial changes of the pancreatic ductal system. The main pancreatic duct was dilated and presented high grade dysplasia, but in the absence of a clear epithelial papillary proliferation we ruled out an IPMN. The increased dimensions of the main pancreatic duct could be explained by inflammation or partially obstructive endoluminal tumor. At some point, the epithelium of the main pancreatic duct clearly displayed cytological atypia and became stratified with a sudden shift to pleomorphic mononuclear round and spindle cells chaperoned by benign looking osteoclast giant cells. The focal atypical epithelial hyperplasia could be the result of both intraductal neoplasia and squamous metaplasia [33, 34], difficult to differentiate sometimes on H&E staining. Immunohistochemistry examination using CK 5/6 and Ki-67 has been pointed as useful [34], but unfortunately was not performed on our case. To the best of our knowledge, there are only three other cases of cephalic UCOGC reported surprising the similar sequence of histopathological changes [15, 24, 33].

We also noted, in the nearby smaller branches of main pancreatic duct, the presence of intraepithelial neoplasia, low- and high-grade. Ductal intraepithelial neoplasia was described in a large number of cases, in some of them in direct connection with the UCOGC [24, 35]. The most frequent preneoplastic lesion associated with UCOGC is mucinous cystic neoplasm (MCN), followed by IPMN and PanIN, with at least some foci of high-grade dysplasia [9, 12]. Beside the classic pattern described, we also identified small cystic structures in the pancreatic parenchyma with a rim of UCOGC, which could be the result of intraductal neoplasia spread replacing ductal epithelium, similar to “cancerization of ducts” described in classic ductal carcinoma [36]. Osteoid change, vascular emboli, perineural invasion, and/or lymph node metastasis – histological features frequently present in the ductal pancreatic adenocarcinoma [9], were not found in our case.

The different scoring systems lead to difficulty in establishing the prognosis. Our case was assessed as low grade tumor – grade I, with abundant large osteoclast giant cells and background cells with minimal atypia and scant mitoses, in accordance with the

histopathological grading based on the scoring system of Netherlands Committee on Bone Tumors [9], but also as grade 3 – poorly differentiated tumor by using the exocrine pancreatic carcinoma grading from WHO 2010 [16] and as grade 4 according to The American Joint Committee on Cancer staging manual 8th edition [37]. These inadvertences require further studies to decide the usefulness of one score *versus* another.

The main clinical and pathology features of UCOGC present in the mainstream are summarized in Table 1 and Table 2. The PubMed search was performed by using the key-words "anaplastic" and "pancreas" alongside "osteoclast-like giant cell" and "pancreas", due to the multiple synonyms for UCOGC. From a total of 321 articles, we eliminated all papers without English text available or describing tumors without osteoclast-like giant cells, and we obtained 61 items. These papers include 30 case reports with tail location, 17 case reports with cephalic location and 14 case series. Therefore, the rarity of this pathological entity, mainly at cephalic site, sustains the value of our paper.

The cephalic location overlaps with the general features of UCOGC described earlier, although we can identify a tendency to smaller lesions (10 cases under 5 cm). Early intraductal neoplasia with dysplastic epithelium and abrupt change of tumor phenotype was rarely registered. The intraductal growth included polypoid masses in the main pancreatic duct and branches or extruding through ampulla.

The review of the literature shows a significant number of cases (9 of 17) associated with ductal neoplasia, intraductal or invasive. From a "ductal variant" point of view, the split carcinogenic process of ductal carcinoma with PanIN origin in acinar cells and IPMN origin in ductal cells could also reflect in UCOGC carcinogenesis, explaining the heterogeneity and variability of tumor behavior. Moreover, the intraductal growth pattern which significantly overlaps with IPMN morphology could imply the IPMN-ductal/UCOGC tumoral transformation axis, although there are cases of IPMN coexisting with ductal carcinoma molecularly unrelated [38, 39]. The PanIN – ductal carcinoma sequence, presumed until recently as originating from ductal epithelium, has been recently stated as acinar – derived with achieved ductal features through acinar – ductal metaplasia [38], which can also be caused by inflammation [40]. A number of two cases associated documented pancreatitis prior to UCOGC diagnosis and one had high-grade PanIN. Muraki et al. also reported one patient with intraductal growth and personal history of pancreatic acute inflammation. On surgical resected specimen is difficult to evaluate pancreatitits without clinical evidence, mainly because of the peritumoral pancreatitis associated with large size.

The divergent survival data result from the combination, in the case series, of the pleomorphic giant cell type and osteoclast-like giant cell type, each of them with different clinical behavior and survival [16].

Conclusions

UCOGC is a rare ductal carcinoma variant with great heterogeneity which provide non-specific symptoms and in shaping morphological landscape, with histogenesis still under debate. Our case report confirms the ductal epithelial origin, pointing out the similar carcinogenic process with ductal carcinoma (through PanIN) and an abrupt shift to undifferentiated carcinoma phenotype. The molecular changes which determine the sudden transition remain to be discovered, further studies being necessary.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Competing interests

The authors declare that they have no competing interests.

Table 1. Cephalic UCOGC, single case reports

Author	Age Sex	Tumor size	Clinic presentation	Gross aspects	Preneoplastic pancreatic lesions	Other invasive carcinoma associated	Relapse/ Survival	Adjuvant therapy	Other mentions
1. Mullick et al., 1996 [41]	83 F	10 cm	Weight loss, low hemoglobin, normal CA 19-9	Solid	NM	UCPGC	NM	NM	History of breast carcinoma, ductal and lobular (6 years ago)
2. Carvounis et al., 2003 [42]	70 F	7 cm	Obstructive unpainful jaundice, normal CA 19-9	Cystic-solid dilated CBD	NM	No	Relapse 9 months	No	Negative lymphnodes
3. Loya et al., 2004 [43]	50 M	7 cm	Jaundice, abdominal pain elevated CA 19-9	Solid-cystic	NM	DC UCPGC	NM	Gemcitabine	
4. Nai et al., 2005 [44]	69 M	4.7 cm	Weight loss	Solid Dilated MPD	NM	Mucus secreting conventional adenocarcinoma (including single cell)	Relapse 6 months (multiple liver metastases) Survival 1 year	NM	Positive lymphnode for UCOGC Osteoid
5. Tezuka et al., 2006 [24]	68 F	4.2 cm	Abdominal pain	Polypoid intraductal tumor Dilated MPD	NM	Focal peripheral glandular pattern	No relapse (surveillance 22 months)	NM	Non invasion tumor
6. Bergmann et al., 2007 [15]	45 F	0.8 cm	Abdominal pain, fatty stools, elevated CRP, normal CA 19-9	Cystic Dilated MPD	HG and LG PanIN	No	NM	NM	Diabetes mellitus type 2 History of thyroid papillary carcinoma (1 year)
7. Koorstra et al., 2008 [45]	39 M	3 cm	NM	Partial cystic ampullary tumor	HG and LG PanIN	No	NM	NM	History of alcoholic pancreatitis P16 Leiden mutation (FAMMM syndrome)
8. Manduch et al., 2009 [46]	66 M	9.5 cm	Wight loss, painless jaundice, melena stool	Ulcerated ampulla with pancreatic solid tumor Dilated CBD	NM	No	Relapse 6 months (lymphnode and liver metastases Survival 1 year)	No	Osteochondroid differentiation (1 cm)
9. Mannan et al., 2010 [47]	40 F	4 cm	Progressive jaundice, elevated serum bilirubin	NM	NM	UCPGC	NM	NM	
10. Maksimov et al., 2011 [33]	68 F	2.5 cm pedunculated mass 3 cm cystic	Painless jaundice, elevate bilirubin and transaminases	Dilated MPD and CBD Cystic uncinate process and polypoid deforming ampulla	HG and LG PanIN	Intratumoral conventional DC (polypoid mass)	No relapse (surveillance 36 months)	NM	Personal history of type 2 diabetes mellitus K-*ras* mutation present
11. Kobayashi et al., 2014 [28]	39 F	4 cm	Epigastralgia, elevated levels of serum amylase and CA 19-9	Cystic-solid MPD with elliptical filling defect	NM	Conventional DC	After 4 years intra-pancreatic metastases with DC component Overall survival – more than 5 years	Gemcitabine after first surgery	
12. Fujii et al., 2016 [3]	68 F	1.9 cm	Fatigue Impaired liver function	Cystic-solid Dilated MPD and CBD	Main and brunch duct HG IPMN intestinal type	No	No (surveillance period 18 months)	S-1	UCOGC with origin in IPMN epithelium
13. Georgiou et al., 2016 [5]	75 F	9 cm	Abdominal pain, fatty stools, weight loss,	Cystic-solid MPD dilated,	NM	DC	Died after 10 months Local recurrence after 6	No	Personal history of acute idiopathic pancreatitis (3 years before)

			elevate CA 19-9	normal CBD			months		CHA invaded
14. Fujimoto et al., 2018 [23]	70 F	Initially 2.2 cm After 11 months 18 cm	Diabetes exacerbation	NM	NM	NM	Died after 12 months	Oral administration of TS-1 (tegafur /gimeracil/ oteracil)	Original diagnosis made after EUS-FNA, unresectable tumor
15. Guo et al., 2018 [13]	65 M	5.8 cm	Weight loss	Cystic-solid Dilated MPD	NM	NM	NO (surveillance period 10 months)	NO	Personal history of diabetes
16. Oka et al., 2018 [48]	72 F	2.5 cm	Elevated serum amylase and CA 19-9	Cystic, not connected to dilated MPD	NM	NM	NO (surveillance period 6 months)	oral tegafur /gimeracil/ oteracil (S-1)	
17. Yepuri et al., 2018 [49]	78 M	2.1 cm	Fatigue, weight loss, abdominal pain	Solid mass	NM	UCPGC	NO (surveillance period 3 years)	NM	Personal history of prostatic cancer and large mantle cell lymphoma

Table 2. UCOGC, case series

Author	Number of reported UCOGC cases	Cephalic localization	Age/Sex	Survival	Gross aspects	Preneoplastic lesion	Other invasive carcinoma associated	Other aspects
1. Alguacil-Garcia et al., 1977 [2]	2	1	NM	NM	Cystic-solid	NM	DC	
2. Deckard-Janatpour et al., 1998 [50]	11	NM	NM	NM	NM	NM	9 cases UCPGC	UCOGC 2 long term survivors
3. Hoorens et al., 1998 [51]	2	2	57/M 44/F	Male patient autopsy discovered tumor	Mean size= 6 cm	NM	DC (both cases)	Same Ki-*ras* codon 12 mutation identified in both UC and DC components
4. Molberg et al., 1998 [52]	9	NM	NM	8 succumbed in under 1 year	Partially or completely cystic Average 9 cm	MCN 2 cases (origin point)	DC 4 cases	Osteoid/bone – 3 cases Chondroid – 1 case 1 case - 14 years survivor
5. Chopra et al., 2007 [53]	2	2	89/M 64/F	NM	2 cm 3.1 cm	No	No	Osteoid – 1 case EUS-FNA diagnosis
6. Layfield et al., 2008 [54]	6	1	59/M	NM	NM	NM	NM	EUS-FNA diagnosis
7. Naito et al., 2009 [55]	7	3	51/F 76/F 46/F	12 months 19 months 15 months	Cystic -7 cm Solid - 1.8 cm Solid - 1.7 cm	NM	NM	2 cases extraductal compression and 1 case intraductal growth pattern (MPD)
8. Nojima et al., 1993 [56]	2	2	70/M 72/M	No evidence of disease (surveillance 32 months) Second case died after 8 month	Solid Case 1 – 6.5 cm Case 2 – 5 cm	NM	DC and UCPGC both cases	Case 2 – positive lymphnodes, liver metastases after 8 months with UC component
10. Sakai et al., 2000 [57]	3	2	49/M 51/M	NM	2 cm 3.8 cm	NM	Well differentiated DC both cases	No OGC harbor mutated K-*ras* found in PGC, DC and mononuclear tumor cells

11. Muraki et al., 2016 [9]	38	61.1%	Mean age=57.9 22 cases F	59.1%/5years	Mean size=5.3 cm 60% cystic 33% intraductal growth	4 cases arose from MCN 4 cases associated with IPMN 18 cases with PanIN	76% associated with DC	PanIN and OGC were often intermingled
12. Reid et al., 2017 [26]	14	7	4F 3M Mean age=63 (range from 43 to 75 years)	From 1.7 to 21.18 months	Cystic/solid Mean size=4.96 cm (range from 2 cm to 9 cm)	No	5 cases DC 1 pure UCOGC 1 case NM	EUS-FNA diagnosed, 6 cases underwent surgery
13. Luchini et al., 2017 [8]	22	NM 17 cases Whipple procedure	12 F 10M	OS = 20 months Pure UCOGC median survival = 36 months	NM Intraductal growth in 12 cases	2 HG MCN 1 HG IPMN 15 PanIN (12 HG and 3 LG)	13 cases DC	8 cases WES
14. Fukukura et al., 2019 [58]	7	4	3M 4F Mean age = 71.1 (range from 59 to 82 years)	NM	Solid 1 case cystic Maximum diameter between 2.6 – 8.3 cm (mean = 4.4 cm)	NM	No	CT and MRI study with histopathology confirmation

Abbreviations: F-female; M-male; NM-not mentioned; DC-ductal carcinoma; UCPGC-undifferentiated carcinoma with pleomorphic giant cells; MPD-main pancreatic duct; CBD-common bile duct; CT-computer tomography; MRI-magnetic resonance imaging; OS-overall survival; WES-whole exome sequencing; EUS-FNA-endoscopic ultrasound fine needle aspiration; IPMN-intraductal papillary mucinous neoplasm; PanIN-pancreatic intraepithelial neoplasia; HG-high grade; LG-low grade; CHA-common hepatic artery

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