

Primary clear cell adenocarcinoma of the pancreas: a case report and literature update

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Abstract: Primary clear cell carcinoma of pancreas is extremely rare. We present a case of a 64-year-old male with a mass in the distal body and tail of the pancreas. He underwent a distal pancreatectomy. The histopathology of tumor cells showed features with abundant clear cytoplasm and prominent cell boundaries. Immunohistochemical analysis of neoplastic cells showed reactions to antibodies against cytokeratin-7 and showed no reactions to antibodies against hepatocyte nuclear factor-1 β , carbonic anhydrase 9, synaptophysin, and chromogranin A. The patient was subsequently diagnosed with a primary clear cell carcinoma of the pancreas. This is the first time we have encountered it. We report this rare case and update the current literature of this tumor.

Keywords: clear cell carcinoma, pancreas, rare tumor

Introduction

According to the WHO classification, primary clear cell carcinoma of the pancreas is classified as a rare “miscellaneous” carcinoma;¹ morphologically it is similar to the clear cell carcinoma of renal. It was first described by Cubilla in 1980.² Because only few cases have been reported in the literature, the systematic overview of this tumor entity is insufficient. We report a rare case of primary clear cell carcinoma of the pancreas, review, and update the medical literature reported of this neoplasm.

Case report

A 64-year-old male presented to our hospital with a year history of epigastric pain, radiating to the back, and 6 kg weight loss. He had no history of carcinoma and had a history of laparoscopic cholecystectomy 10 years ago. He had smoked 20 cigarettes per day for 30 years and drank alcohol on occasion. The family history was negative for malignant diseases. Physical examination revealed tenderness over the epigastric area. There were no enlarged superficial lymph nodes nor any palpable mass in the abdomen; the liver and spleen were not enlarged. The laboratory findings were all within the normal ranges except tumor markers. Tumor marker assay showed that serum carcinoembryonic antigen (CEA) was 18.56 ng/mL (normal: 0–5 ng/mL), the serum cancer antigen (CA) 19–9 was 649.15 U/mL (normal: 0–37 U/mL), CA125 was 132.97 U/L (normal: 0–35 kU/L), CA242 was 393.93 U/L (normal: 0–20 kU/L), neuron-specific enolase was 11 ng/mL (normal: 0–25 ng/mL), CYFRA21–1 was 1.7 ng/L (normal: 0–5 ng/L). Abdominal computed tomography (CT) showed a 40 × 45 mm heterogeneous irregular hypodense mass in the distal body and tail of the pancreas (Figure 1A), and it was enhanced after infusion of contrast material (Figure 1B). Positron emission

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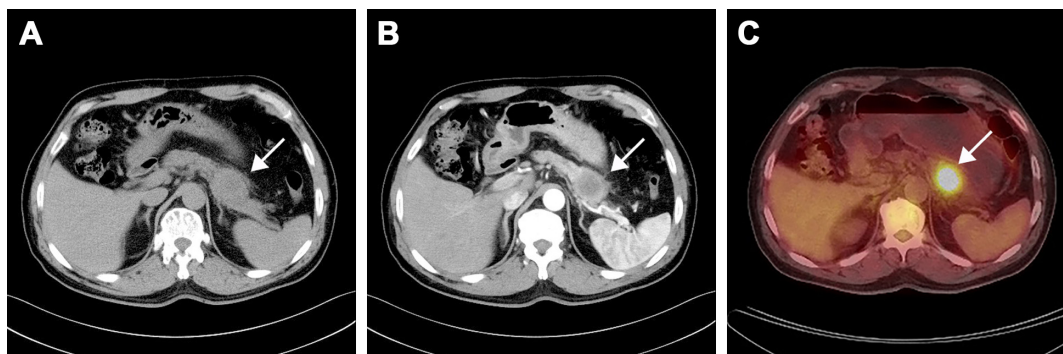


Figure 1 CT showed a 40 × 45 mm heterogeneous irregular hypodense mass in the distal body and tail of the pancreas (A), and it was enhanced after infusion of contrast material (B). PET-CT showed diffuse abnormal uptake only in the pancreatic mass (C).
Abbreviation: PET-CT, positron emission tomography-computed tomography.

tomography-CT showed diffuse abnormal uptake only in the pancreatic mass (Figure 1C).

Preoperatively, it was diagnosed as an adenocarcinoma of the pancreas. Distal pancreatectomy and splenectomy were performed, and the specimen was sent for histopathological examination (Figure 2A). Microscopically, highly atypical glands were composed of round or oval bulky cells with abundant clear cytoplasm and well-defined cell borders (Figure 2B and C). These tumor cells were arranged as solid trabeculae, cords, and tubules. The hobnail appearance of cell arrangement was seen in some tumor cells. Nuclei were small, moderately pleomorphic with irregular borders, and often were eccentrically placed. These features were present in more than 90% of the tumor cells. Immunohistochemistry showed strong and diffuse staining for cytokeratin-7 (CK-7) (Figure 3A), and the immunohistochemistry staining was negative for chromogranin A (CGA), synaptophysin (SYN), hepatocyte nuclear factor-1 β (HNF-1 β) (Figure 3B), and carbonic anhydrase 9 (CA9) (Figure 3C). The patient recovered well and was discharged 10 days after surgery. CT scan revealed multiple hepatic metastasis 3 months after surgery, then he received gemcitabine chemotherapy and died 2 months later.

Discussion

Clear cell carcinoma occurs mostly in the kidney, lung, ovary, and thyroid, but this tumor extremely rarely originates from the pancreas.³ This is also the first time we have encountered primary pancreatic clear cell carcinoma, diagnosed by pathology and immunohistochemistry. We summarized our case and the available 12 cases of pancreatic clear cell carcinoma reported previously (Table 1). The age of the patients (nine males and three females) was 46–75 years, an average age of 64.4 years. The clinical symptoms are not specific, mainly manifested as abdominal pain, radiating to the back, jaundice, anorexia weight loss, and so on. Tumor biomarkers in these patients, such as serum CA19–9, CA125, CA242, CEA, can be elevated or normal. There are no specific diagnostic criteria for it. The diagnosis relies mainly on typical pathological features with abundant clear cytoplasm and prominent cell boundaries. Immunohistochemistry is a complementary method to distinguish from other tumors. Immunohistochemistry almost showed reactions to antibodies against CK-7 in all cases, while showed no reactions to neuroendocrine markers such as CGA, SYN in all cases. Sequencing of the K-ras oncogene was analyzed in three cases,^{4–6} and a mutation at codon 12 in K-ras oncogene

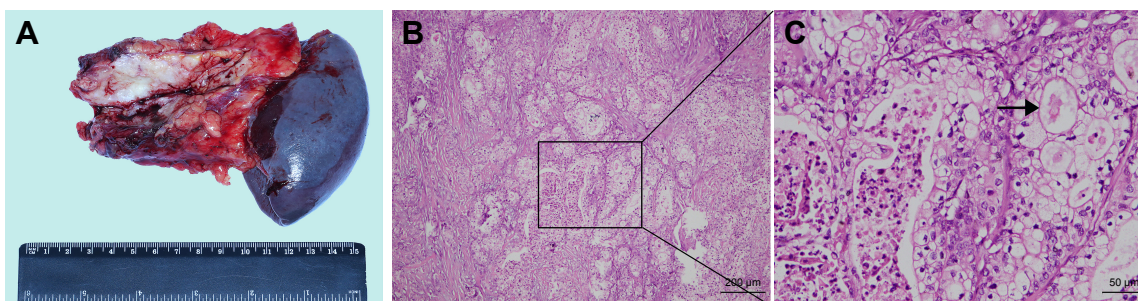


Figure 2 Gross photograph showing a firm and grayish white tumor from the spleen and the rest of the pancreas (A). Microscopically, it was predominantly composed of cells with abundant clear cytoplasm and well-defined cell borders (B, C).
Note: Black arrow points to a typical clear neoplastic cell.

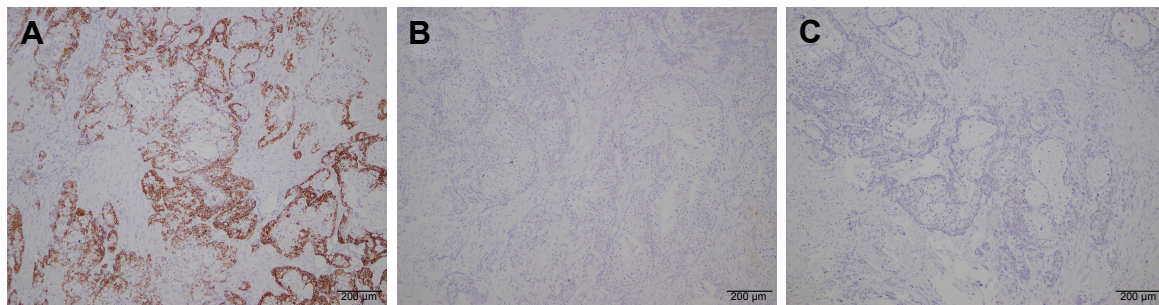


Figure 3 Immunohistochemically, tumor cells showed positivity for CK-7 (**A**) and negative for HNF-1 β (**B**) and CA9 (**C**).
Abbreviations: CA9, carbonic anhydrase 9; CK-7, cytokeratin-7; HNF-1 β , hepatocyte nuclear factor-1 β .

Table 1 The previously reported cases of primary clear cell adenocarcinoma of the pancreas

Author	Year	Age/sex	Location in pancreas	Morphology	Immunohistochemical profile
Present case	2018	64 M	Body and tail metastatic to liver	Abundant clear cytoplasm and prominent cell boundaries	Positive: CK-7 Negative: HNF-1 β , CA9, SYN, CGA
Modi Y et al	2013	75 F	Body and tail metastatic to liver	Highly atypical glands with abundant clear cells with well define borders	Positive: vimentin, CK-7, MUC, PAS, PASD, CEA, CA19-9 Negative: AFP, CK-20, CGA, SYN, Hep Par-1, HMB-45, and GPC3
Lee et al	2009	66 F	Tail, metastatic to liver	Nests of clear cells with rhabdoid features	Positive: P-CK, CK-7, CEA, EMA Negative: CK-20, CGA, SYN, SMA, and HMB-45
Jamali et al	2007	75 M	Uncinate process	Vacuolated cytoplasm and raisinoid nuclei with rhabdoid components	Positive: CK, Vimentin Negative: unspecified
Ray et al	2005	46 M	Head, metastatic to omentum	Pleomorphic and hyperchromatic nuclei with abundant clear cytoplasm	Positive: CK-7, CEA Negative: PSA, TG, HMB-45, SYN, CGA
Batoroev and Nguyen	2004	60 M	Head and body	Vacuolated cytoplasm and pleomorphic nuclei with conspicuous nucleoli	Positive: PAS, PASD, mucicarmine, CEA Negative: vimentin
Sasaki et al	2004	61 F	Body	Clear cell nests with scanty fibrous stroma	Positive: CK-8, CK-19, CA-199, AAT Negative: CEA, NSE, CGA, SYN, insulin, glucagon, somatostatin, gastrin, trypsin, and HMB45
Ray et al	2004	75 M	Tail	Pleomorphic cells with abundant clear cytoplasm (>95% clear cells)	Positive: CK-7, CAM 5.2, CK20, CEA, NSE Negative: SYN, CGA, vimentin, p53, HMB-45, CD10, PASD, AAT
Luttges et al	1998	53 M	Head	Primarily intraductal with solid invasive clear cell component	Positive: CK-7, CK-8, CK-18, CK-19, PASD, CEA, p53, AAT Negative: vimentin, CGA, SYN
Taziaux et al	1994	70 M	Head, extension into duodenum	Cords and nests in highly vascular stroma	Positive: KL-1 (epithelial), vimentin Negative: CGA, PSA
Kanai et al	1987	71 M	Body and tail, widely metastatic	Solid, trabecular, and nested	Positive: PAS, alcian blue Negative: sudan III
Urbanski and Medline	1982	57 M	Body, widely metastatic	Multiple clear cells interspersed throughout the spindle and giant cells	Positive: alcian green, PAS, PASD Negative: oil red
Cubilla and Fitzgerald	1980	Unspecified	Unspecified	Unspecified	Positive: mucin Negative: unspecified

Abbreviations: AAT, α -1-antitrypsin; AFP, alpha-fetoprotein; CA9, carbonic anhydrase 9; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CGA, chromogranin A; CK, cytokeratin; EMA, epithelial membrane antigen; GPC3, glypican-3; Hep Par-1, hepatocyte paraffin-1; HMB-45, human melanoma black-45; HNF-1 β , hepatocyte nuclear factor-1 β ; MUC, mucicarmine; PAS, periodic acid-Schiff; PASD, periodic acid-Schiff with diastase; PSA, prostate-specific antigen; SMA, smooth muscle actin; SYN, synaptophysin; TG, thyroglobulin.

was detected in two cases,^{5,6} providing molecular evidence of ductal origin. Based on the above characteristics, it was believed that pancreatic clear cell carcinoma is a variation of pancreatic ductal adenocarcinoma.⁵ HNF-1 β may be a useful marker to identify these clear cell carcinomas, and its overexpression may aid in stratifying survival rate,⁷ but in our case, HNF-1 β was negative. Primary pancreatic clear cell carcinoma must be distinguished from the pancreatic neuroendocrine tumor, solid pseudopapillary tumor, mixed ductal-endocrine carcinoma, and pancreatic metastasis from clear cell renal cell carcinoma.⁸ Of these, the most confusing tumor seems to be metastatic renal cell carcinoma.^{9,10} However, it is not very difficult to distinguish this tumor from it. History of renal tumors, preoperative CT, and MRI findings contribute to differential diagnosis. Postoperative immunohistochemistry of renal clear cell carcinoma showed positive reactions to antibodies against CD10, CA9, and Pax2, while immunonegative to CK-7.^{11–13} Because it is a rare tumor with very few cases reported previously, the incidence and prognosis are not well known for this neoplasm. However, we found that most of the reported cases showed aggressive behavior portending poor outcome, especially when the tumor was located in the tail of the pancreas.

Conclusion

We presented an extremely rare case of pancreatic clear cell ductal adenocarcinoma, which can be regarded as a rare variant of ductal adenocarcinoma in the proper morphology context supported by immunohistochemistry. Genetic analysis for detecting K-ras mutations and biomarker studies, such as HNF-1 β , would aid in the identification of this rare neoplasm, but it is not absolute.

Acknowledgments

Written informed consent was acquired from the patient with approval of case detail and related patient information for

publication use. Institutional approval was not required to publish this case report.

Disclosure

The authors report no conflicts of interest in this work.

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