Case Report

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Osteoclast-Like Giant Cell Tumor of the Pancreas Associated with Mucus-Secreting Adenocarcinoma

Case Report and Discussion of the Histogenesis

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Key Words
Giant cell · Osteoclast-like · Adenocarcinoma · Pancreatic tumor · Immunohistochemistry · Histogenesis

Abstract
Background/Aims: The osteoclast-like giant cell tumor of the pancreas is a rare entity that closely resembles giant cell tumor of the bone, which has also been observed in many other organs. Some tumors also contain areas of ductal adenocarcinoma. Conflicting opinions exist regarding the tumor origin, whether it is mesenchymal or epithelial, neoplastic or reactive. ***Methods:*** We report the case of a 69-year-old Brazilian man with a mass in the head of the pancreas, the histological examination of which revealed a predominant component of osteoclast-like giant cells within a background of pleomorphic mononuclear cells with osteoid formation and other areas composed of conventional mucus-secreting adenocarcinoma. ***Results:*** Immunohistochemistry showed that carcinoma cells of the usual type expressed epithelial antigens (EMA and cytokeratin) and lysozyme; the giant cells expressed vimentin, CD45, CD68, and lysozyme; and the mononuclear cells expressed macrophage marker (HAM56), vimentin, and lysozyme, and only some of them expressed epithelial markers, CD45, and CD68. ***Conclusion:*** Our immunohistochemical findings reveal that the giant cells in this case are of mesenchymal origin may be from the bone marrow cells. We believe that it is important to determine the histogenesis in each case to carry out the pertinent adjuvant therapy.

Introduction

Osteoclast-like giant cell tumor of the pancreas (OGTP) is a rare entity first described by Rosai [1], and characterized by osteoclast-like giant cells and mononuclear stromal cells identical to those seen in giant cell tumor of the bone. It has also been observed in many other organs.

When the tumor affects the pancreas, the average patient age is around 60 years, although the age might range from 32 to 82 years, with women being more frequently affected than men (12:8) [2]. The main symptoms are abdominal pain, weight loss, jaundice and palpable mass. Most tumors are in the head of the organ and invasion into adjacent structures is common, metastases being found in 50% of the patients at the time of diagnosis [3].

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Although electron microscopic and immunohistochemical studies have been performed, the origin of this tumor, whether epithelial or mesenchymal, is still obscure [4, 5]. There is also a controversy regarding the prognosis of this neoplasm [2].

We report the case of a patient with an OGTP with osteoid formation and areas of adenocarcinoma pattern. In this patient all the metastases were of the giant cell pattern. Based on our immunohistochemical findings the probable histogenesis of this tumor is discussed.

Case Report

A 69-year-old Brazilian man presented continuous weight loss for 4 months, and epigastric pain and jaundice during the last month prior to his admittance to treat an acute pancreatitis. Abdominal ultrasound and computed tomography scan showed a solid mass measuring 4.7 × 3.5 cm (fig. 1) in the head of the pancreas, and a dilated pancreatic duct.

Laparotomy confirmed a solid mass in the head of the pancreas, but there was no evidence of vascular invasion (superior mesenteric vein and portal vein), nor were liver metastases or carcinomatosis present. He underwent a Whipple procedure. Six months after the surgery the control computed tomography scan showed many hepatic metastases due to which chemotherapy was started. The patient died 1 year after having started the treatment.

Methods

Standard hematoxylin-eosin (H&E)-stained and mucicarmine-stained sections from formalin-fixed, paraffin-processed tissue were obtained and examined under light microscopy. For the immunohistochemical reactions, 5-μm cut sections in silane-coated glass slides were submitted to antigen retrieval comprised of trypsin digestion or heating for 4 min in citrate buffer, 10 mmol/l. Primary antibodies used were: cytokeratin 7 (clone OV-TL 12/30; Dako) used at a dilution of 1/50, cytokeratin 20 (clone Ks 20.8; Dako) at 1/50, pan-cytokeratin (clone AE1/AE3; Dako) at 1/200, epithelial membrane antigen (EMA; clone E-29; Dako) at 1/100, leukocyte common antigen (LCA; CD45 clone Ros 220 ALB12; Immunotech) at 1/200, vimentin (clone V9; Dako) at 1/300, CD68 (clone KP-1; Dako) at 1/100, macrophage marker (clone HAM 56; Dako) at 1/200, and lysozyme (Dako) at 1/100. Incubations were at 4 °C overnight (16 h), and biotinylated peroxidase-conjugated streptavidin method was used. Color was developed by incubating slides in 0.006% diaminobenzidine in PBS for 4 min.

Results

The resection specimen contained an irregular firm yellowish hemorrhagic tumor in the head of the pancreas measuring 4.5 × 4.5 × 3.5 cm that infiltrated the duodenal papilla. A hemorrhagic polyp measuring 0.7 × 0.3 cm was present in the proximal portion of the duodenum.

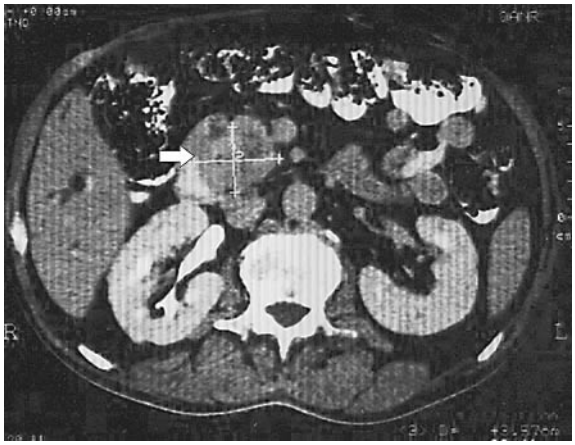
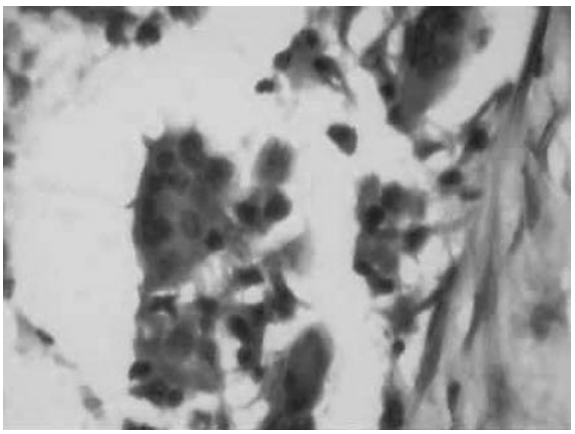


Fig. 1. Computerized tomography scan showing a solid mass in the head of the pancreas (arrow).

Microscopically, most of the tumor consisted of osteoclast-like giant cells within a background of mononuclear cells. The latter showed a marked degree of nuclear pleomorphism and atypical mitoses were frequent. The giant cells contained up to 15 round nuclei, each with a single nucleolus (fig. 2). In contrast to the mononuclear cells, there was no atypia and mitoses were not evident. Foci of osteoid formation were observed among these cells (fig. 3). Few areas of the tumor were composed of well-differentiated mucinous adenocarcinoma (fig. 4), which contained cysts lined by tumor cells with a mucicarmine-positive secretion. The mucicarmine stain was not positive in the giant cells, but was positive in some mononuclear cells. The hemorrhagic polyp in the duodenum and one peripancreatic lymph node had the same proliferation of giant cells and mononuclear cells and no adenocarcinoma cells.

The results of the immunohistochemical study are detailed in table 1 and illustrated in figure 5. Essentially, the adenocarcinomatous component expressed epithelial markers (cytokeratin and EMA) (fig. 5A). Some of the mononuclear cells expressed epithelial markers and others expressed mesenchymal markers, and the giant cells expressed LCA (fig. 5B), vimentin, CD68 (fig. 5C), macrophage marker HAM 56 and lysozyme (fig. 5D). They were negative for cytokeratin and EMA.



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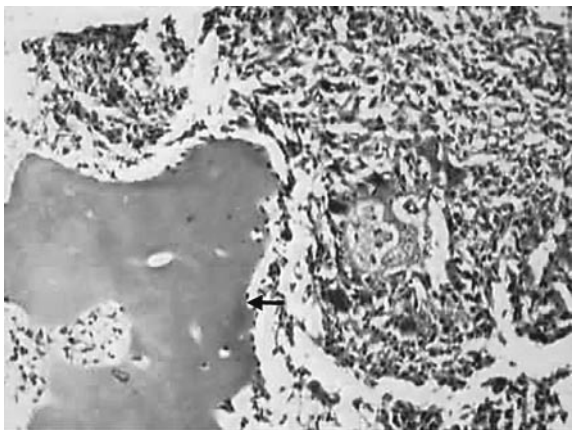

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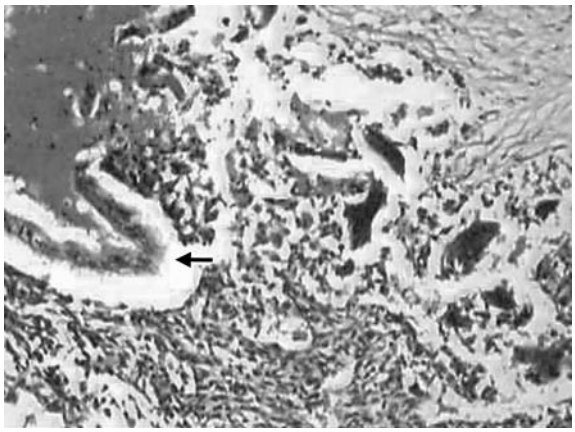

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Fig. 2. Giant cells showing numerous bland-appearing nuclei. HE. × 400.
Fig. 3. Osteoid formation (arrow) intermingled with mononuclear cells and giant cells. HE. × 250.
Fig. 4. Adenocarcinomatous component (arrow) amongst mononuclear cells and giant cells. HE. × 250.

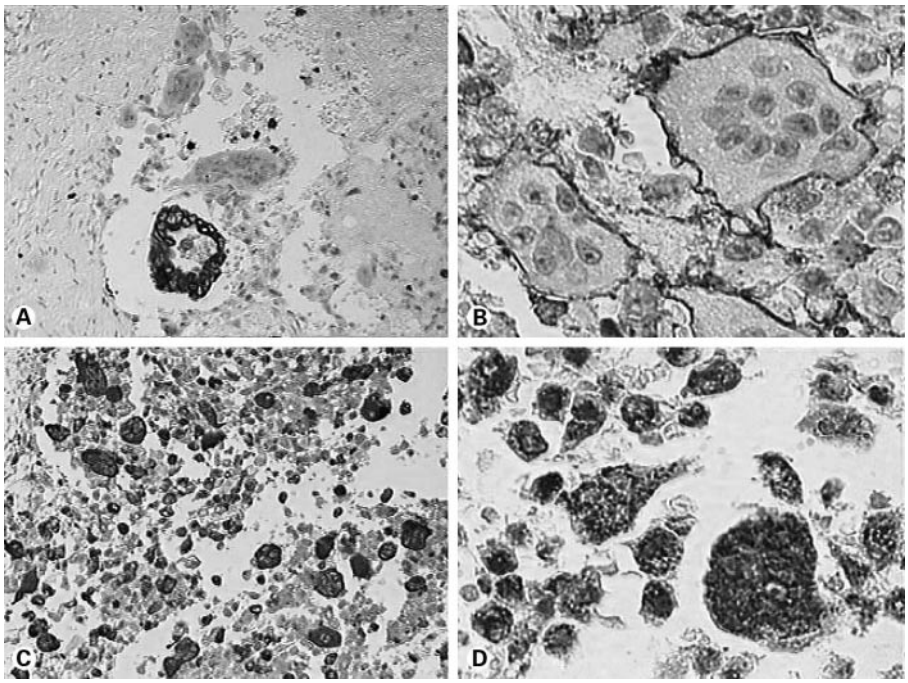

Fig. 5. Immunohistochemical reactions. **A** Neoplastic gland showing positivity for cytokeratin. Immunostain for panepithelial keratin. × 100. **B** Giant cells showing the presence of LCA on the cell surface. Immunotain for LCA. × 400. **C** Mononuclear stromal cells and giant cells showing positivity for CD68. Immunostain for CD68. × 100. **D** Mononuclear stromal cells and giant cells showing positivity for lysozyme. Immunostain for lysozyme. × 250.

Table 1. Immunohistochemical profile

	Adenocarcinomatous component	Mononuclear cells	Giant cells
Cytokeratin 7	+++	+	–
Cytokeratin 20	++	–	–
Panepithelial keratin (AE1/AE3)	+++	+	–
Epithelial membrane antigen (EMA)	+++	+	–
Leukocyte antigen (LCA)	–	+	+++
Vimentin	–	+++	+++
CD 68	–	+	+++
Macrophage marker (HAM 56)	–	+++	–
Lysozyme	+++	+++	+++

– = Negative; + = positive in some cells; ++ = positive in many cells; +++ = strongly positive.

Discussion

Giant cell tumors of the pancreas are rare nonendocrine neoplasms, and two histopathologic types are generally recognized. The first one, OGTP, cannot be distinguished under light microscopy from giant cell tumor of the bone. The second type, pleomorphic giant cell carcinoma (PGCP), is a sarcoma-like tumor with bizarre pleomorphic mononucleated and multinucleated giant cells [1, 6], which may easily be confused with rhabdomyosarcoma, choriocarcinoma, liposarcoma, poorly-differentiated squamous cell carcinoma, and other malignant neoplasms [6].

There are about 40 cases of OGTP reported in the literature [7]. They have been noted to occur in the parotid gland [8], thyroid gland [9], skin [10], orbit [11], kidney [12], and breast [13]. However, this lesion seems to have the highest predilection for the pancreas. They may be present in a pure form or associated with an adenocarcinomatous component, which was first described by Posen [14]. In the review of the literature, only 1 case described by Mentes and Yüce [15] was associated with a benign epithelial neoplastic component.

The OGTP must be differentiated from PGCP by the lack of nuclear pleomorphism and atypia in the giant cell component associated with the latter. PGCP is generally considered a sarcomatous metaplasia of ductal adenocarcinoma which is epithelial in its origin [16]. Conversely, the origin of OGTP has been discussed, and both mesenchymal and epithelial origins have been reported in the literature.

Some authors have reported the presence of glands within the tumor and the coexistence with adenocarcinoma, which led them to think its origin is epithelial. On the other hand, the fact that these tumors have a close resemblance to bone giant cell tumors could make one believe that their origin is mesenchymal [17].

Rosai [1], who first described this entity, suggested its epithelial origin – specifically acinar – using electron microscopic studies that showed the presence of desmosomes, microvilli, abundant granular endoplasmic reticulum and conspicuous intracisternal granules, in close alignment to other authors' findings [4, 18]. However, these ultrastructural features have also been demonstrated in some mesenchymal tumors, including giant cell tumors of the bone [19].

The first immunohistochemical studies were performed by Berendt et al. [4], who demonstrated positivity in the mononuclear cells and some giant cells for epithelial markers (carcinoembryonic antigen, CEA; and low-molecular-weight keratin) and lack of immunostaining with a panel of histiocytic markers (α_1-antitrypsin, α_1-antichymotrypsin, lysozyme, and S-100 protein).

One year later, Fischer et al. [19] showed a mesenchymal differentiation for these tumors. In their immunohistochemical studies, the giant cells and the mononuclear cells showed positivity for vimentin, but not for cytokeratin, lysozyme, α_1-antitrypsin, and α_1-antichymotrypsin. Mononuclear cells in osteoid tissue additionally contained osteonectin and could, therefore, be identified as osteoblasts.

Other studies demonstrated positivity for LCA [20, 21] and CD68 [17, 20] as well, supporting a nonepithelial origin for OGTP and suggesting a derivation similar to giant cell tumor of the bone.

In our case the giant cells demonstrated immunopositivity for vimentin, LCA, macrophage marker HAM 56, CD68, and for the first time in the literature for lysozyme. They were negative for epithelial markers (cytokeratin and EMA), revealing its mesenchymal origin. Epithelial markers were positive in the adenocarcinomatous component and in some mononuclear cells.

We conclude that the background of mononuclear cells represents a mixture of poorly-differentiated carcinoma cells, stromal cells and reactive cells of leukocytic lineage.

Only a few cases reported in the literature depicted the presence of osteoid formation [19], but we believe that the presence of osteoid is not enough to demonstrate a mesenchymal origin for this tumor, because it can be seen in metaplastic carcinomas as well.

Newbould et al. [21] suggested that the giant cells represent a component of the tissue response to the tumor, but even when an epithelial tumor is present, metastatic foci may contain giant cells. This is the case of the present tumor, in which the metastases were composed only of giant and mononuclear cells. Batsakis et al. [8] suggested that there may be two forms of the tumor: a reactive proliferation associated with an underlying epithelial tumor and a neoplasm arising de novo as a result of some other stimulus.

Suster et al. [5] proposed that OGTP encompasses a spectrum of lesions that may exhibit varying stages and degrees of differentiation, which has been observed in certain other neoplasms. By reviewing the literature, one can observe that two morphologically identical but histogenetically dissimilar types of OGTP could be found: one following an epithelial line of differentiation, and the other exhibiting nonepithelial features.

Those OGTP with epithelial differentiation may have the same prognosis for the usual adenocarcinomas of the pancreas. OGTPs with mesenchymal differentiation may have a similar outcome as seen in giant cell tumors of the bone [20], which might explain the differences in long-term survival noted in published cases of OGTP, that varies from 4 months to 10 years [7, 20].

Machado et al. [17] concluded in their study that a pure form of OGTP without adenocarcinomatous component could represent a sign of benignity or better outcome.

There is no reported experience of radiotherapy or chemotherapy in the management of OGTP. Acknowledging the radiosensitivity of the giant cell tumor of the bone, one may extrapolate possible benefits of radiation in the adjuvant therapy in those cases with mesenchymal differentiation. In the setting of an epithelial differentiation, one may reasonably consider chemotherapy [7].

Difficulties in making treatment decisions obviously arise from the rarity of this neoplasm and its controversial histogenesis. En bloc resection may not always be feasible and thus raises the risk of intraoperative tumor spill, when it is cystic.

It is important and necessary that future reports detail treatment modalities, patterns of spread, and clinical outcomes. For now, we believe that immunohistochemical studies should be performed in each case of OGTP to determine its histogenesis, which may provide guidelines for the treatment, mainly in the pure form of this tumor.

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