

CASE REPORT

Combined Osteoclastic Giant Cell and Pleomorphic Giant Cell Tumor of the Pancreas: A Rarity. An Immunohistochemical Analysis and Review of the Literature

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ABSTRACT

Context The combination of an osteoclastic giant cell tumor and a pleomorphic giant cell carcinoma of the pancreas is distinctly unusual and is associated with an adverse outcome. The origin of these two components within a tumor has long been debated based on the immunohistochemical and ultra-structural analysis.

Case report Herein we describe a tumor with amalgamation of these two distinct histomorphologies along with a minute focus of well-differentiated ductal adenocarcinoma (on multiple sections) in a 50-year male. On immunohistochemical analysis, osteoclastic giant cells were reactive for CD68 and vimentin confirming histiocytic/mesenchymal derivation whereas pleomorphic giant cells and mononuclear cells were reactive for cytokeratin which proved their epithelial nature.

Conclusions Although the present case had an equal proportion of both components, it is very important to correctly assess the predominant histology since osteoclastic giant cell tumor has a better prognosis as compared to the more aggressive pleomorphic giant cell carcinoma component.

INTRODUCTION

Pancreatic carcinoma is a common gastrointestinal malignancy second only to colonic carcinoma and has a highly aggressive course. Predominant osteoclastic giant cell morphology in a malignant pancreatic tumor, analogous to giant cell tumor of bone, is extremely rare and comprises less than 1% of exocrine pancreatic tumors [1]. These are also seen in a variety of other organs - such as the breast, thyroid, parotid, colon, heart, soft tissue etc. but, overall, they are rare and have an uncertain histogenesis [2]. Pleomorphic giant cell carcinomas (PGCs) are relatively frequent as compared to osteoclastic giant cell tumors (OGTs) and these can be seen focally in ordinary pancreatic ductal carcinomas; however, the co-existence of OGTs and PGCs in the same tumor with a focus of ductal carcinoma is very rare [3].

Both OGTs and PGCs have a controversial histogenesis, which has been debated in the literature since the time when Rosai first described this in 1968 [4]. Several authors on electron microscopic and immunohistochemical evaluation are in favor of an epithelial origin [2, 4, 5, 6], whereas some authors suggest a mesenchymal derivation [1, 7, 8, 9]. Thus, the true origin of OGTs and PGCs remains unclear and also

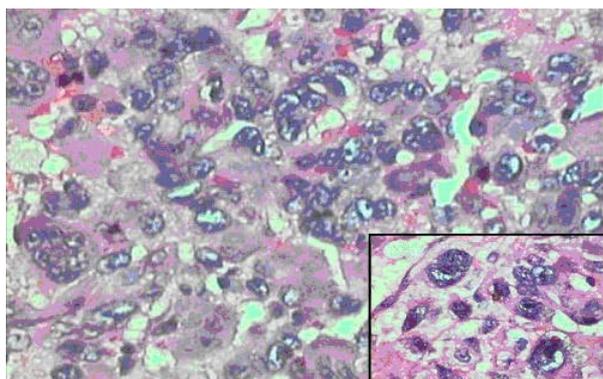


Figure 1. Blend of osteoclastic giant cells, pleomorphic giant cells and mononuclear cells. Osteoclastic giant cells have bland nuclear features whereas pleomorphic giant cells have large vesicular nuclei with prominent nucleoli (also inset). (H&E, 100×) (Inset: H&E, 200×)

their relationship to each other is also obscure which may be attributed to their rarity, thus rendering their thorough evaluation difficult. We describe the case of a 50-year-old male with a pancreatic tumor having both these elements and with a component of ductal adenocarcinoma involving the peri-ampullary region, along with immunohistochemical analysis, which stands as only the second case of its kind in the world literature [3].

CASE REPORT

A 50-year-old male presented having had episodic epigastric pain for 2 years with a 3-month history of deep, boring pain radiating to the back, vomiting 3 to 4 times a day, abdominal pain, jaundice and passage of dark colored urine. There was no prior history of gastrointestinal disease or alcohol abuse, but the patient was a chronic smoker. A general examination revealed icterus and on abdominal examination, there was an ill-defined mass in the epigastric region with mild tenderness. Laboratory examination was within normal limits except for elevated levels of CA 19-9 serum marker, which was 144 U/L (reference range: 0-37 U/L). Abdominal ultrasonography and a computed tomographic scan revealed a mass measuring 7x5 cm in the head of the pancreas with cystic change and dilated intra-hepatic biliary radicals. A chest X-ray was within normal

limits. At laparotomy a cystic, necrotic mass was seen in the head of the pancreas with invasion of the lower common bile duct, whereas the rest of the pancreas was firm in consistency. A Whipple's procedure (pancreatico-duodenectomy) was carried out. The patient recovered well after surgery with a decrease in serum CA 19-9 levels. He was subsequently treated with chemotherapy (gencitabine) and is on regular follow-up without recurrence or metastasis.

Pathologic Description

The pancreatico-duodenectomy specimen contained a greyish brown, solid mass measuring 6x5 cm and mainly occupying the head of the pancreas. On cut section, the tumor was composed of firm greyish brown tissue with areas of hemorrhage and cavitating necrosis. The remaining pancreas was firm in consistency.

Multiple histologic sections from representative areas of the tumor showed distinct OGT, PGC and well-differentiated ductal adenocarcinoma with an intimate mixture of these in some places. The OGT areas were comprised of numerous osteoclastic giant cells, a few of which having up to 50 nuclei. The nuclei were oval to round, uniform with vesicular chromatin and conspicuous nucleoli (Figure 1). The stromal mononuclear cells were oval to spindle shaped with moderate acidophilic cytoplasm and their nuclei resembled those of the giant cell. Stroma was scant to moderate, fibrous,

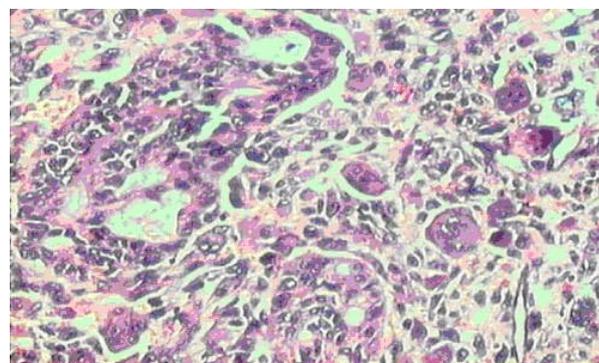


Figure 2. Ductal adenocarcinoma (well-differentiated) with mucin, along with osteoclastic and pleomorphic giant cells. (H&E, 100×)

without foci of calcification and/or bone formation.

The PGC exhibited bizarre cytological features with pleomorphic, hyperchromatic nuclei, with coarsely clumped chromatin, large eosinophilic nucleoli and prominent mitotic figures. There were not many nuclei in the giant cells with most cells being mononuclear giant forms having a high N:C ratio (Figure 2, inset). In addition, there was a component of a well-differentiated ductal adenocarcinoma within these foci infiltrating the peri-ampullary region and with perineurial invasion (Figure 2).

Osteoclastic giant cells were strongly positive for CD68 and vimentin, but were negative for low molecular weight cytokeratin. The pleomorphic multinucleate and mononuclear giant cells along with the ductal carcinoma

cells were strongly positive for low molecular weight cytokeratin but lacked immunoreactivity for CD68 and vimentin (Figure 3).

DISCUSSION

This case, which showed an admixture of OGT and PGC along with a well-differentiated ductal adenocarcinoma component, is a distinctly rare entity [1, 3]. OGT which is also called as 'osteoclastoma of the pancreas' or 'epulis-osteoid type giant cell carcinoma of the pancreas', is rare with only 34 cases reported in the literature, mostly in the form of case reports, as discussed in a recent series [9]. Although, in comparison, PGC's are more commonly encountered, a true mixed tumor - i.e. OGT and PGC - with a

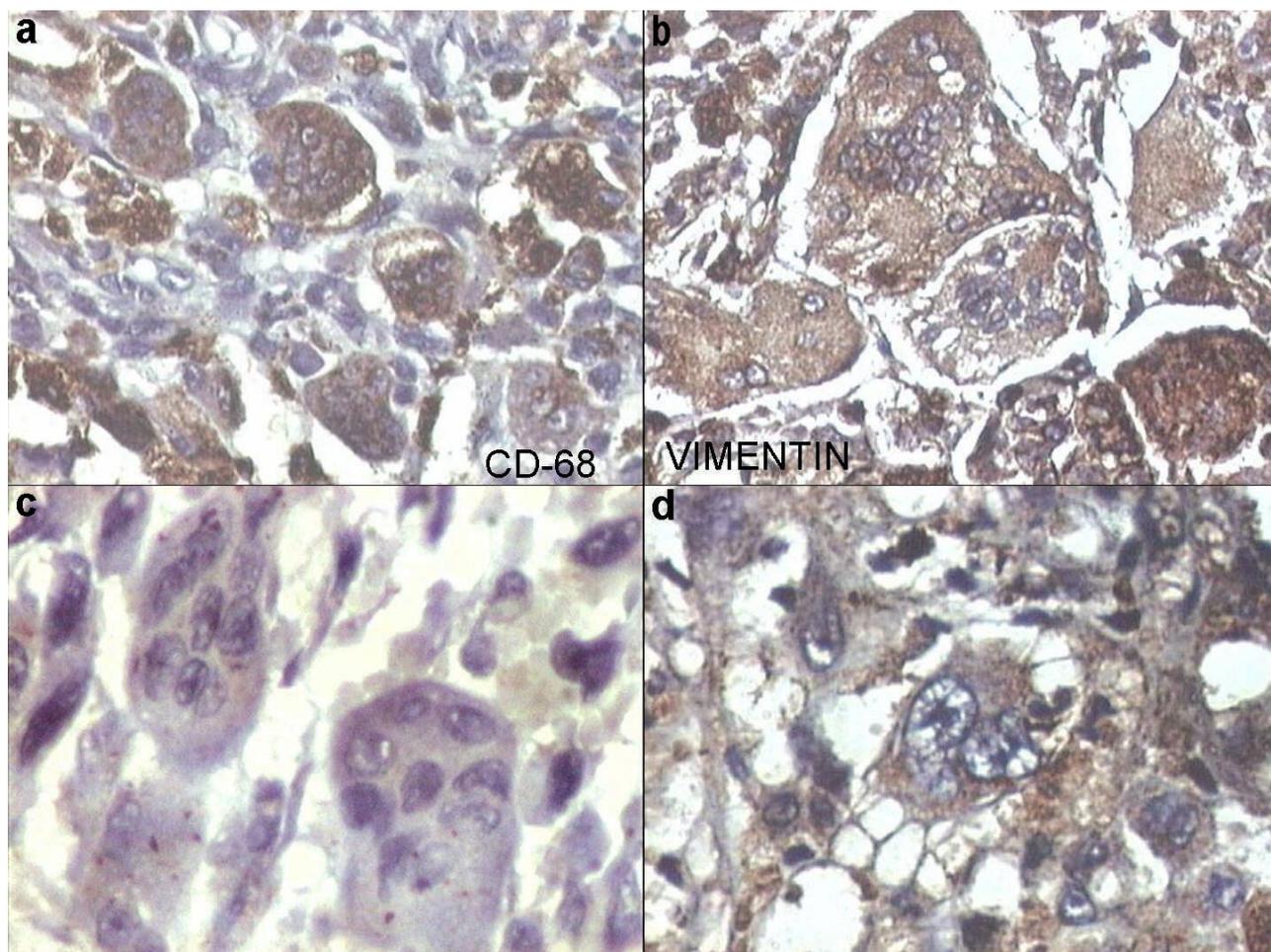


Figure 3. Immunohistochemical results. Osteoclastic giant cells positive for CD68 (a. 100×) and vimentin (b. 200×), but negative for cytokeratin (c. LMW; 200×). d. Pleomorphic giant cells and mononuclear cells positive for cytokeratin (LMW; 200×).

ductal adenocarcinoma component has been described only once in the past [3].

This unusual tumor presents in the 6th or 7th decade with a nearly equal gender ratio [9]. It has been found that OGTs have a better prognosis as compared to PGCs because they have a predilection to local spread, are slower to metastasize, and rarely metastasize to the lymph nodes. PGCs are fatal in a short time with a shorter duration of survival. This can be attributed to early lymph nodal and distant metastasis [1]. However, given a situation of combined tumor, it is difficult to comment upon the prognosis due to its rarity. Clinical and radiological evaluation revealed no evidence of metastasis in the present case, although this cannot be totally ruled out.

Morphologically, the heterogeneity of this tumor indicates that these may be inter-related and the possibility of a collision tumor is less likely. This feature is compatible with the divergent lines of differentiation in a tumor capable of diverse morphologic expression [1]. Based on light microscopy, immunohistochemistry, and electron microscopy and its frequent association with ductal carcinoma, PGC is postulated to originate from ductal epithelial cells. PGC represents a sarcomatous transformation, and it requires extensive sampling because the foci of ductal adenocarcinoma are sparse [3]. This observation was also made in the present case, in addition to a prominent component of OGT. As far as the histogenesis of OGT is considered, it is controversial with most authors favoring an epithelial derivation from acinar cells [2, 4] or ductal cells [5] rather than mesenchymal cells [1, 6, 10] and reactive mesenchymal cells [7, 8]. However, the bland nuclear features, positivity for CD68 and vimentin, and negativity for low molecular weight cytokeratin in the present case negates the epithelial origin of the osteoclastic giant cells and the mononuclear stromal cells, and favors a mesenchymal/histiocytic origin. Watanabe *et al.* [3] has put forth four possibilities as to the histogenesis of this tumor as carcinosarcoma, adenocarcinoma with reactive osteoclastic giant cells,

adenocarcinoma with peculiar metaplasia, and metastasis of giant cell tumor of bone, but ultimately concluded that it was a carcinoma (PGC with ductal adenocarcinoma) and sarcoma (OGT component) as the OGT component showed lymphatic invasion. The negativity of cytokeratin in the OGC areas ruled out metaplastic change and skeletal survey did not reveal any bony lesion.

The positivity of pleomorphic giant cells (mononuclear and multinucleated forms) for low molecular weight cytokeratin and lack of reactivity for CD68 and vimentin confirms their epithelial nature, in contrast with the observation of authors who thought they were of mesenchymal origin [1, 11]. Lewandrowski *et al.* concluded that mononuclear stromal cells correspond to poorly differentiated fibroblasts with a propensity to form mononuclear and multinucleated giant cells [1]. Gatteschi *et al.* showed with molecular biologic studies that neither pleomorphic nor osteoclastic giant cells have *c-Ki-ras* or *p53* mutation and do not express mutated *p53* protein. They were skeptical about the epithelial origin of both OGTs and PGCs, as these two genetic changes are very common in pancreatic cancers of ductal origin [11].

The multinucleated giant cells are identical to the osteoclasts and thus to the giant cell tumor of the bone, but these are not a unique feature of epithelial tumors [1, 9]. Although the epithelial origin of OGTs described by several authors cannot be negated, in the present case, immunohistochemical analysis pointed to a mesenchymal origin for OGTs. Positive immunohistochemistry for low molecular weight cytokeratin and the accompanying ductal adenocarcinoma component with elevated serum CA 19-9 levels favored an epithelial origin for PGCs.

Thus, it can be concluded that, as OGTs and PGCs arise from a precursor cell capable of differentiating along divergent lines and giving rise to a spectrum of morphologic and immunohistochemical phenotypes, OGTs and PGCs may represent two ends of a biological spectrum of a single neoplasm.

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Abbreviations OGT: osteoclastic giant cell tumor; PGC: pleomorphic giant cell carcinoma

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