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Osteoclast-type giant cell tumour of the pancreas

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Summary. Two cases of osteoclast-type giant cell tumour of the pancreas (OGTP) are presented and compared with similar tumours of other locations and pancreatic carcinomas. One of the tumours was analyzed by immunohistochemical methods. The mononuclear stromal cells and osteoclast-like giant cells, which characterize this very rare neoplasm, reacted with an antibody against vimentin, but were not decorated by antibodies against lysozyme, alpha-1-ACHT, alpha-1-AT. Pleomorphic mononuclear cells in osteoid additionally contained osteonectin and could thus be identified as osteoblasts. Only the tumour glands stained positively with panepithelial keratin antibodies and antibodies against the keratin polypeptides 7, 18, 19. These results demonstrate for the first time the mesenchymal differentiation of the OGTP, which in some cases is also able to form epithelial structures. The immunohistochemical reactions and the characteristic morphology of the tumour show the OGTP to be an entity which must be differentiated from pancreatic carcinoma, especially from its giant cellular subtype.

Key words: Pancreatic osteoclast-type giant cell tumour – Differentiation – Histogenesis – Immunohistochemistry

Introduction

OGTP is an extraordinaryly rare neoplasm which in most cases cannot be distinguished histologically from giant cell tumour of bone. Similar tumours have been observed in many other locations, including the breast, thyroid, lung, liver, skin, heart, ovary, parotid gland and soft tissues (reviewed in Berendt et al. 1987). OGTP is known under several synonyms, such as multinuclear giant cell neoplasm (Robinson et al. 1977), osteoclastoid type of giant cell carcinoma (Cubilla and Fitzgerald 1984), "osteoclastoma" of pancreas (Trepeta et al. 1981), demonstrating that its origin is far from settled. So far, the OGTP is usually subsumend into the pancreatic carcinomas (Klöppel et al. 1982; Cubilla and Fitzegerald 1984). Nevertheless, the immunohistochemical findings in a case of our own favour a mesenchymal derivation. This stimulated us to discuss the histogenesis of this neoplasm in context with the literature on OGTP and similar tumours of other locations.

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Material and methods

One tumour was obtained during surgery. One part was fixed in formaldehyde, the other was frozen in liquid nitrogen and stored at −70° C. From the second tumour slices of formaldehyde-fixed biopsy and autopsy material were available. Both tumours were stained with haematoxylin and eosin (H & E), PAS, and Goldner's connective tissue stain.

The immunohistological reactions were detected either with the avidin – biotin (ABC) method (Hsu et al. 1981), the peroxidase-anti-peroxidase (PAP) method (Sternberger 1979), or the alkaline phosphatase – anti-alkaline phosphatase (standard APAAP) method (Stein et al. 1985). The following mouse monoclonal antibodies were used (Table 1): KL-1, a broad-specificity keratin antibody raised against keratin polypeptides of 55–57000 daltons (Viac et al. 1983) (Dianova, Hamburg, FRG); lu-5, a broad specificity keratin antibody (von Overbeck et al. 1985) obtained from Dr. C. Staehli, Central Research Division, Hoffmann La Roche, Basle, Switzerland; CK-7, an antibody specific for keratin polypeptide 7 (Toelle et al. 1985) (Amersham International; Boehringer GmbH, Mannheim, FRG), CK-2, an antibody specific for keratin polypeptide 18 (Debus et al. 1984); KA-4, an antibody with high specificity for keratin polypeptide 19 and a less strong reactivity with the keratin polypeptides 14, 15, 16 (Nagle et al. 1985); this antibody was a gift from Dr. R. Nagle, University of Arizona); BW 431/31, an antibody specific for CEA and not crossreacting with NCA 55 and NCA 95 (Bosslet et al. 1985); this antibody was a gift from Dr. K. Bosslet, Behring Werke, Marburg, FRG;

Table 1. Immunohistochemical reactions of osteoclast-type giant cell tumour of pancreas

Primary antibody	Antigen specificity	Methods	Multinuclear giant cells	Mononuclear stromal cells	Osteoblasts	Epithelial cells
KL 1	For most keratin polypeptides (KP)	1, 3	–	–	–	+
lu-5	For most KP	1	–	–	–	+
CK-7	KP 7	1	–	–	–	+
CK-2	KP 18	1	–	–	–	+
KA-4	KP 19 (14, 18)	1	–	–	–	+
BW 431/31	CEA	1	–	–	–	–
V 9	Vimentin	1, 3	+	+	+	–
DE-R-11	Desmin	1	–	–	–	–
Anti-human osteonectin	Human osteonectin	2	–	*	+	–
Rabbit antiα1-antitrypsin	α1-antitrypsin	2	–	–	–	–
Rabbit antiα1-antichymotrypsin	α1-antichymotrypsin	2	–	–	–	–
Rabbit anti-lysozyme	Lysozyme	2	–	–	–	–
Rabbit antihuman S-100	S-100 protein	2	–	–	–	–

1: Monoclonal primary antibody, frozen section, ABC-method
2: Polyclonal primary antibody, formaldehyde fixation, PAP-method
3: Monoclonal primary antibody, formaldehyde fixation, APAAP-method

* Some mononuclear stromal cells near osteoid-containing areas react with anti-human osteonectin

V9, an antibody specific for vimentin (Osborn et al. 1984), and DE-R-11, an antibody specific for desmin (Debus et al. 1983). Monoclonal antibodies were used as hybridoma supernatants, with the exception of KA-4, which was used as a 1:300 dilution of ascites fluid. The following polyclonal primary antibodies were used: anti-human osteonectin (a gift from Dr. J.D. Termine, National Institute of Health, Bethesda, USA); alpha-1-antitrypsin (DAKO, Hamburg, FRG), alpha-1-antichymotrypsin (DAKO, Hamburg, FRG), and lysozyme (DAKO, Hamburg, FRG).

Case reports

The first case was of a 73-year-old woman who was admitted to hospital with a palpable mass under the xiphoid cartilage. She felt weak, was in a poor nutritional state and suffered from epigastric colic. Sonography and abdominal CT showed a tumour mass with cystic cavities, measuring 8 × 10 cm in the body and tail of the pancreas. The tumour displaced the stomach and seemed to be delimited sharply from the other abdominal structures. The chest roentgenogram failed to reveal any metastatic spread. At laparotomy, inoperable fleshy masses arising from the pancreas were found, which grew continuously into the stomach wall and peritoneum. On palpation blood and necroses were discharged from the tumour. No further therapeutic efforts were made, and the patient died two months later.

The second case was a 62-year-old man who was hospitalized for painless jaundice which had been present for 4 weeks. The blood sedimentation rate was 107 mm in the first hour. Laparotomy disclosed a tumour near the papilla of Vater measuring 4 × 4 cm, from which biopsies were taken. An uncontrollable coagulation disturbance developed postoperatively. The patient died of delayed shock 4 days after the surgical intervention. The autopsy revealed residues of the neoplasm in the head of the pancreas. Lymph node metastases or hematogeneous tumour spread were not detected.

Results

On light microscopy both tumours are composed of spindle-shaped or pleomorphic mononuclear stromal cells and numerous multinuclear osteoclast-like giant cells (Fig. 1a, c). The stromal cells contain a faintly eosinophilic cytoplasm and a polygonal, more or less polymorphic nucleolus. Most nuclei show a distinct nuclear membrane and an enlarged central nucleolus. The mitotic rate is up to 6/HPF, including atypical mitotic figures. The giant cells contain up to 60 nuclei, which resemble the nuclei of less polymorphic stromal cells. However they never show mitotic figures. The giant cells and stromal cells are lying in close apposition. Some mononuclear cells seem to be enclosed by giant cells.

Osteoid areas are another feature in case 1, including medium-sized, polymorphic, mononuclear cells with abundant mitoses and some atypical mitotic figures (Fig. 1b). The other neoplasm shows no osteoid formation.

Connective tissue staining discloses only a small amount of collagen. The tumours are vascularized by cavernous or sinusoidal blood spaces

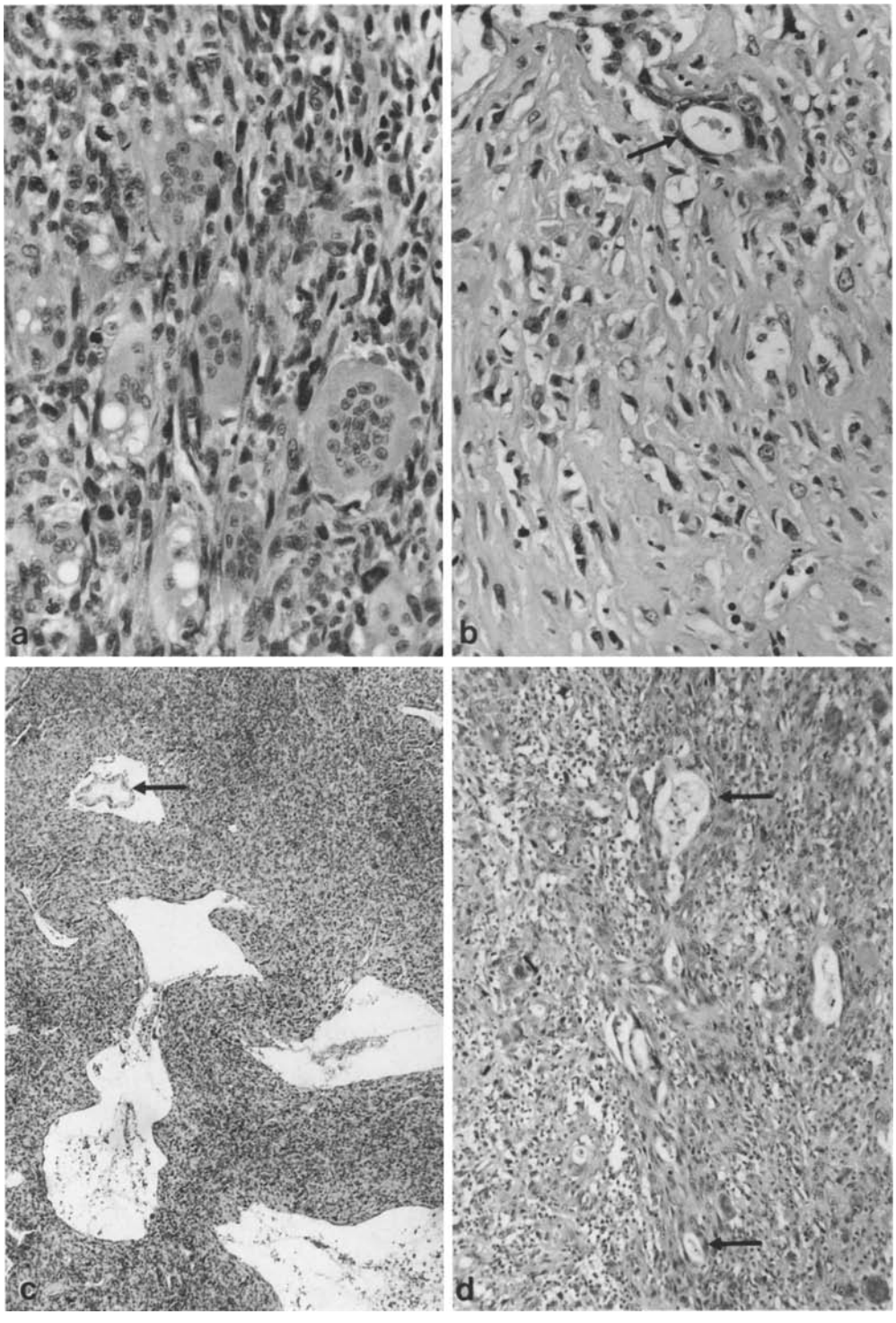

Fig. 1. Osteoclast-type giant cell tumour of pancreas, histological features: **a** Mononuclear stroma cells and numerous multinuclear giant cells (H & E, ×160); **b** Osteoid formations with pleomorphic and spindle-shaped cells and a small tumour gland (*arrow*) (H & E, ×160); **c** Sarcomatous tumour tissue with cavernous blood lacunae and a small tumour gland distinctly delimited from the stroma (*arrow*) (H & E ×25.6); **d** Tumour glands with a continuous transition of epithelial cells to sourrounding spindle-shaped stromal cells (*arrows*) (HE, ×64) (Fig. 1a–c: case 1; Fig. 1d: case 2)

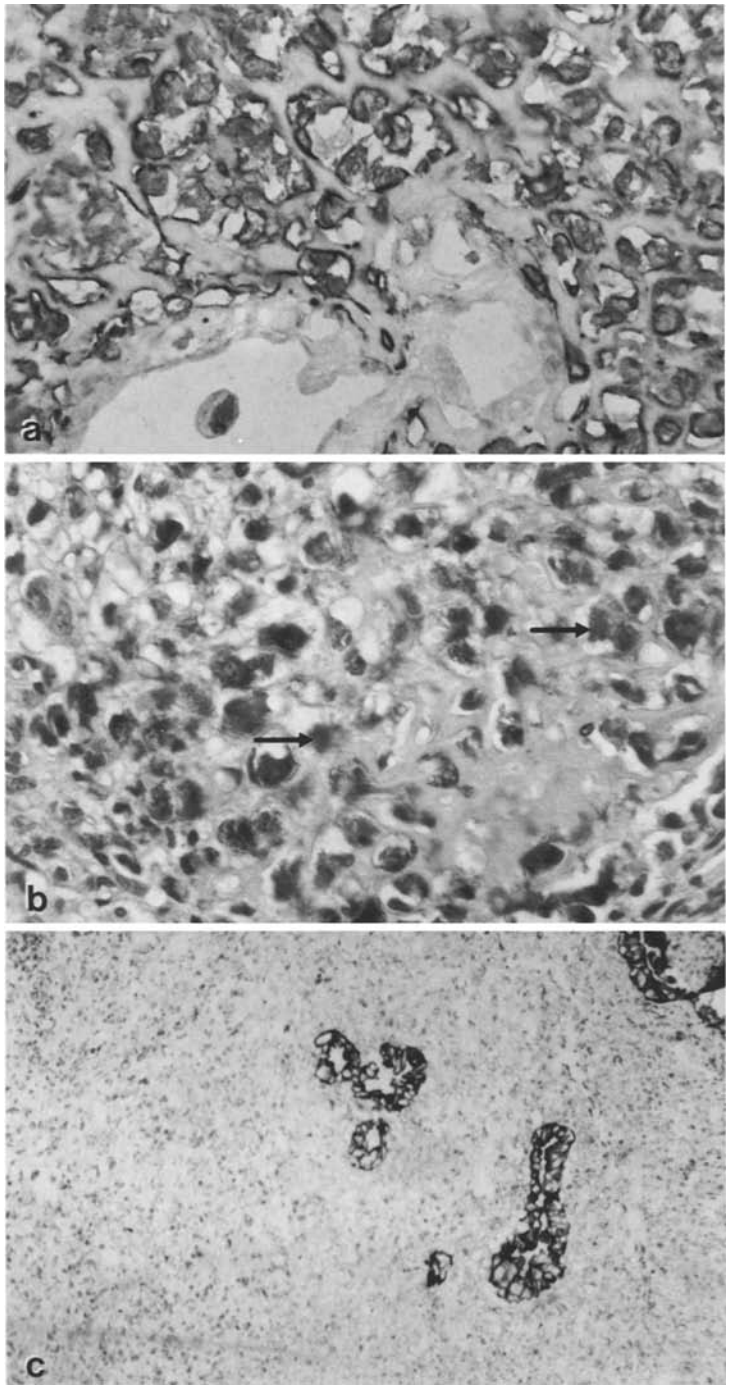

Fig. 2. Osteoclast-type giant cell tumour of pancreas, immunohistochemical features: **a** The sarcomatous tumour tissue and the multinuclear giant cells are marked with the vimentin antibody V 9, the epithelial cells of the tumour glands remain unstained, however (ABC, cryostat section, × 256); **b** The pleomorphic osteoid-forming cells react strongly with a human osteonectin antibody (*arrows*) (PAP and nuclear counterstain, formaldehyde fixation, × 256); **c** Only the tumour glands are marked by the keratin antibody lu-5 (ABC, cryostat section, × 64)

sourrounded by an endothelial layer and stromal cells (Fig. 1 c).

Both tumours show scanty glands and small solid epithelial nests. The glands are lined by cuboid or cylindric, PAS-negative cells with moderate nuclear pleomorphy. In case 1 the glands are delimited sharply from the stroma (Figs. 1 b, c, 2 a, c). The other tumour shows continuous transitions from epithelial to spindle-shaped stromal cells (Fig. 1 d).

Table 2. Osteoclast-type giant cell tumour of the pancreas: review of age, histologic differentiation, metastatic spread and follow-up

Reference	Age (years)	Sex	Adenoid differentiation	Osteoid	Haematogenous metastases	Lymph node metastases	Follow-up (months)
1 Rosai 1968	82	f	–	–	–	+	4
2 Rosai 1968	74	f	–	–	–	–	10
3 Freund 1973	32	f	–	–	–	–	+17
4 Alaguacil-Garcia and Weiland 1977	48	m	–	–	–	–	15 years
5 Alaguacil-Garcia and Weiland 1977	93	f	–	+	unknown	unknown	+10
6 Robinson et al. 1977	63	m	–	–	Lung	–	5
7 Posen et al. 1980	45	f	+	–	unknown	unknown	?
8 Trepeta et al. 1981	68	m	+	–	Lung, liver	+	+7
9 Jeffrey et al. 1983	55	m	–	–	Liver	+	+3
10 Cubilla and Fitzgerald 1984	45	m	+	+	Lung	–	+4 years
11 Berendt et al. 1987	55	f	–	–	–	–	+4
12 Fischer et al. (this paper)	74	f	+	+	–	–	+4
13 Fischer et al. (this paper)	62	m	+	–	–	–	+1

+ death

The mononuclear stromal cells, the cells in the osteoid formations and the giant cells are marked strongly with the vimentin-specific antibody V9 (Fig. 2a, Table 1) but show no reaction with any of the keratin antibodies, nor with the CEA-antibody BW 431/31. Neither the histiocytic markers alpha-1-antitrypsin, alpha-1-antichymotrypsin, lysozyme nor the antibodies against S-100 protein and desmin decorate these tumour cells. The osteoblastic nature of the mononuclear cells in the osteoid formations is demonstrated by their strong reaction with anti-osteonectin (Fig. 2b).

Only the tumour glands, solid epithelial nests, and some scattered single tumour cells react with the panepithelial keratin antibodies KL-1 and lu-5 (Fig. 2c) and with the antibodies CK-7, CK-2 and KA 4 specific for the keratin polypeptides 7, 18 and 19. The epithelial cells are not marked by the CEA-antibody BW 431/31. No coexpression of keratin antibodies and the vimentin antibody V-9 is detected.

Discussion

Both our tumours fulfill the morphological criteria of an OGTP whose stromal elements are identical with giant cell tumour of bone by light microscopy.

Since the first description (Rosai 1968), 13 cases of OGTP, including our own, have been published. Five tumours contained areas with an adenoid differentiation, 3 neoplasms showed osteoid formations. The histological differentiation, the epidemiological data and the metastatic spread of these tumours are summarized in Table 2. Considering that 7 of 11 patients died within one year after the onset of symptoms, the prognosis of OGTP is poor.

The pleomorphic giant cell carcinoma of the pancreas must, above all, be distinguished from OGTP. Pancreatic giant cell carcinoma is characterized by bizarre cells and nuclei, a sarcomatoid pattern and abortive adenoid differentiation (Cubilla and Fitzgerald 1984). The giant cells of these tumours contain only a few very pleomorphic nuclei in contrast to OGTP.

From the onset the peculiar histology of OGTP has stimulated the discussion about its orign. Most authors presume an epithelial derivation of these neoplasms. Adenoid differentiation in some tumours and the ultrastructural identification of microvilli (Rosai 1968), filopodia, and desmosome-like junctions on the mononuclear cells and the multinuclear giant cells (Rosai 1968; Robinson et al. 1977; Trepeta et al. 1981; Berendt et al. 1987) have seemed to prove this hypothesis. However, these ultrastructural features have also been demonstrated in some mesenchymal tumours, including giant cell tumour of bone (Guillan and McMahon 1973; Eusebi et al. 1984).

The immunohistochemical findings in one of our cases are not consistent with the assumption of a predominantly epithelial differentiation of OGTP. Only the tumour glands of our OGTP were marked with the panepithelial monoclonal keratin antibodies lu-5 and KL-1 and with the monoclonal antibodies CK-7, CK-2 and KA-4 specific for the keratin polypeptides 7, 18, and 19. This pattern of keratin polypeptides characterizes epithelial cells of many organs with adenoid differentiation and the carcinomas arising from them, e.g. ductal pancreatic carcinomas (Osborn et al. 1986). In contrast, pancreatic acini merely contain the keratin polypeptides 8 and 18 (Osborn et al. 1986). The spindle-shaped and pleomorphic cells as well as

the multinuclear giant cells showed no reaction with any of the tested keratin antibodies. These findings correspond to the immunohistochemical reactions in two osteoclast-type giant cell tumours of the parotid gland (Eusebi et al. 1984; Balogh et al. 1985), and one of the liver (Andreola et al. 1985). Berendt et al. (1987), however, described keratin-positive mononuclear and multinuclear cells in the first OGTP that was investigated immunohistochemically. We believe that this immunohistochemical reaction of the polyclonal DAKO keratin antibody with formaldehyde-fixed material might have been non-specific. It would be interesting to repeat the staining with a new keratin antibody, such as KL-1. In our case, only the vimentin antibody stained the spindle shaped cells and giant cells and thus demonstrated their mesenchymal differentiation (Osborn et al. 1984). Coexpression of vimentin and keratin antibodies could not be detected; this is in agreement with the light microscopic finding of a distinct delimitation of epithelial structures from sarcomatous stroma. Scattered single cells strongly marked with various keratin antibodies and surrounded by a keratin-negative stroma demonstrate that the epithelial transformation of this tumour seems to be a sudden phenomenon without detectable transitions. Coexpression of epithelial and mesenchymal markers might possibly be found in tumours with continuous histological transitions from mesenchymal to epithelial tissue components, as in our second case.

In the mesenchymal parts of the tumour, three different types of cells could be distinguished. Most mononuclear cells surrounded by osteoid contained osteonectin, a non-collagenous protein of bone matrix which characterizes osteoblasts (Termine et al. 1981; Jundt et al. 1987). The considerable nuclear pleomorphism and high mitotic rate of these osteoblasts suggest an osteosarcomatous differentiation of these parts of the OGTP. The second mononuclear type of cells was osteonectin-negative and showed a sarcomatous growth pattern. These cells, together with the third type of cells, the multinuclear giant cells, characterize the morphological pattern of OGTP, which is indistinguishable from giant cell tumour of bone by light microscopy.

The origin of these giant cells is still unclear. Some authors have suggested that the cells might be non-neoplastic, reactive cells of the macrophage system because mitoses are never found in them, and because nuclear atypia is absent or much less marked than in the mononuclear tumor cells (Cubilla and Fitzgerald 1984). Immunohistochemical findings contradict this assumption. The giant cells react neither with markers for histiocytes/macrophages (alpha-1-antitrypsin, alpha-1-antichymotrypsin, lysozyme) (Alguacil-Garcia et al. 1984; Eusebi et al. 1984; Balogh et al. 1985; Berendt et al. 1987; our own case) nor with markers for myelocytic/monocytic cells (Leu-M 1, Leu-M 3) (Balogh et al. 1985), but they contain vimentin, which characterizes mesenchymal cells. Thus it seems more likely that the giant cells originate from mononuclear mesenchymal tumour cells by fusion, analogous to giant cell tumour of bone (Schulz 1980; Schajowicz 1981). This cytogenesis is supported by ultrastructural similarities of polygonal mononuclear cells and giant cells (Robinson et al. 1977). Thus giant cells seem to be differentiated "end cells" of the tumour without proliferation capacity.

For the first time we demonstrate the predominantly mesenchymal differentiation of a typical OGTP. In the light of these results, this tumour, whose special morphology corresponds to OGT of other locations, has to be classified as an entity which must be distinguished from pancreatic carcinomas and their variants.

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