

Case Report

Successful treatment of a case with pancreatic neuroendocrine carcinoma with focal hepatoid differentiation: a case report and literature review

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Abstract: A 33-year-old Chinese woman was admitted to our hospital because of an elevated serum alpha-fetoprotein (AFP) level (300 ng/mL) found in a regular medical checkup. Computed tomography imaging of the abdomen revealed a 1.6 × 2.2 cm low-attenuation mass in the head of the pancreas, with no enlarged lymph nodes and no metastatic liver nodules, and a pancreaticoduodenectomy was performed and the tumor was completely removed. The tumor was solid, unencapsulated and poorly demarcated, measuring 2 × 1.4 × 1.8 cm, and the cut surface was grey-yellowish. Histologically, most of the areas of the tumor were composed of small monotonous and round shaped neuroendocrine cells, and approximately 20% of the areas were cells with indistinct cytoplasmic borders, large oval nuclei, prominent nucleoli and abundant eosinophilic cytoplasm, resembling the appearance of HCC. Immunohistochemical stains revealed that the neuroendocrine areas were diffusely positive for chromogranin, and the hepatoid areas showed diffuse and strong positive reaction to AFP. After surgery the AFP level reduced to normal. She received six cycles of postoperative chemotherapy and three years after the surgery was found to have an elevated serum AFP level again which gave rise to the suspicion of tumor recurrence, and a positron emission tomography-computed tomography confirmed the speculation by showing a hypermetabolic lymph node behind the body of the pancreas. She then underwent radiotherapy and the AFP level reduced to normal. Up till now she has survived 46 months since the initial diagnosis. This case and previous cases suggest that the serum AFP could be a useful marker for early detection of the disease, but careful differential diagnosis should be performed, and AFP could also be a marker for evaluation of therapeutic response and recurrence of the AFP-producing hepatoid carcinomas of pancreas.

Keywords: Pancreas, hepatoid carcinoma, endocrine carcinoma, alpha-fetoprotein

Introduction

After Ishikura et al. [1] first reported a HCC-like differentiation in a primary gastric tumor in 1985, this unique feature has been presented in multiple other extrahepatic sites, including ovary, esophagus, duodenum, pancreas, colon and rectum, gallbladder, endometrium, uterine cervix, fallopian tube, lung, kidney and urinary bladder [2]. Hepatoid carcinoma refers to a rare tumor entity that resembles hepatocellular carcinoma (HCC) in terms of cytological and architectural features, often mixed with areas of a more common tumor differentiation. It is mostly described in the stomach, and seldom in pancreas (16 cases reported until now). Here we report a case of Alpha-fetoprotein-producing

neuroendocrine carcinoma of the pancreas with focal hepatoid differentiation.

Clinical course

A 33-year-old Chinese woman was admitted to our hospital in April 2009 because of an elevated serum alpha-fetoprotein (AFP) level (300 ng/mL) found in a regular medical checkup. The patient displayed no signs or symptoms. The serum AFP level at that time was 407.5 ng/mL, and the cancer embryo antigen (CEA) and CA19-9 level were normal. The serum albumin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were within normal ranges. The coagulation function tests and serologic tests for hepatitis B and hepatitis C



Figure 1. CT scan of the abdomen showing the low-attenuation mass within the head of the pancreas (arrow).

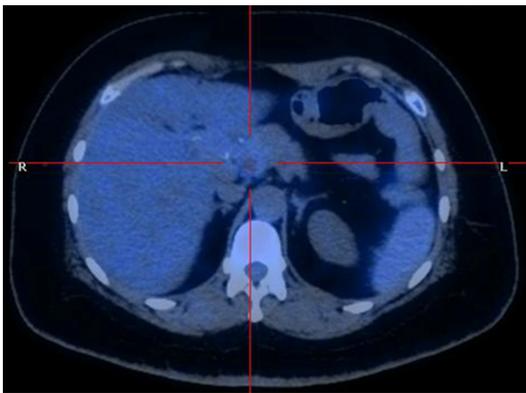


Figure 2. PET-CT showing a hypermetabolic lymph node behind the body of the pancreas (center of the crosshair).

virus were negative. Computed tomography (CT) of the abdomen revealed a 1.6 × 2.2 cm low-attenuation mass in the head of the pancreas, with no enlarged lymph nodes and no metastatic liver nodules (**Figure 1**). The patient underwent a pancreaticoduodenectomy and had an uncomplicated recovery. The primary pathologic diagnosis was undifferentiated carcinoma of pancreas, with partly neuroendocrine differentiation and partly hepatoid differentiation (revised pathologic diagnosis in the following paragraph). Her AFP level reduced to 232.3 ng/mL the day after the surgery, and about one month later, returned to normal range. Then the patient completed six cycles of chemotherapy (gemcitabine 1,000 mg/m²

intravenously on days 1, 8 and 15 of a 28-day cycle), and no severe complications were observed. A scheduled follow-up was maintained, and the CT images and AFP levels were used to monitor the tumor status.

In July 2012, the patient's AFP level went up to 93.1 ng/mL (CEA and CA19-9 being normal), meanwhile the CT scan showed no signs of local relapse or metastasis. Thus a positron emission tomography-computed tomography (PET-CT) was performed, which showed a hypermetabolic lymph node behind the body of the pancreas (**Figure 2**). The patient firstly received radiation therapy (45 Gy/8 fractions), and the AFP level reduced to normal (9.1 ng/mL) when the seventh fraction ended, then the patient began chemotherapy with the same regimen as before. Up till now she has finished two cycles of chemotherapy with the AFP level within normal range and has survived 46 months since the initial diagnosis. In December 2012, we were able to test her serum neuron specific enolase (NSE) and chromogranin A level, which was 0.2 ng/mL and 39.91 ng/mL respectively, both in normal range.

Pathological findings

In December 2012, during a multidisciplinary conference, this case was thoroughly reviewed and the slides were re-examined. Following the latest guidelines and consensuses, the revised pathologic diagnosis was neuroendocrine carcinoma (G3) of the pancreas with focal hepatoid differentiation.

Macroscopic examination showed a solid tumor unencapsulated and poorly demarcated, measuring 2 × 1.4 × 1.8 cm, and the cut surface was grey-yellowish. Histologically, most of the areas of the tumor were composed of small monotonous and round shaped neuroendocrine cells, and were rich in sinusoids. The cells were arranged in sheet pattern, with relatively basophilic cytoplasm compared with the hepatoid component (**Figure 3A**). Approximately 20% of the areas of the tumor were cells arranged in solid nests with indistinct cytoplasmic borders, large oval nuclei, prominent nucleoli and abundant eosinophilic cytoplasm, resembling the appearance of HCC (**Figure 3B**). No bile production was identified.

Immunohistochemical stains were performed to confirm the speculation. The neuroendocrine

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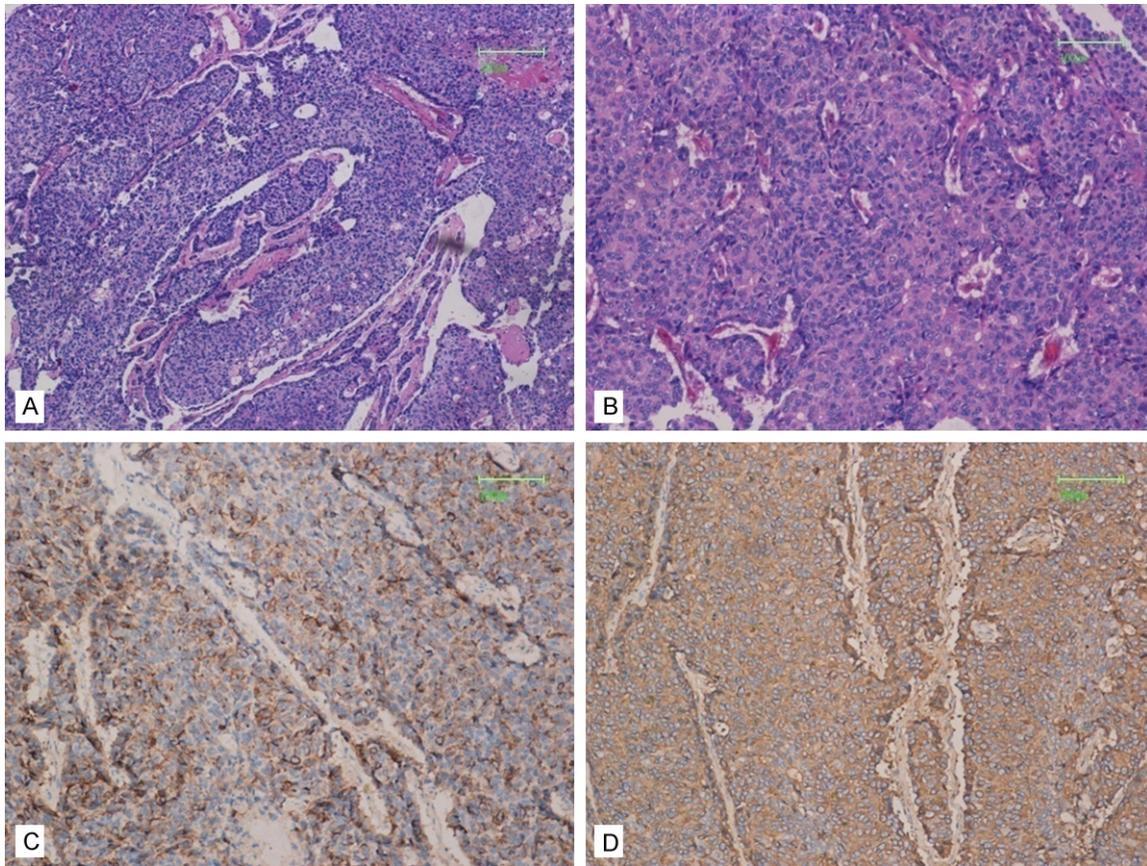


Figure 3. A: Hematoxylin-eosin staining of the neuroendocrine areas of the tumor. Small monotonous and round shaped cells were arranged in sheet pattern, with relatively basophilic cytoplasm compared with the hepatoid component (original magnification, $\times 100$). B: Hematoxylin-eosin staining of the neuroendocrine areas of the tumor ($\times 200$). Cells with indistinct cytoplasmic borders, large oval nuclei, prominent nucleoli and abundant eosinophilic cytoplasm were arranged in solid nests, resembling the appearance of HCC. C: Immunohistochemical analysis of the neuroendocrine areas for chromogranin ($\times 200$). D: Immunohistochemical analysis of the hepatoid areas for AFP ($\times 200$).

areas were diffusely positive for chromogranin (CHG) stain (**Figure 3C**). The hepatoid areas showed diffuse and strong positive reaction to AFP in the cytoplasm (**Figure 3D**). All areas were negative for CEA.

Discussion

The first hepatoid carcinoma of pancreas was reported in 1987, [3] since then 17 cases (including the present case) has been reported in English literature. **Table 1** summarizes the clinical and pathologic characteristics of the hepatoid carcinomas of pancreas. Nine male and eight female patients with a median age of 51 years (ranged from 21 to 80), and no significant difference identified regarding the mean age between two sexes (student's t-test using SPSS 16.0). Four patients were asymptomatic

[4-6], ten patients showed nonspecific symptoms such as epigastric pain, nausea, emesis, jaundice and weight loss [2, 7-14]. Meanwhile three patients showed specific symptoms associated with the certain proteins secreted by the tumor, such as subcutaneous nodules for lipase [3], dermatosis and diabetes mellitus for glucagon [8], and nocturnal sweating for insulin [15]. The tumor sizes in greatest dimension ranged from 1 to 11 cm, with an average of 6.2 cm. Ten tumors were located at the distal part of the pancreas, six were located at the head and one was diffuse. Seven of the 14 tumors were "pure" hepatoid tumors, and ten were mixed with other components characterized by endocrine, acinar and ductal differentiations. The most common elevated serum protein was AFP (8/17), and in our case it was the direct reason for patient to seek a doctor. CEA, CA19-

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Table 1. Clinical and pathologic characteristics of the hepatoid carcinomas of pancreas

Cases/year	Age/ sex	Clinical Presentation	Size (cm)	Location	Other components	Serum protein elevated	Metastasis	Survival
1. Hruban/1987 [3]	53/F	Increasing abdominal girth, polyarthritis, tender subcutaneous nodules	1	Distal	Acinar cell	Lipase	Liver, lymph node	2.75 mos, died
2. Tanno/1999 [7]	65/F	Epigastric and back pain, weight loss, anorexia	6	Distal	Ductal cell	AFP, CEA, CA19-9, CA12-5, DUPAN-2	Liver, lymph node	6 mos, died
3. Yano/1999 [2]	57/M	Jaundice, epigastric pain, vomiting and fever	9	Head	-	AFP, CEA	-	3 mos, died
4. Paner/2000 [8]	57/M	Epigastric mass, nausea, emesis, diarrhea, sever dermatosis, anemia, diabetes mellitus	6	Distal	Endocrine (glucagonoma)	Glucagon	Liver	102 mos, died
5. Paner/2000 [8]	28/M	Severe abdominal and back pain	8	Diffuse	Ductal cell	-	Gastric, ileal, colonic serosa	14 mos, died
6. Lam/2001 [15]	64/F	Nocturnal sweating	7	Distal	Endocrine (insulinoma)	Insulin	Liver	22 mos, died
7. Hughes/2004 [11]	51/M	Upper gastrointestinal hemorrhage	6	Distal	-	-	-	14 mos, alive
8. Shih/2006 [4]	32/M	-	7	Distal	-	-	-	18 mos, alive
9. Oh/2006 [9]	21/M	Nausea and vomiting, jaundice	3	Head	Endocrine	AFP, lipase	-	7 mos, alive
10. Matsueda/2006 [13]	49/F	Weight loss	ND	Distal	-	AFP, PIVKA-II	-	48 mos, alive
11. Hameed/2007 [17]	41/F	Gastro-esophageal reflux and jaundice	4.5	Head	Endocrine	AFP	Liver	26 mos, died
12. Liu/2007 [12]	80/M	Nausea, emesis, diarrhea, weight loss	6	Head	-	-	Colon	8 mos, alive
13. Jung/2010 [13]	46/M	Dyspepsia	9	Head	Endocrine	AFP	Lymph node	ND
14. Petrelli /2012 [6]	37/M	-	11	Distal	-	Amylase, lipase	Liver, lymph node	12 mos, died
15. Kai/2012 [5]	79/F	-	7	Distal	-	-(AFP not investigate)	Stomach, left adrenal gland	2 mos died
16. Kelly/2012 [14]	53/F	Epigastric pain	ND	Distal	-	AFP (postoperative)	-	22 mos, alive
17. Present case	33/F	-	2	Head	Endocrine	AFP	-	46 mos, alive

ND: not decribed.

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9, CA12-5 elevations were also documented, but were relatively rare. The proteins secreted by the other component of the tumor could also be detected in the serum. At the time of detection, 10 of 17 hepatoid tumors had metastases, with liver as the most common metastatic sites. Nine of 17 patients died of the disease, with a median survival of 12 months (ranged from 2 to 102 months).

There is no standard criteria to diagnose a hepatoid carcinoma, but similarity to HCC is required, which could be supported by morphological and immunohistochemical findings. Well differentiated hepatoid carcinoma displays polyhedral cells with abundant eosinophilic cytoplasm with a round, vesicular centrally placed nucleus and prominent nucleoli, arranged in trabecular, medullary or glandular patterns. Less differentiated hepatoid carcinoma displays haphazardly arranged pleomorphic cells [8]. Positive immunostaining for liver-produced proteins, such as AFP, and Hep Par 1 and the demonstration of albumin mRNA by in situ hybridization aids the diagnosis. The presence of bile production maybe more conclusive, but is relatively rare findings (8/17). Of 17 cases 12 showed positive immunohistochemical results for AFP and ten cases for CEA. Although the periodic acid-Schiff positive, diastase-resistant intracytoplasmic hyaline globules are a common finding in hepatoid carcinomas of other sites, stomach especially [8], it was found in only three hepatoid carcinomas of pancreas. In our case?

Since most of the patients showed nonspecific or no symptoms (14/17), and many of them had an elevated serum AFP level (8/17), the serum AFP could be an indicator for the hepatoid carcinoma of pancreas. But AFP could also be expressed in patients with malignant tumors such as HCC, germ-cell tumors, and some gastrointestinal tumors, even other types of pancreatic tumors (pancreatic ductal carcinoma, acinar cell carcinoma, islet cell tumor, and poorly differentiated pancreatic adenocarcinoma) [16], thus a careful differential diagnosis should be performed. In other types of AFP-producing pancreatic tumors, serum AFP level is a useful marker for evaluation of therapeutic response and recurrence [16]. In the hepatoid carcinomas of pancreas with an elevated serum AFP level, the serum AFP level was also

demonstrated to be able to evaluate the therapeutic response and recurrence [2, 10, 12, 15]. Our observation also supported this conclusion: The patient's AFP level reduced to normal range after the surgery, and three years later AFP level was elevated again which gave rise to the suspicion of tumor recurrence, and a PET-CT confirmed the speculation. The AFP level decreased when the patient received radiotherapy.

14 patients underwent surgical resection, of whom eight patients had metastases before the operation. After surgery two patients underwent radiotherapy, two patients underwent transcatheter arterial embolization (TAE) for hepatic metastases, six patients underwent postoperative chemotherapy using various agents including 5-fluorouracil, cisplatin, carboplatin, gemcitabine, adriamycin, streptozocin, dacarbazine, irinotecan and di-amino triazenoimidazol carboxamide. Of 14 patients underwent surgery, six patients died of the disease with a median survival time of 12.5 months (ranged from 2 to 102 months). Of the three patients with unresectable tumors, one patients received chemotherapy (regimen not described) but the effect was unsatisfactory (died 14 months later) [8], one patient received sorafenib treatment (died 12 months later) [6], and one patient received no medication (died 6 months later) [7]. The poor survival of the patients with unresectable tumors indicates that the stage of the disease is an important prognostic factor. Among the patients that had died, three "pure" hepatoid carcinomas had an average survival time of 5.7 months; four hepatoid carcinomas mixed with an endocrine component had an average survival time of 38 months, indicating that the latter may had a relatively favorable prognosis. But due to the small number of the cases, these differences could not be statistically significant, and no definite conclusion could be drawn.

From our own experience, an early detection allowed a complete surgical resection of the tumor followed by chemotherapy, which gave the patient a disease-free survival of three years, and the radiotherapy following the timely discovery of recurrence by monitoring the AFP level was also effective (AFP level reduce from 93.1 to 9.1 ng/mL). The choice of gemcitabine as the chemotherapy agent was based on the

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primary pathologic diagnosis of undifferentiated carcinoma of pancreas, with partly neuroendocrine differentiation and partly hepatoid differentiation. The diagnosis was made in 2009 when our understanding of neuroendocrine tumor of pancreas was limited. But since there was no agreed agent and the result was acceptable, we decided to continue to use the present regimen.

In summary, we have presented a case of AFP-producing neuroendocrine carcinoma of the pancreas with focal hepatoid differentiation, which was discovered solely because of an elevated serum AFP level. A review of literature shows that patients with unresectable hepatoid tumors of pancreas tend to have poor survival, and the serum AFP could be a useful marker for early detection of the disease, but careful differential diagnosis should be performed. It could also be a marker for evaluation of therapeutic response and recurrence of the AFP-producing hepatoid carcinomas of pancreas.

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Disclosure of conflict of interest

None.

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