Case Report

Hepatoid carcinoma of the pancreas combined with serous cystadenoma: a case report and review of the literature

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Abstract: Pancreatic hepatoid carcinoma (HC) is an extremely uncommon neoplasm of pancreas that resembles hepatocellular carcinoma (HCC). We report a case of incidentally detected pancreatic HC combined with a serous microcystic cystadenoma, in a 47-year-old man, while he was being evaluated for renal calculi. Contrast enhanced computed tomography (CECT) of abdomen revealed a lesion with mild heterogeneous enhancement in the tail of pancreas and another proximal lesion having moderate enhancement, and a calculus in the neck of gallbladder. Serum chromogranin, carcinoembryonic antigen (CEA) and CA 19-9 levels were within normal limits. He underwent laparoscopic distal pancreatectomy with splenectomy and cholecystectomy. Pathologically the distal tumor was encapsulated and characterized by eosinophilic cytoplasm, vesicular nucleus with prominent nucleolus and intranuclear eosinophilic inclusions. The cells were arranged in trabecular pattern separated by sinusoids. Canalicular and intercellular bile plugs were seen. On immunohistochemistry tumor cells were positive for hepatocyte specific antigen and weakly positive for alpha fetoprotein (AFP). The proximal tumor showed features of serous microcystic adenoma. Based on these findings, the case was diagnosed as hepatoid tumor of pancreas combined with serous microcystic cystadenoma. Post operative AFP was 1.75 IU/mL. The patient is on follow up for the last eight months and there is no evidence of recurrence.

Keywords: Pancreas; hepatoid carcinoma (HC); serous cystadenoma; alpha fetoprotein (AFP)

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Introduction

Hepatoid carcinoma (HC) is a neoplasm exhibiting features of hepatocellular carcinoma (HCC) in terms of morphology and immunohistochemistry which grows outside the liver. Since its first description by Ishikura *et al.* in the stomach which is the most common location, it has been described in different organs such as lung, pancreas, esophagus, papilla of Vater, colon, urinary bladder, renal pelvis, ovaries, biliary tract and the gallbladder (1-9). The true incidence and exact behavior of pancreatic HC still remain unclear as only few case reports are available in the literature. This paper reports a case of incidentally detected HC combined with a serous cystadenoma arising from pancreas in a 47-year-old male patient.

Case report

A 47-year-old gentleman was referred to our institute because of an incidentally detected pancreatic mass while being evaluated for renal calculi. He had recurrent left sided loin to groin pain and associated backache for 6 months. Physical examinations on admission were unremarkable. Ultrasound of abdomen showed bilateral renal calculi and a fairly well defined hypoechoic lesion measuring 2.3 cm × 2 cm in relation to the tail of pancreas with mild internal

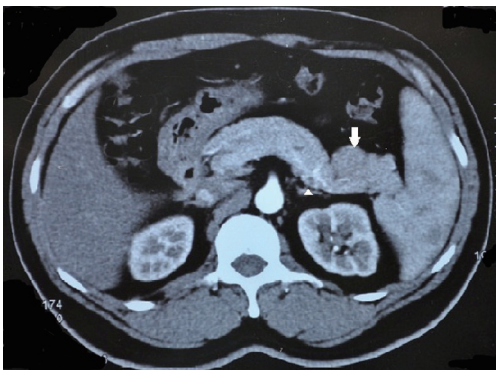

Figure 1 CECT of patient showing an exophytic lesion with mild heterogeneous enhancement in the tail of pancreas (arrow) and another smaller moderately enhancing lesion proximally (arrow head). CECT, contrast enhanced computed tomography.

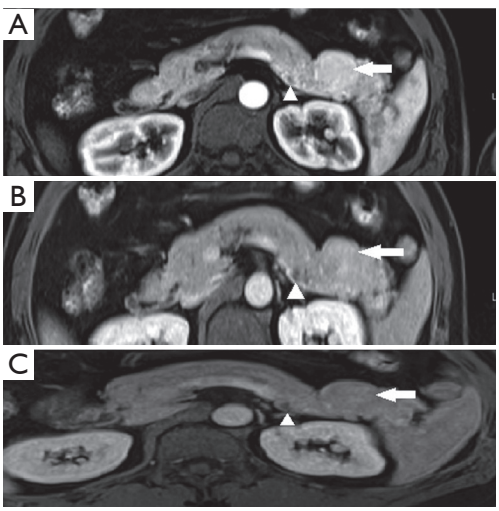

Figure 2 MR multiphase contrast imaging of pancreas showing enhancement patterns of tumors. (A) Arterial phase; (B) portal phase; (C) venous phase. Distal lesion (arrow) shows moderate uniform enhancement in arterial phase, washout in portal phase and further wash out in venous phase. The proximal (arrow head) lesion has moderate enhancement at periphery and a non enhancing area at the center.

vascularity. Contrast enhanced computed tomography (CECT) of abdomen showed two morphologically different lesions in the distal body and proximal tail of pancreas (*Figure 1*). Larger lesion was with well-defined margins and partially exophytic from the tail with mild heterogeneous enhancement. Smaller lesion was moderately enhancing and situated in the junction of body and tail of pancreas close

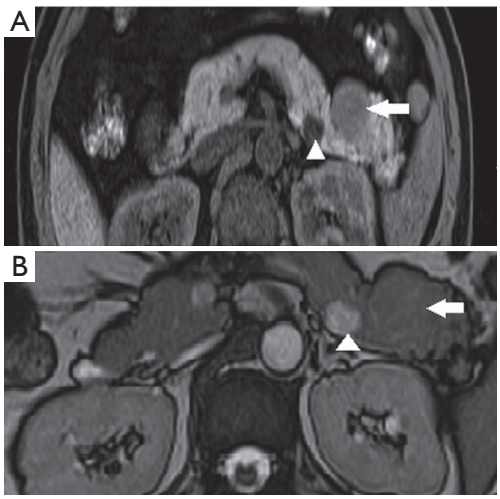

Figure 3 MRI signal intensity characteristics. (A) Distal tumor (arrow) is mildly hypointense and proximal tumor (arrow head) is moderate hypointense in VIBE sequence; (B) distal (arrow) tumor isointense and proximal tumor (arrow head) is hyperintense in TRUFI sequence. VIBE, volumetric interpolated breath-hold examination.

to posterior margin. The margins of lesion demonstrated higher enhancement. MRI also revealed similar findings and a small calculus in the neck of gall bladder. The distal lesion was of size 3.13 cm × 2.98 cm × 2.67 cm and mildly hypointense in T1W1, nearly isointense in T2W1 image. It showed moderate uniform enhancement in arterial phase, partial washout in portal phase and further wash out in hepatic venous phase (*Figure 2*). The tumor was mildly hypointense in VIBE (volumetric interpolated breath-hold examination) sequence, isointense in TRUFI (true fast imaging with steady-state free precession) sequence and minimally hyperintense in diffusion weighted imaging (DWI)-B400 with high apparent diffusion coefficient (ADC) in the central part with peripheral areas showing mild restriction in ADC images (*Figures 3*,*4*). The proximal lesion was of size 1.55 cm × 2.11 cm × 1.57 cm with moderate enhancement at periphery and a central non enhancing area (*Figure 2*). Laboratory panel showed (our lab's normal range in brackets); CA 19-9: 13.61 U/mL (0-35 U/mL), carcinoembryonic antigen (CEA): 1.68 ng/mL (0-3 ng/mL), chromogranin A: 41.35 ng/mL (<100 ng/mL), amylase: 113 U/L (28-100 U/L) and lipase: 153 U/L (13-60 U/L). With a possibility of non-functional neuroendocrine tumor, patient was taken up for surgery. Laparoscopic distal pancreatectomy with splenectomy and cholecystectomy

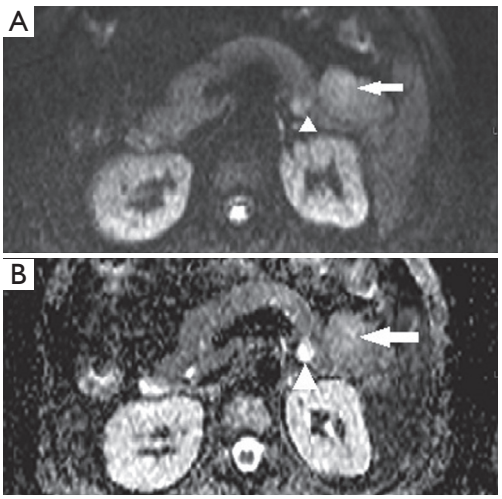

Figure 4 MRI signal intensity characteristics. (A) Distal lesion (arrow) has minimal hyperintensity and proximal one (arrow head) is hyperintense in diffusion weighted imaging (DWI)-B400; (B) proximal lesion (arrow head) has high apparent diffusion coefficient (ADC) in ADC image, while the distal lesion (arrow) has high ADC in the central part with mild restriction in the periphery.

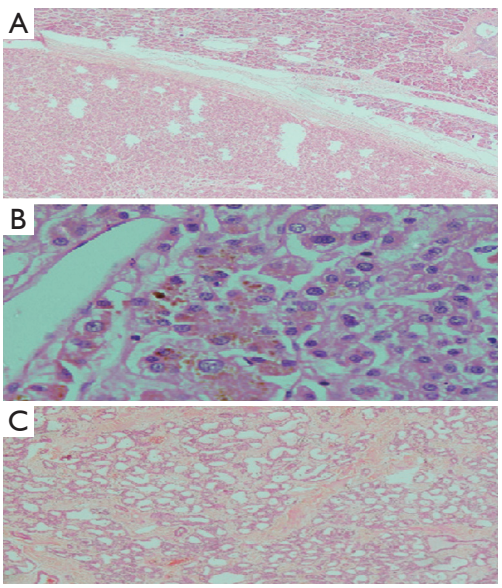

Figure 5 (A) Microscopy of distal tumor showing normal pancreas with a well encapsulated neoplasm composed of cells arranged in trabecular pattern and separated by sinusoids (H&E, ×40); (B) tumor cells are polygonal with abundant granular cytoplasm, centrally placed nucleus with prominent nucleoli. Canalicular and intracellular bile plugs are evident (H&E, ×200); (C) smaller proximal lesion showing serous cystadenoma-cystic spaces lined by cuboidal epithelium (H&E, ×100).

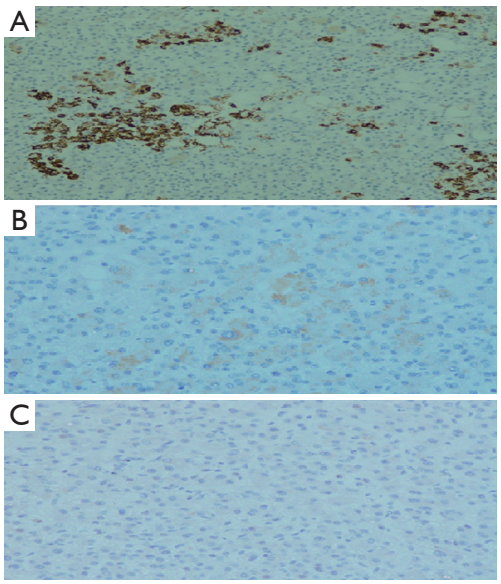

Figure 6 (A) Immunohistochemical (IHC) staining of the distal tumor for hepatocyte specific antigen-neoplastic cells are strongly positive (×100); (B) immunohistochemical (IHC) staining of the distal tumor for AFP-weakly positive (×200); (C) immunohistochemical (IHC) staining of the distal tumor for chromogranin-negative (×200).

were done. There was no evidence of any hepatic, peritoneal or lymph node metastasis.

Cut section of the distal lesion was well circumscribed, encapsulated and let out bile. Cut section of the proximal tumor showed tiny cystic spaces. Microscopic examination of the distal tumor revealed an encapsulated neoplasm with features of hepatocellular tissue. It was composed of cells in trabecular pattern separated by sinusoids (*Figure 5A*). Tumor cells had moderate eosinophilic granular cytoplasm and vescicular nucleus with prominent nucleolus and intranuclear eosinophilic inclusions. Canalicular and intercellular bile plugs were seen (*Figure 5B*). There was no bile ductule or portal triad. Kupffer cells were, however, present. Smaller proximal neoplasm had multiple cystically dilated spaces lined by cuboidal cells (*Figure 5C*). Peripancreatic lymph nodes showed reactive hyperplasia only. Resection margins were negative for neoplasm. Immunohistochemically the distal tumor was strongly positive for hepatocyte specific antigen (*Figure 6A*), glypican 3 (focal) and cytokeratins (AE1/AE3, CK8 and CK18), with weak positivity for alphafetoprotein (*Figure 6B*). Tumor cells were immunonegative for chromogranin (*Figure 6C*), EMA and CK-7. The liver like tissue showed CD 34

expressing capillarized sinusoids. Gallbladder revealed no specific pathology. Based on these findings the distal tumor was diagnosed as hepatoid tumor of pancreas and the proximal one as serous microcystic cystadenoma. Alpha fetoprotein (AFP) detected 2 weeks post resection was 1.75 IU/mL (<6.0 IU/mL). At eighth month of follow up AFP is 3.14 IU/mL and CECT of abdomen shows no evidence of recurrence.

Discussion

HC of the pancreas is an extremely rare neoplasm and only 23 cases have been reported in the literature so far (*Table 1*). The first pancreatic form of HC was reported by Hruban *et al.* in 1987 (10). The etiology and pathogenesis of pancreatic HC is still not clear and proposed theories of its origin mainly revolve around the transdifferentiation of pancreatic cells into hepatocytes and the common embryologic foregut derivation of the pancreas and liver (13,23). Though reported ages at presentation range from 21 to 80, most patients (16/23, 69%) were above 50 years of age. There is a clear male predominance (14/23, 60%). The most common presenting symptom was pain (6/23, 26%), either back or epigastric, followed by jaundice and weight loss. Many cases reported in the literature were asymptomatic or incidentally discovered (6/23, 26%) like our patient. More than 50% of Pancreatic HCs were located in the body or tail of the pancreas (13/23). Liver and lymph nodes are the most frequent sites of metastasis (23,31).

Preoperative diagnosis is often challenging, even with appropriate imaging and cytological examination. In a contrast enhanced CT scan of abdomen HC often reveals as a heterogeneous mass with irregular enhancement (32) as it is observed in this reported case. MR imaging features of pancreatic HC in our case are similar to neuroendocrine tumors, except for mild diffusion signals in the lesion (*Table 2*). When diagnosing primary pancreatic HC, it is important to exclude metastatic HCC by clinical and pathological examination. Serum AFP levels is found to be elevated in most cases and can be used postoperatively to assess completeness of resection and extent of response to chemotherapy, and to detect recurrence of the tumor during follow up (24,31,33,34). However, AFP secretion can also be noticed in other pancreatic tumors like acinar and ductal neoplasms, neuroendocrine tumors and pancreatoblastomas (13,35,36). Diagnosis mainly depends on specific pathological findings. The characteristic pathological features are medium to large polygonal cells with eosinophilic to clear cytoplasm, vesicular nuclei and prominent nucleoli growing in a perisinusoidal pattern, along with the demonstration of the presence of bile and an immunohistochemical profile characteristic of HCC (37). Bile production in the tumor as in our case though a rare finding is more conclusive for hepatoid neoplasm (13). IHC markers used for diagnosis include immunoreactivity with polyclonal antibodies against AFP, CEA, and more specific markers like hepatocyte-specific Hep-Par1 antibody and albumin mRNA detected by *in situ* hybridization (13,20).

Immunohistochemical profiling with cytokeratins (CK) can be helpful in differentiating hepatoid tumours from HCC. Hepatoid tumors are most often positive for pancytokeratin marker AE1/AE3 (92%), CK 19 (94-100%) and CK18, and negative for CK7 (38,39). CK20 positivity is seen in about 25-47% of hepatoid neoplasms (38,39). CK19 and 20 expression is very rarely seen in HCC (38-40). Monoclonal antibody HepPar1 is expressed by normal and neoplastic hepatocytes, and is considered more sensitive than AFP to diagnose HCC. It is also found to be positive in some cases of HCs, but diffuse positivity for HepPar1 is more consistent with HCC than hepatoid neoplasm (20,38,39). HCs can be differentiated from other AFP producing tumors like pancreatoblastoma and acinar cell carcinoma of pancreas by their histopathological features and by expression of liver specific proteins on immunohistochemistry. The presence of small acinar structures, mesenchymal components, or the characteristic squamous corpuscles would favor a diagnosis of pancreatoblastoma and in case of acinar cell carcinoma immunoreactivity with trypsin, chymotrypsin, or lipase can be detected.

Pancreatic HC can present in pure forms or in association with histologically different components such as adenocarcinoma or neuroendocrine tumors (20,24). Those with pure hepatoid or hepatocellular differentiation seem to have better survival and recurrence rates than patients with mixed-type tumors (27). In our case it was associated with a serous microcystic cystadenoma in an adjacent location. Only one out of 23 cases reported in the literature had microcystic cystadenoma as an associated component (15) (*Table 1*).

Surgical resection is considered as the mainstay of treatment whenever possible. Some authors have advocated adjuvant chemotherapy because of the metastatic potential of the tumor while others have found no added benefit (20). A certain degree of response to chemotherapy and multi-target tyrosine kinase inhibitor sorafenib was reported in locally unresectable, metastatic or recurrent disease (25).

Table 1 Review of main features of hepatoid carcinomas of the pancreas reported in the literature and our case

Sl No.	First author	Age/ sex	Presentation	AFP	CEA	Location	Associated component	Metastasis	Managed by	Follow up available (months)	Outcome
1	Hruban/1987 (10)	53/F	Subcutaneous fat necrosis	N/A	N	Tail	Acinar	Liver	Chemotherapy	2.75	Died of disease
2	Gardiner/1992 (6)	61/F	Jaundice and fatigue	E	E	Head	Ductal adeno-carcinoma	No	Whipple's procedure	N/A	N/A
3	Tanno/1999 (11)	65/F	Epigastric and back pain, anorexia, weight loss	E	E	Body-tail	Ductal adeno-carcinoma	Lymph node	Palliative care	6	Died of disease
4	Yano/1999 (12)	57/M	Jaundice, epigastric pain, vomiting and fever	E	E	Head	Ductal adeno-carcinoma	No, 3 months	Pancreaticoduodenectomy	3	Died of disease
5	Paner/2000 (13)	57/M	Vomiting, diarrhea, weight loss, skin rash	E	E	Tail	Glucagonoma	Liver, died months	Distal pancreatectomy with splenectomy plus chemotherapy	101	Died of disease
6	Paner/2000 (13)	28/M	Abdominal and back pain	E	E	Multi-focal	Ductal adeno-carcinoma	Wide-spread	Debulking plus chemotherapy	14	Died of disease
7	Lam/2001 (14)	64/F	Hypoglycemia	E	N/A	Tail	Insulinoma	Liver	Distal pancreatectomy with splenectomy plus chemoembolization of hepatic lesions and systemic chemotherapy	22	Died of disease
8	Cuilliere/2002 (15)	70/M	Incidental	N	N	Body	Serous cystadenoma	No	Distal pancreatectomy with splenectomy	12	Alive, NER
9	Hughes/2004 (16)	51/M	GI bleed	N	N	Tail	No	No	Pancreaticoduodenectomy	14	Alive, NER
10	Matsueda/ 2006 (17)	49/F	Weight loss	E	N	Wide-spread	No	Liver (detected after 12 months)	Total pancreatectomy, chemotherapy for mets, right lobectomy after 39 months of first surgery	48	Alive
11	Shih/2006 (18)	32/M	Asymptomatic	N	E	Tail	No	No	Distal pancreatectomy with splenectomy	18	Alive, NER
12	Oh/2006 (19)	21/M	Asymptomatic	E	N/A	Head	Neuroendocrine tumor	No	Pylorus-preserving pancreaticodudenectomy	7	Alive, NER

Table 1 (*continued*)

Table 1 (*continued*)

Sl No.	First author	Age/ sex	Presentation	AFP	CEA	Location	Associated component	Metastasis	Managed by	Follow up available (months)	Outcome
13	Hameed/2007 (20)	41/F	Jaundice, abdominal pain	E	E	Head	Neuroendocrine tumor	Liver	Pancreaticoduodenectomy plus chemotherapy and transarterial, chemoembolization	27	Died of disease
14	Cardona/2007 (21)	58/M	Back and flank pain	N	N/A	Body	No	No	Distal pancreatectomy with splenectomy	15	Alive, NER
15	Kubota/2007 (22)	56/M	Diabetes	N/A	N/A	Tail	No	No	Distal pancreatectomy with splenectomy	36	Alive, NER
16	Liu/2007 (23)	80/M	Nausea, diarrhea, weight loss	N	N/A	Head	No	No	Simple tumorectomy and partial transverse colon resection	8	Alive
17	Jung/2010 (24)	46/M	Dyspepsia	E	E	Head	Neuroendocrine tumor	No	Radical pancreaticoduodenectomy	4	Alive, NER
18	Petrelli/2012 (25)	37/M	Abdominal mass	N/A	N	Body	No	Liver, lymph node, lung	Chemotherapy-sorafenib	12	Died of disease
19	Kai/2012 (26)	79/F	Incidental	E	E	Tail	No	Infiltrating stomach and left adrenal gland. Liver metastasis 1 month post surgery	Distal pancreatectomy with splenectomy and gastrectomy	2	Died of disease
20	Kelly/2012 (27)	53/F	Epigastric pain	E	N/A	Body-tail	No	Liver metastases detected 22 months after diagnosis	Distal pancreatectomy with splenectomy. Completion pancreatectomy for residual tumour. Adjuvant chemotherapy	22	Alive
21	Huang/2012 (28)	52/M	Incidental	N/A	E	Head	Neuroendocrine tumor	No	Pylorus-preserving pancreaticoduodenectomy. Chemotherapy with sunitinib	16	Alive, NER
22	Majumder/ 2013 (29)	60/M	Left upper quadrant pain, jaundice	N	N/A	Head	No	Liver	Chemotherapy	3	Died
23	Steen/2013 (30)	61/F	Incidental	N	N/A	Tail	No	No	Distal pancreatectomy with splenectomy	72	Alive, NER
24	Our case	47/M	Incidental	N/A	N	Tail	Serous cystadenoma	No	Distal pancreatectomy with splenectomy (laparoscopic)	8	Alive, NER

M, male; F, female; E, elevated; N, normal; N/A, not available; AFP, serum alpha fetoprotein at diagnosis; CEA, carcinoembryonic antigen; NER, no evidence of recurrence.

Table 2 MRI signal intensity and contrast characteristics of pancreatic hepatoid carcinoma in our case

Variables	Characteristics
T1WI	Mildly hypointense
T2WI	Nearly isointense, with subtle central high signal
STIR	Mild hyperintense signal
TRUFI	Isointense
DWI, B50, B400, B800	Mixed signals, central areas more hyperintense
ADC images	High ADC in central part. Mild restriction in the periphery
Inphase-outphase	Some areas show signal drop
VIBE	Mild hypointense
Arterial phase	Moderate uniform enhancement
Portal phase	Partial washout
Late venous phase	Nearly isointense
5 minutes delayed	Minimally lower signals than parenchyma, homogeneous

STIR, short tau inversion recovery; TRUFI, true fast imaging with steady-state free precession; ADC, apparent diffusion coefficient; VIBE, volumetric interpolated breath-hold examination.

Petrelli *et al.* reported a case of metastatic HC (mainly to the liver, lymph nodes, and lungs) in a 37-year-old male treated with the multi-target tyrosine kinase inhibitor sorafenib (400 mg BD). It provided disease control for 8 months, which was confirmed by imaging and biochemical data. But they were forced to discontinue the therapy because of worsening liver failure (25). In 2012, Karayiannakis *et al.* reported an overall survival of 20 months in a 60-year-old female patient with hepatoid adenocarcinoma of the gallbladder treated with surgery followed by sorafenib for 15 months until her disease progressed (33). Lucas *et al.* reported a case of hepatoid adenocarcinoma of peritoneal cavity (which was closely related to colon) treated with FOLFOX (5-fluorouracil, leucovorin and oxaliplatin) after complete resection of the tumor. They report more than 3 years of follow up without any evidence of recurrence (38). Successful disease control with a regimen of 5-FU plus paclitaxel has been reported in a 64-year-old male patient with metastatic gastric hepatoid adenocarcinoma by Takeyama *et al.* in 2007 (34).

HCs of the gastrointestinal tract are generally considered as very aggressive neoplasms and have an unfavorable prognosis (39). Survival appears to be mainly depends upon the extent of the disease and completeness of resection. Longest survival reported with metastatic HC after resection is 8.5 years (13) (*Table 1*). Steen *et al.* reported more than 5-year survival without any recurrence after complete resection of a HC localized to the tail of pancreas, without any adjuvant therapy (30). Owing to its rarity further studies and long term follow up are needed to standardize the treatment and to correctly assess prognostic features.

Conclusions

In conclusion, though HC of pancreas is extremely rare it should be considered in preoperative differential diagnosis of pancreatic tumors especially when the lesion is associated with atypical clinical presentation and image findings. The diagnosis is mainly based on histopathological and immunohistochemical features and an early detection is vital as complete resection of the tumor appears to be the best option of the treatment.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Informed consent was obtained from the patient for publication of this case report and any accompanying images.

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