

CASE REPORT

Mixed Exocrine-Endocrine Tumor of the Pancreas

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ABSTRACT

Context Neoplasms of the pancreas usually show ductal, acinar or endocrine differentiation. Tumors with mixed exocrine and endocrine components are unusual. We herein describe a case of a mixed ductal-endocrine tumor.

Case report A 65-year-old woman was referred to our department with a diagnosis of carcinoma of the tail of the pancreas. The patient had a short history of upper abdominal pain, nausea and melena. Upper gastrointestinal endoscopy revealed gastric fundus varices and CT scan demonstrated an inhomogeneous tumor located in the tail of the pancreas infiltrating the spleen and the splenic vein. The patient underwent distal pancreatectomy and splenectomy, and had an uneventful recovery. Pathological examination revealed a mixed ductal-endocrine tumor. The endocrine component was immunoreactive for glucagon, gastrin and somatostatin, and non-reactive for insulin.

Conclusions Because of the rarity and unpredictable biologic behavior of these tumors, the need for adjuvant therapy has not yet been well-defined. The patient has had a follow-up CT scan every six months, and one and a half years later remains disease free.

INTRODUCTION

Pancreatic cancer is one of the most lethal forms of human cancer. Malignant pancreatic tumors are usually classified into those of the exocrine pancreas or those of the endocrine pancreas, and are generally categorized into three types (ductal, acinar or endocrine) [1]. Mixed exocrine-endocrine neoplasms of the pancreas are rare tumors, characterized by the association of an exocrine - ductal or acinar - component and a significant endocrine component which comprises at least one-third to one-half of the tumor tissue [2]. The pathologic diagnosis of duct-islet cell carcinomas was initially based on endocrine-marker positivity plus histological demonstration of ductular formation and mucin production [3]. However, this approach was not correct, as focal mucin production or glandular structure could simply be part of an endocrine tumor, not representing true ductal differentiation [2, 4]. On the other hand, 40 to 80% of pancreatic ductal carcinomas may contain endocrine cells, scattered among or under the tubules of ductal carcinoma cells. This endocrine element comprises only a small percentage of the tumor cell population (less than 30%) and does not have the histology of an endocrine carcinoma [5, 6, 7, 8, 9, 10, 11]. Therefore, it is now accepted that the diagnosis of ductal-endocrine cell tumors of the pancreas requires identification



Figure 1. Large tumor in the tail of the pancreas.

of endocrine marker reactivity in at least one-third to one-half of the tumor [6, 11, 12]. Furthermore, the small number of patients and differences in stage at presentation does not permit us to safely assess the level of aggressiveness of mixed pancreatic tumors, but aggressive behavior is likely. However, mixed ductal-endocrine carcinomas seem to have the same prognosis as common ductal pancreatic carcinomas [13, 14] and, as diagnosis is confirmed only postoperatively, the treatment approach does not seem to be altered.

We herein report a case of a mixed ductal-endocrine tumor in order to discuss histological findings and therapeutic dilemmas.

CASE REPORT

A 65-year-old woman was admitted to the Gastroenterology Department of our hospital

because of melena. The patient had complained of progressive fatigue, weakness, upper abdominal pain, anorexia and nausea for three-months. The admission profile was normal apart from mild anemia and a remarkably elevated erythrocyte sedimentation rate. Upper gastrointestinal endoscopy revealed gastric fundus varices with superficial ulceration. CT scan demonstrated an inhomogeneous tumor located in the tail of the pancreas (Figure 1) while ultrasonography and MRI revealed ischemic splenic necrosis and splenic vein thrombosis. The patient, with a diagnosis of carcinoma of the tail of the pancreas, was referred to our department for surgical treatment.

At laparotomy, a large tumor was palpated in the splenic hilum. Dissection of gastrocolic ligament permitted a clearer view of the omental bursa and revealed the presence of a mass originating from the tail of the pancreas, infiltrating the spleen and the splenic vessels (Figure 2). There were no signs of invasion to other adjacent organs, no infiltrated nodes or any other sign of disseminated disease. The spleen and the tail of the pancreas were easily mobilized after ligation of the splenic artery on the superior border of the pancreas. The splenic vein was infiltrated by the tumor and thrombosed. Distal pancreatectomy and splenectomy were performed; the patient had an uneventful recovery and left hospital 8 days later.

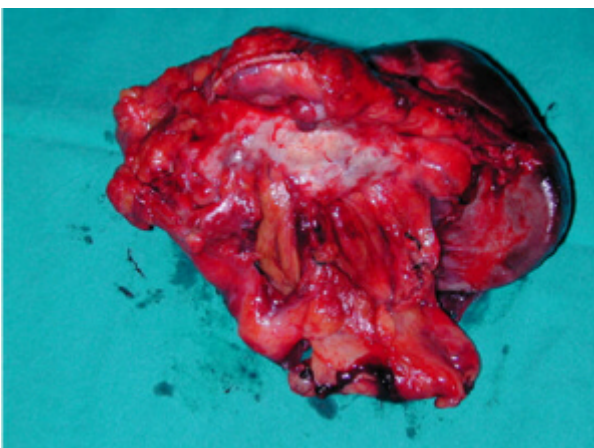


Figure 2. The tumor (measuring up to 12cm) infiltrated the spleen and the splenic vessels.

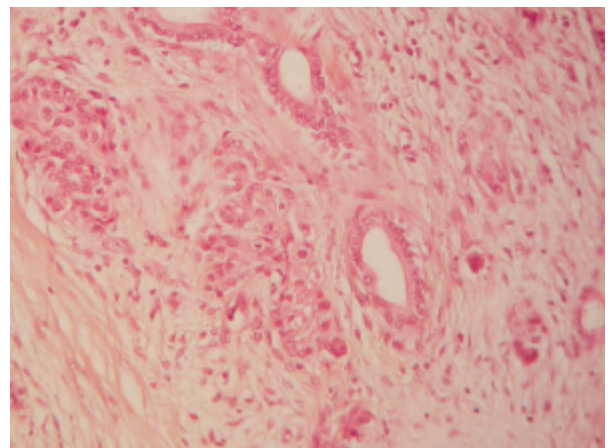


Figure 3. Exocrine component of the tumor. Well-differentiated ductal adenocarcinoma.

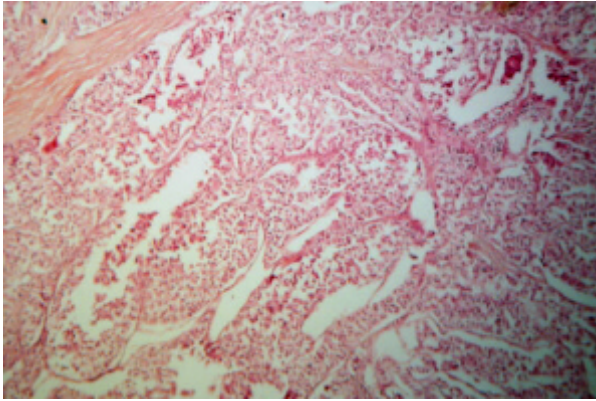


Figure 4. Endocrine component of the tumor. Neoplastic cells are present in irregular islands with central necrosis.

Histopathological Study

The tumor measured 12x9x7cm and invaded the spleen. On light microscopy, a cellular neoplasm originating from the pancreatic parenchyma was revealed. Two distinct populations of neoplastic cells were present. One with features of well-differentiated ductal adenocarcinoma (Figure 3) and the second presenting features of an endocrine neoplasm (Figure 4). Interestingly, despite splenic invasion, none of the dissected lymph nodes at the splenic hilum, and the superior and inferior border of the pancreas were infiltrated by neoplastic cells.

Neoplastic cells were oval and/or polygonal with amphiphilic cytoplasm and were focally clear. The cells were small to medium in size with considerably polymorphic nuclei and few mitoses. The neoplastic cells were

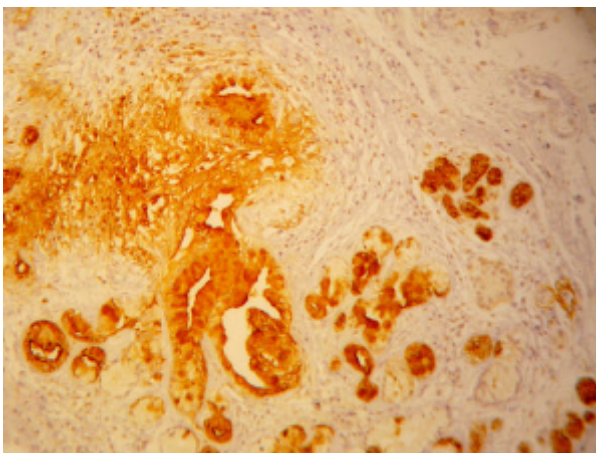


Figure 5. Exocrine component of the tumor. Well-differentiated ductal adenocarcinoma. Immunoreactivity for CA 19-9 is noted.

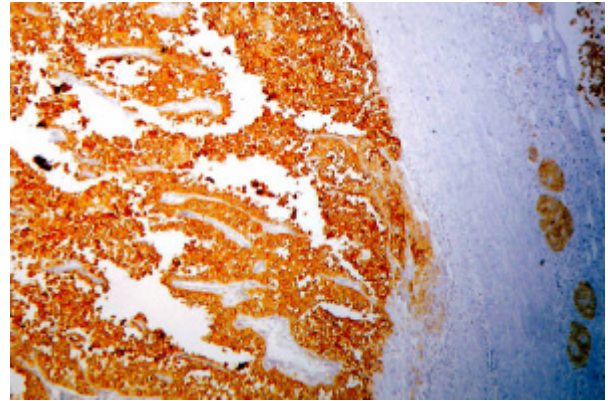


Figure 6. Endocrine component of the tumor. Immunoreactivity of the neoplastic cells for chromogranin.

arranged in acini with central necrosis focally. Delicate strands consisting of connective tissue and vessels coursed the neoplasm. A trabecular pattern was also revealed focally, and considerable fibroblastic reaction was noticed around the acini.

On immunohistochemistry, the following were revealed:

- intense diffuse cytoplasmic and membranous positivity of the neoplastic cells for AE1/AE3;
- focal mild membranous and cytoplasmic positivity for CA 19-9 (Figure 5);
- intense diffuse cytoplasmic positivity for neuron specific enolase (NSE);
- negativity for CA 125, CA 15-3 and insulin;
- focally granular cytoplasmic positivity for chromogranin (Figure 6);
- diffuse cytoplasmic and membranous positivity for synaptophysin (Figure 7);
- focal granular cytoplasmic positivity for gastrin, somatostatin and glucagon.

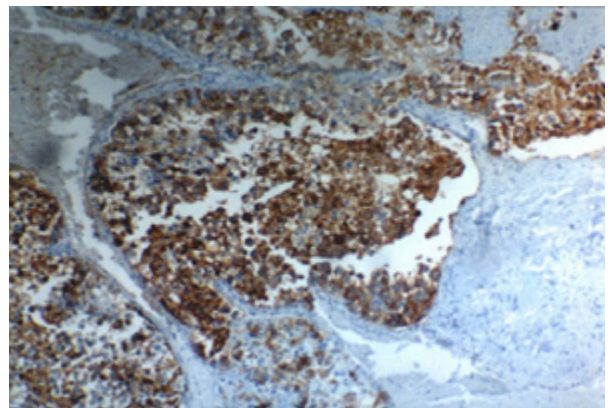


Figure 7. Endocrine component of the tumor. Diffuse cytoplasmic and membranous immunoreactivity for synaptophysin.

The endocrine component of the tumor represented almost 40% of the tumor cells and, therefore, the tumor can be classified as a mixed ductal-endocrine pancreatic tumor.

No adjuvant therapy was administered and the patient is enrolled in a strict follow up protocol and has remained disease free for one and a half years.

DISCUSSION

It is well-known that the pancreas is composed of two separate organs, namely an exocrine and an endocrine pancreas [15]. The exocrine pancreas includes two types of cells, ductal and acinar cells, while the endocrine pancreas consists of islet cells. Pancreatic tumors usually originate from one of these cell types, most often from ductal cells [16, 17].

In a series of 645 pancreatic tumors reported by Cubilla and Fitzgerald [15], ductal cell carcinomas represented 88.8% of pancreatic tumors, while endocrine cell tumors and acinar cell carcinomas represented only 7.4% and 1.2% of tumors, respectively. Mixed cell type carcinomas were very rare representing only a 0.2% of all cases in the same report [15].

Eleven cases of mixed ductal-endocrine tumors of the pancreas have been previously reported in the literature [5, 6, 13, 14, 16, 17, 18, 19, 20, 21]. Chatelain *et al.* [13] reviewed these cases. Mixed ductal endocrine carcinomas of the pancreas are often described in middle-aged patients (mean age 58.5 years) with an equal distribution between men and women. They are usually large and located in the head of the pancreas (60% of cases). Patients complain of jaundice, weight loss or abdominal pain while an endocrine syndrome is rare (described only in 2 cases) [6, 18]. Summarizing data of all cases reported are presented in Table 1 (including our patient). Our patient presented with vague abdominal pain caused by a large tumor located in the tail of the pancreas. In the patients reported in the literature, four died from 5 to 24 months after diagnosis, while six (including our patient) were reported to be

Table 1. Summarizing statistics of mixed ductal-endocrine pancreatic carcinomas (12 cases, including the present one) [5, 6, 13, 14, 16, 17, 18, 19, 20, 21].

Characteristics	Frequency
Location	
- Head	7 (58.3%)
- Body	2 (16.7%)
- Tail	3 (25%)
Symptoms	
- Abdominal pain	4 (33.3%)
- Weight loss	5 (41.6%)
- Jaundice	5 (41.6%)
- Diarrhea	1 (8.3%)
- Nausea/vomiting	1 (8.3%)
- Verner-Morrison syndrome	1 (8.3%)
- Zollinger-Ellison syndrome	1 (8.3%)
Tumor size	
- Less than 100 mm	5 (41.6%)
- Equal to or greater than 100 mm	4 (33.3%)
- Not specified	3 (25%)
Treatment	
- Pancreatoduodenectomy	5 (41.6%)
- Distal pancreatectomy	4 (33.3%)
- Enucleation	1 (8.3%)
- Chemotherapy	2 (16.7%)

disease free 4 to 72 months after the initial diagnosis. In addition, in 1999, Terada *et al.* [6] reported an autopsy case of an endocrine tumor (gastrinoma with Zollinger-Ellison syndrome) that terminated as a mixed ductal-endocrine carcinoma 24 years later.

It is noteworthy that most of the cases reported referred to resectable tumors, thus permitting an accurate diagnosis of mixed ductal/endocrine tumor. Such a diagnosis is hard to prove in unresectable tumors by small biopsies or cytology, as a mixed ductal/endocrine tumor is defined as a tumor whose 30-50% cell population is immunoreactive to endocrine markers. However, real occurrence of these tumors is probably underestimated, as unresectable tumors are virtually undiagnosed.

The histogenesis of mixed exocrine-endocrine tumors of the pancreas is still controversial. The co-existence of exocrine and endocrine elements in these tumors can be attributed to their common embryologic origin. In recent years, Pearse's view that all endocrine cells are derived from the neural crest has largely been abandoned in favor of a common

precursor stem cell of endodermal origin from which both endocrine and exocrine cells are derived [6, 22, 23, 24, 25].

Cases such as the one reported from Terada *et al.* [6] suggest that pancreatic endocrine tumors may evolve into mixed ductal-endocrine carcinomas, in this way reinforcing the hypothesis of the existence of a common stem cell, from which both exocrine and endocrine pancreatic elements derive. Moreover, in 2001, Regitnig *et al.* [25] reported a case of pancreatic insulinoma with insular-ductular differentiation in its liver metastasis, indicative of a common stem cell origin of the exocrine and endocrine components.

Pour and Schmied, in a recent review [22] of several human studies and experimental studies on Syrian hamsters conducted within the last 20 years, concluded that pancreatic cancer derives from pancreatic stem cells which are distributed within the ductal trees and within the islets. In the same review, it was noted that, in a hamster pancreatic cancer model, most pancreatic adenocarcinomas develop within islets, most probably from stem cells which are also considered the progenitor cells for tumors developing within ducts.

Finally, Peters *et al.* [26], in a review article on the embryologic development and growth of the endocrine pancreas, noted that, in the adult pancreas, ductal cells can be stimulated to differentiate into islet cells under certain conditions. However, it is not clarified and it remains to be seen whether all duct cells retain a stem cell potential and which transcription and growth factors are necessary for the induction of islet cell neogenesis. It is, therefore, more or less accepted that exocrine and endocrine cells of the pancreas originate from branching multipotential epithelial cells with the features of ductal cells.

Depending on the point at which neoplastic transformation occurs along the pathway of proliferation and differentiation of these cells, a pancreatic neoplasm may exhibit ductal, acinar, or endocrine features. If the transformation occurs at an early stage, more than one line of differentiation may be expressed.

Two types of ductal-endocrine cell carcinomas can be distinguished [3]. One represents a collision of two histogenetically distinct tumors growing into one another, with the two components remaining largely restricted to separate regions despite some areas of intermingling. The tumor presented can be classified as this type, since two distinct neoplastic cell populations were present. The other type represents an amphicrine neoplasm with a uniform cell population in light microscopy, which shows bi-directional differentiation ultrastructurally or immunohistochemically.

In summary, mixed tumors of the pancreas are rare, and both their clinical features and pathogenesis remain unclear. They are considered to have the same prognosis as common ductal pancreatic carcinomas [13, 14] and their treatment approach remains unaltered as, in most cases, diagnosis is established postoperatively.

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Keywords Carcinoma, Acinar Cell; Carcinoma, Pancreatic Ductal; Neuro-endocrine Tumors; Mixed Tumor, Malignant; Pancreas; Pancreatic Neoplasms

Abbreviations NSE: neuron specific enolase

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