Original Paper

Acinar Cell Carcinoma of the Pancreas: is the Absence of Neuroendocrine Component Related to a More Malignant Behavior?

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Pancreas; Acinar cell carcinoma; Immunohistochemical Study

ABSTRACT

Background/Aims: Acinar cell carcinomas are uncommon malignant tumors of the pancreas, accounting for 1-2% of all the cases of exocrine pancreatic tumor. Some authors have estimated acinar cell tumors to be as aggressive as ductal adenocarcinoma of the pancreas whereas other series showed acinar cell tumors to have a favorable clinical outcome. This discrepancy in prognosis may be related to the cellular components of the tumor.

Methodology: With the aim to evaluate the possible relationship between the presence of neuroendocrine differentiation and behavior of these tumors, the authors reviewed all patients presenting acinar cell carcinoma of the pancreas in the last 5 years with emphasis in the immunohistochemical evaluation.

Results: Four patients presented neuroendocrine differentiation on immunohistochemical evaluation and had a more benign outcome. Two patients without neuroendocrine component had a disseminated disease at presentation. This data suggests that this tumor is less aggressive than ductal adenocarcinoma and even with nodal involvement, long term survival after complete resection can be achieved.

Conclusions: It is possible that the absence of neuroendocrine component may be related to a less favorable outcome and adjuvant therapy may be necessary. Due to the rarity of this pancreatic tumor, this relationship remains to be confirmed with a multicentric study including a larger number of patients.

INTRODUCTION

Acinar cell carcinomas are uncommon malignant tumors of the pancreas, accounting for 1-2% of all cases of exocrine pancreatic tumor (1-7). It is defined as a carcinoma exhibiting evidence of pancreatic enzyme production by neoplastic cells (8).

The number of reported patients with acinar cell carcinoma is relatively small, therefore it is difficult to determine the prognosis and the best modality of treatment for this disease. The available information is from case reports and small series (3,6). Some series have estimated acinar cell tumors to be as aggressive as the more common ductal adenocarcinoma of the pancreas (8-10). Five year survival rates of 6% or less were reported and data about the best treatment for this disease is still controversial (1,6). However, another series estimated acinar cell tumors to be more benign with a clinical course similar to neuroendocrine tumors (6). This discrepancy in prognosis may be related to the cellular components of the tumor (7). Indeed, it has been observed that some tumors have a mixed form of acinar and neuroendocrine cell lines. With the aim to evaluate the possible relationship between the presence of neuroendocrine differentiation and behavior of these tumors, the authors reviewed all patients presenting acinar cell carcinoma of the pancreas in the last 5 years with emphasis on the immunohistochemical study.

METHODOLOGY

Between January 2000 to October 2004, 6 patients with acinar cell carcinoma of the pancreas were identified in the database of the Hospital Sirio Libanês. Four patients underwent complete surgical resection and 2 patients underwent biopsy. There were 4 women and 2 men. The mean age was 49.8 years (range 29-64).

Five patients had epigastric or left upper quadrant abdominal pain and one patient presented two episodes of back pain and hyperamylasemia as initial presentation. Three patients had significant weight loss of 8-10kg. The mean follow up time was 22.5 months (range 6–54 months). Patients' data are listed in **Table 1**.

Acinar cell carcinoma was diagnosed based on typical histological and immunohistochemical fea-

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tures that included trabecular and solid formations of tumor cells of round nuclei of uniform size within abundant eosinophilic cytoplasm. Growth lobulation of markedly cellular neoplastic tissue by fibrous strands were other common findings. Immunohistochemical studies were performed using monoclonal and polyclonal antibodies (DakoCytomation A/S, CARPINTERIA, CA, USA) as follows: Cytokeratin 18 (monoclonal antibody, clone DC 10, dilution 1:100), Alpha 1-antitrypsin (polyclonal antibody, dilution 1:1000); Synaptophysin (polyclonal antibody, dilution 1:100) and Chromogranin A (monoclonal antibody, clone DAK-A3, dilution 1:100). All studies were performed and/or reviewed by the same pathologist (KRL).

TABLE 1 Clinical Features

n	Age (y)	Sex	Tumor size (cm)	Site	Symptom	Weight loss	Operation (concomitant resection)
1	64	f	10	body,tail	abdominal pain		dp
2	41	f	15	body,tail	abdominal pain	8 kg	dp (stomach, colon)
3	50	f	5.2	body	acute pancreatitis		dp
4	29	m	10	body,tail	abdominal pain	10 kg	biopsy
5	51	f	1.4	head	abdominal pain		pppd
6	64	m	10	body,tail	abdominal pain	10 kg	biopsy

dp: esplenopancreatectomy; pppd: pylorus preserving pancreaticoduodenectomy

RESULTS

The tumor size ranged from 1.4-15cm in diameter (mean 8.6cm). A characteristic peripheral enhancement on the arterial phase CT scan was present in the largest tumors. Three patients underwent distal pancreatectomy with splenectomy; in one patient, segments of stomach and colon were removed *en bloc* along with the tumor. Another patient had a pylorus preserving pancreaticoduodenectomy. Two patients with peritoneal seeding and liver metastasis at the time of presentation underwent tumor biopsy.

Among the 4 resected tumors, 3 presented vascular and neural invasion and lymph node metastasis. Despite this fact all patients are alive without neoplasm recurrence except one patient who underwent resection of a small liver metastasis discovered 11 months after pancreatectomy. This patient is alive and without evidence of recurrence 15 months after hepatectomy. These 4 patients presented neuroendocrine differentiation on the immunohistochemical study **(Table 2)**. Two patients with advanced tumor at the presentation disclosed pure form of pancreatic acinar cell carcinoma without neuroendocrine differentiation. The first one succumbed 6 months after the diagnosis despite systemic chemotherapy with gemcitabine. In the second, liver metastasis dramatically increased in size from 2-15cm in a short period of time (40 days) despite aggressive chemotherapy. This patient ultimately died 45 days later.

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DISCUSSION

There is a scarcity of information regarding acinar cell carcinoma of the pancreas. Male incidence seems to be greater than female and higher survival rates in women has been reported without reasonable explanation (6,7). In this paper there was a female predominance and also a better survival among them.

Acinar cell carcinoma can manifest in many ways, depending on the tumor location, with jaundice being infrequent. Abdominal pain is the most common symptom, followed by abdominal mass. Tumors measuring more than 10cm, as found in 4 patients in this study, are more common in acinar cell carcinoma (7). Pancreatitis secondary to these tumors is extremely rare (11). Recurrent episodes of acute pancreatitis were the only clinical manifestation in one patient **(Table 1)**. In most cases the symptoms are non-specific. A specific syndrome of subcutaneous nodules can be seen in some cases due to high levels of lipase causing panniculitis, polyarthralgia, and blood eosinophilia (6-8,12-16). This syndrome was not observed in any of the patients in this study. For these patients, lipase determination can be used to assess tumor response to therapy (7).

Pathologic review of acinar cell tumors disclosed 2 cellular patterns (6): the acinar pattern with cells growing in well-formed acini and the solid pattern with sheets and clusters of cells separated by a thin fibrovascular stroma. There is a unique immunohistochemical staining pattern: strongly positive for trypsin and negative or only focally positive for synaptophisin and chromogranin (5,6,8). Four cases of this series have neuroendocrine component and the tumors appear to be less malignant. Two of the

TABLE 2 Pathological Features and Outcome

n	Neural	Vascular	Lymph node	Neuroendocrine differentation	Follow up Recurrence	(Months)	Status	Reoperation
1	+	+	+	yes	no	54	alive, NED	
2	+	+	+	yes	yes, liver	26	alive, NED	liver resection
3	-	-	-	yes	no	31	alive, NED	
4				no	-	6	died	
5	+	+	+	yes	no	12	alive, NED	
6	+	+	+	no	-	6	died	duodenal obst.

NED: no evidence of disease; duodenal obst.: duodenal obstruction

cases in this study with the pure form of acinar cell carcinoma had very aggressive tumors with liver metastases and peritoneal carcinomatosis. In one of these patients liver a metastasis increased by about 7 times in size during a 40-day period. Neuroendocrine component may be related to a more benign outcome, as the 4 cases in this study with endocrine cells are still alive without evidence of the disease 1-5 years after pancreatic resection. On the other hand, the lack of neuroendocrine differentiation may be related to a poorer prognosis.

Older patients, presence of lipase secretion and size superior to 10cm were reported as negative prognostic factors, related to a shorter survival time (6). Two of the patients had a tumor size equal to or greater than 10cm, with lymphatic, vascular and neural invasion, but also with neuroendocrine differentiation, and are still alive. It is possible that the absence of neuroendocrine component in the immunohistochemical study may be related to a less favorable outcome and adjuvant therapy may be necessary. We may be dealing with 2 different types of tumor from opposite sides in the scale of malignancy. However, due to the rarity of this pancreatic tumor, this finding remains to be confirmed with a multicentric study including a larger number of patients.

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