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Case Report

A case report of mixed acinar-neuroendocrine carcinoma of the pancreas misdiagnosed as well-differentiated neuroendocrine tumor on biopsy

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Abstract: Pancreatic mixed acinar-neuroendocrine tumors (MANCs) are rare tumors exhibiting acinar and neuroendocrine differentiation, with each component making up more than 30% of the tumor. *Case Report*: We report an interesting case of MANC in a male presenting with an incidental pancreatic head mass and multiple liver mestastases. The biopsy of his liver metastases revealed a tumor morphologically consistent with low-grade well-differentiated neuroendocrine tumor (NET). The patient was offered chemotherapy for NET before surgical resection of the pancreatic tumor and liver metastases. The primary pancreatic tumor was diagnosed as MANC. Although some foci of metastatic tumor showed morphology and immunohistochemical findings similar to that of the pancreatic primary, many metastatic foci demonstrated morphology of a well-differentiated NET with retained expression of acinar markers. *Conclusions*: Pancreatic MANCs often exhibit varied morphologies to some extent that components of these neoplasms can mimic low-grade well-differentiated NET, posing a diagnostic challenge especially in small tissue biopsies.

Keywords: Mixed acinar-neuroendocrine carcinoma, acinar cell carcinoma, neuroendocrine tumor

Introduction

Acinar cell carcinoma (ACC) is a relatively rare malignant neoplasm of the pancreas, comprising 1-2% of pancreatic neoplasms in adults [1]. Although most carcinomas of the pancreas show ductal differentiation, ACCs exhibit acinar cell differentiation and accordingly produce pancreatic exocrine enzymes such as trypsin, chymotrpysin, lipase and amylase [1]. Of note, as many as 40% of ACCs have been shown to demonstrate scattered positivity for neuroendocrine immunohistochemical stains such as CD56, synaptophysin and chromogranin [1]. However, a small subset of ACCs shows a significant neuroendocrine component that comprises greater than 25-30% of the neoplasm [1-3]. These tumors that show both substantial acinar and neuroendocrine differentiation are designated mixed acinar-neuroendocrine carcinomas (MANCs) [1, 2]. Both ACC and MANCs exhibit a wide range of histopathological patterns such as cribigorm, glandular, solid and acinar, while typically lacking desmoplasia [4]. Cytologically these tumors are composed of cells with eosinophilic ganular cytoplasm, and monotonous nuclei with prominent nucleoli [5]. It is noted that ACC and MANCs share many overlapping architectual and cytological features with pancreatic neuroendocrine tumor (NET), and immunohistochemical staining is essential to distinguish between these entities [6]. Studies on the histopathological characteristics of ACC and MANCs demonstrated a similar clinicopathological behavior between the two tumors, with worse survival and more aggressive behavor than those with grade 1 pancreatic NET [7]. Herein, we describe a unique case of MANC of the pancreas in which liver metastases showed variable grades and morphologies, with some powerfully mimicking low-grade well-differentiated NET.

Case report

The patient is a 70-year-old male with a history of diabetes, atrial fibrillation, hypertension, obesity, gout and obstructive sleep apnea who

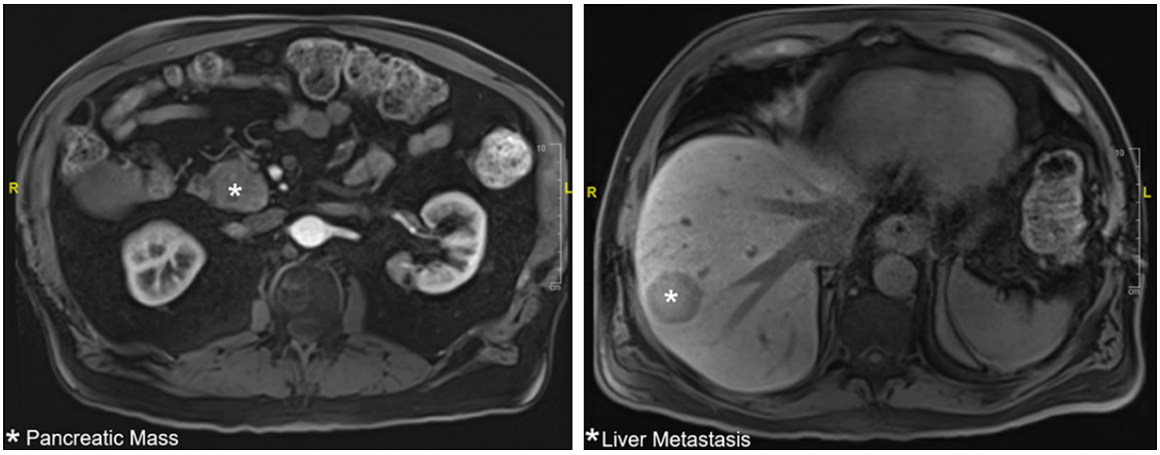

Figure 1. 4.6 cm mass (asterisk) in the pancreatic head (*left*) and multiple heterogeneous lesions (asterisk) in the liver consistent with liver metastases on magnetic resonance imaging (MRI).

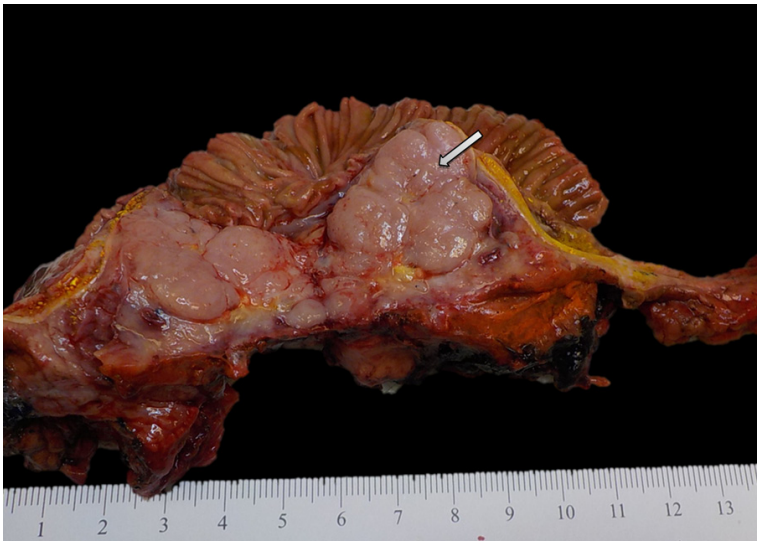

Figure 2. Pathological examination of the pancreatoduodenectomy specimen revealed a poorly circumscribed, nodular and solid neoplasm (arrow).

was incidentally found to have a pancreatic head mass (4.6 cm) on a magnetic resonance imaging (MRI) scan during a hospital admission for diabetic ketoacidosis. Multiple liver lesions measuring up to 3.9 cm (**Figure 1**) concerning for metastasis were also noted. Subsequent Ga-68 dotatate PET/CT showed mild tracer uptake in both the pancreatic mass and liver lesions. The findings were compatible with weakly somatostatin receptor positive pancreatic primary tumor with liver metastasis. His carcinoembryonic antigen (CEA, 10.5 ng/ml, normal range 0-2 ng/ml) and cancer antigen 19-9 (CA19-9, 12 u/ml, normal range 0-35 u/ml) levels were elevated. One of the liver lesions was biopsied revealing a tumor morphologically consistent with well-differentiated neuroendocrine tumor. However, immunohistochemical stains (i.e., chromogranin A or synaptophysin) to confirm the neuroendocrine differentation, or to confirm other differentiation were not performed. Following neoadjuvant chemotherapy with seven cycles of capecitabine and temozolomide, the patient underwent pancreaticoduodenectomy (Whipple procedure) and five segmental liver resections to remove metastatic lesions. Gross evaluation of the Whipple specimen revealed a 6.0 cm poorly circumscribed solid mass in the pancreatic head with a vaguely lobulated, fleshy, tan-pink cut surface (**Figure 2**).

Histologically, the tumor of the pancreas showed poor treatment response. The tumor was composed of solid sheets, nests and pseudo-glands of relatively monomorphic cells with granular cytoplasm and prominent nucleoli (**Figure 3A** and **3B**; hematoxylin & eosin stains, 40× and 400×). Apoptosis, mitoses and areas of necrosis were frequently seen. Pancreatic tumor cells were diffusely positive for two immunohistochemical markers of acinar differentiation, chymotrypsin and BCL10 (**Figure 3C**; BCL10 immunostaining, 200×). However, these

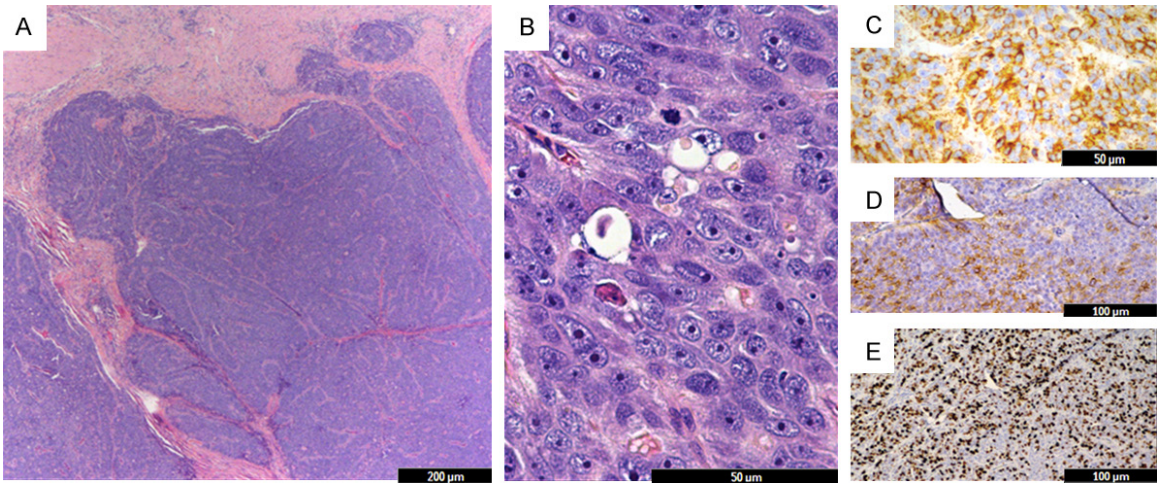

Figure 3. Pancreatic tumor diagnosed as MANC. Hematoxylin & eosin stains, 40× (A) and 400× (B); BCL10 immunostain, 200× (C); CD56 immunostain, 100× (D); Ki-67 immunostain, 100× (E).

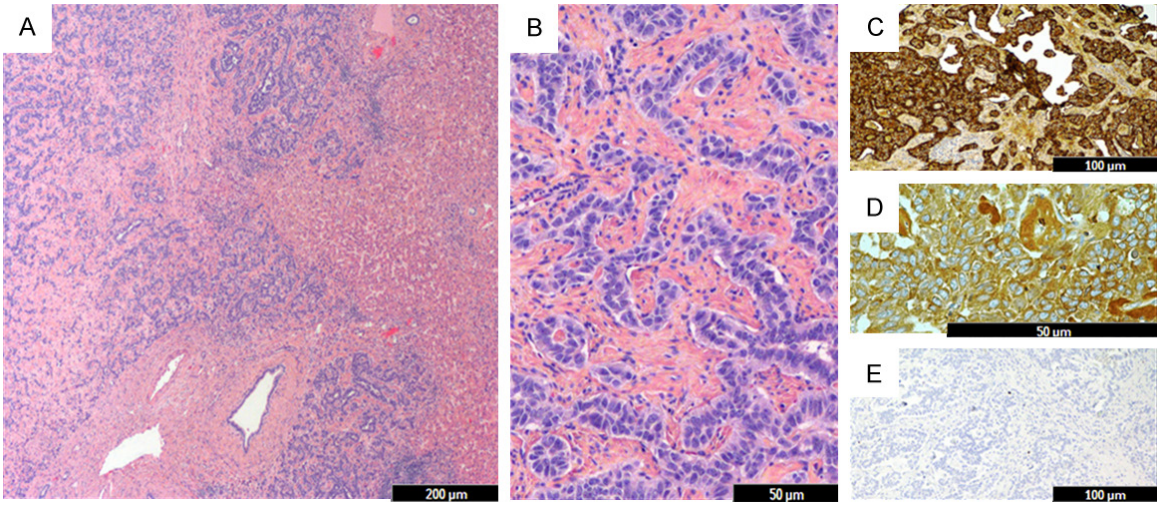

Figure 4. Liver metastases showed a traditional neuroendocrine architecture. Hematoxylin & eosin stains, 40× (A) and 200× (B); chromogranin immunostain, 100× (C); Chymotrypsin immunostain, 400× (D); Ki-67 immunostain, 100× (E).

tumor cells were only focally positive for neuroendocrine IHC stains synaptophysin, chromogranin and CD56 (**Figure 3D**; CD56 immunostaining, 100×). The proliferation index was very high at approximately 50% (**Figure 3E**; Ki-67 immunostaining, 100×).

As for the liver metastases, some foci of metastatic tumor showed morphology and immunohistochemical findings similar to that of the pancreatic primary. However, many metastatic foci demonstrated a more traditional neuroendocrine architecture made up of chords, ribbons and trabeculae (**Figure 4A** and **4B**; hematoxylin & eosin stains, 40× and 200×). These areas uniquely exhibited diffuse immunoreactivity for synaptophysin and chromogranin (**Figure 4C**; chromogranin immunostain, 100×), while still maintaining positivity for chymotrypsin (**Figure 4D**; chymotrypsin immunostaining, 400×). The corresponding proliferation index of these tumor cells was less than 1% (**Figure 4E**; Ki-67 immunostaining, 100×). Overall, the findings were consistent with a diagnosis of MANC.

Because of the diagnosis of MANC, the patient was placed on adjuvant FOLFIRINOX. He developed recurrent tumor in the liver and was

placed on Cisplatin/Etoposide for 5 cycles, followed by radiofrequency ablation of the residual liver metastases. He currently receives immunotherapy with radiation and shows good responses. His most recent imaging studies revealed no evidence of local recurrence in the pancreas, and stable liver lesions without clear evidence of viable tumor.

Discussion

MANCs are defined as having co-expression of both acinar and neuroendocrine IHC markers (such as CD56, synaptophysin and chromogranin), wherein each component of differentiation exceeds 30% [1, 2]. Here we reported a pancreatic tumor that uniquely showed foci of liver metastases with a morphology of well-differentiated NET exhibiting a low proliferation index (Ki-67 less than 1%) and strong, diffuse expression of neuroendocrine markers - a finding which was not seen in the pancreatic primary. Nevertheless, acinar differentiation as demonstrated by chymotrypsin positivity was maintained in these low-grade areas, confirming the mixed nature of the neoplasm.

Most cases of MANCs demonstrate an apparently uniform cell population with bidirectional immunohistochemically detected differentiation [2], however in rare instances MANCs show histologically distinct acinar and neuroendocrine patterns. The different histological patterns of MANCs might be attributable to the histogenesis of these tumors. Exocrine and neuroendocrine cells are hypothesized to originate from the same primitive stem cell, and the neuroendocrine cells in MANCs may remain in a primitive state. Another theory involves amphicrine cells that can differentiate to both acinar and neuroendocrine cells [8, 9]. Our case provides evidence for heterogeneous histogenesis of MANCs.

A study involving the genomic profiling of forty-four pancreatic ACCs (fourteen of which were MANCs) demonstrated that MANCs have similar clinical and genomic features when compared to their pure ACC counterparts [10]. For this reason, MANCs should be regarded as an ACC-subtype rather than subtype of neuroendocrine tumor or carcinoma, highlighting the importance of distinguishing this entity from a typical neuroendocrine neoplasm, especially a low-grade NET.

The findings in our case illustrate the varied morphology that can be seen within MANCs and the extent to which components of these neoplasms can mimic low-grade well-differentiated NET. Therefore diagnosis of MANCs on biopsy can be especially challenging due to morphological variability and limited quantity of tissue, and requires immunohistochemistry to demonstrate the endocrine and exocrine components.

Disclosure of conflict of interest

None.

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