Hepatoid Microcarcinoma of the Pancreas: A Case Report and Review of the Literature

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Hepatoid differentiation in pancreatic carcinoma is a rare phenomenon. It occurs either as a pure form or as a component with other subtypes. Herein, we report a 52-year-old man with an ampullary large cell neuroendocrine carcinoma presenting with obstructive jaundice for 2 months. A 0.5-cm nodule was found in the pancreatic head. Morphologically, the nodule was composed of exclusively hepatocytic tumor cells and sinusoids with dysplastic cytology and capsular invasion. The patient did not have a hepatic mass or ectopic normal liver tissue. This is the first reported case of ampullary large cell neuroendocrine carcinoma coinciding with a pancreatic hepatoid microcarcinoma. The clinicopathological features of pancreatic hepatoid carcinomas and their histogenesis are discussed. *(Chang Gung Med J 2012;35:285-91)*

Key words: large cell neuroendocrine carcinoma, ampulla of vater, hepatoid carcinoma, pancreas, ectopic hepatocellular carcinoma

Extrahepatic carcinoma with hepatoid differentiation can occur in a variety of organs, especially in the stomach and ovaries.[1] Hepatoid foci often arise in a background of usual adenocarcinoma.[1,2] Exclusive hepatocytic differentiation is extremely rare. In the pancreas, hepatoid carcinomas are regarded as a heterogeneous group of tumors with or without another histological component, and carcinomas with pure hepatocytic features have been designated variously as hepatoid carcinoma or ectopic hepatocellular carcinoma.[2-10] To date, only eight such pancreatic carcinomas have been reported. Herein, we describe the ninth case which was small.

CASE REPORT

A 52-year-old man with type 2 diabetes mellitus for 10 years had progressive jaundice, anorexia, and epigastralgia for 2 months. The laboratory panel showed elevated bilirubin (total/direct: 2.5/1.2 mg/dL) and alkaline phosphatase (360 U/L) levels in the serum. Computed tomography revealed an irregular, hypovascular lesion occupying the ampulla of Vater without notable lymphadenopathy or hepatic lesions. Endoscopic retrograde cholangiopancreatography revealed a stricture at the ampulla of Vater, and a nasobiliary drainage tube was placed to relieve the obstructive jaundice. Serological tests for hepatitis B and C viruses were negative, and the level of carcinoembryonic antigen was slightly elevated at 6.2 ng/mL. Subsequently, the patient underwent a pylorus-preserving pancreaticoduodenectomy.

The received specimen had an ulcerative, white tumor (1.6 x 1.5 x 1.0 cm) at the ampulla of Vater. The tumor infiltrated the adjacent pancreatic parenchyma and caused dilation of the common bile

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duct. A well-circumscribed, yellowish-green pancreatic nodule 0.5 cm in diameter was found in the pancreatic head (Fig. 1).

Microscopically, the ampullary tumor displayed an organoid growth pattern with acinar or cribriform structures and peripheral nuclear palisading (Fig. 2A). However, no tumor cell rosette was found. The tumor cells were large and polyhedral and had a moderate amount of amphophilic or basophilic cytoplasm and large vesicular nuclei containing conspicuous nucleoli (Fig. 2B). Marked nuclear pleomorphism and brisk mitotic activity (> 20/10 high power fields) were noted with the presence of atypical mitotic figures. The stroma appeared fibrotic or desmoplastic with areas of myxoid change or pink hyalinization. Immunohistochemically, the ampullary tumor cells were positive for cytokeratin (CK) 7 (Fig. 3A), CAM 5.2, chromogranin A (Fig. 3B), and synaptophysin but were negative for CK 20, CD56, CDX-2, thyroid transcription factor-1, and hepatocyte-paraffin-1 (Fig. 3C). Therefore, this ulcerative tumor was classified as a primary large cell neuroendocrine carcinoma (WHO 2010 histological grade 3, G3) of the ampulla of Vater.

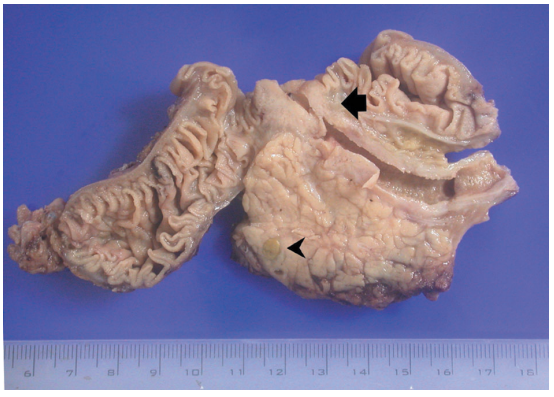

Fig. 1 An ulcerative tumor obliterating the common bile duct is seen at the ampulla of Vater (arrow). A yellow-greenish nodule (arrowhead) is seen in the pancreatic head.

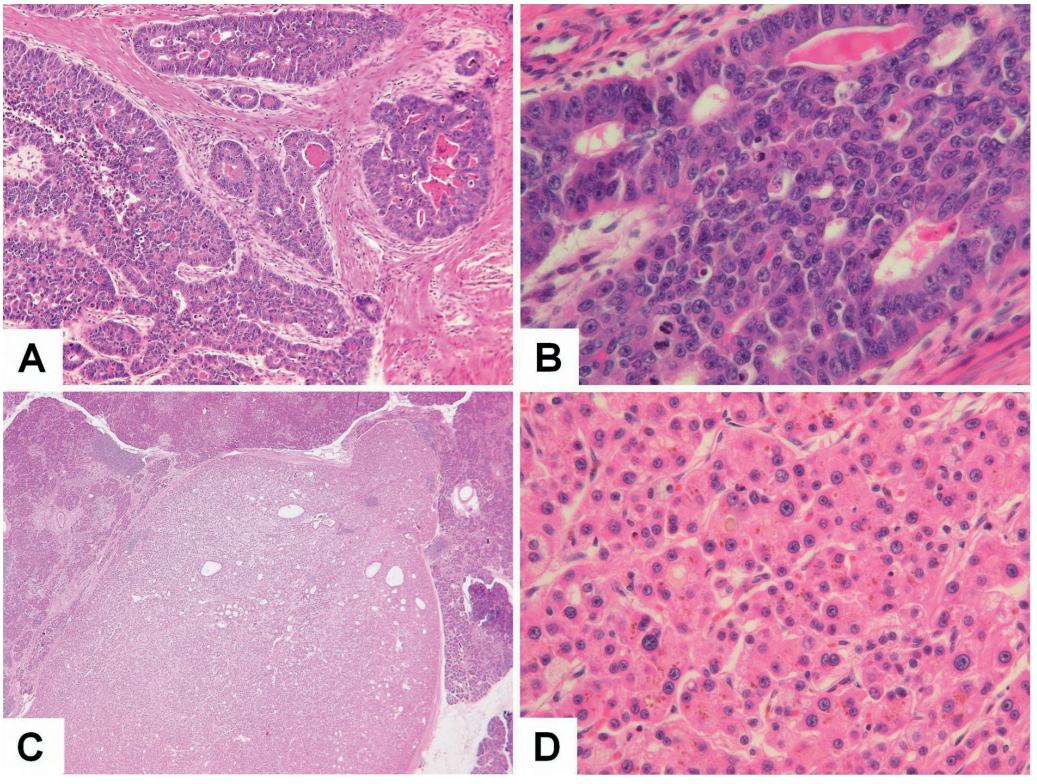

Fig. 2 (A) (B) The ampullary tumor is composed of large malignant cells in cribriform and pseudoglandular structures (hematoxylin-eosin x 100, x 400). (C) The intrapancreatic nodule is encapsulated with focal capsular invasive tonguelike structures (hematoxylin-eosin x 20) (D) Dysplastic hepatoid cells are arranged in trabecular or acinar patterns with abundant bile plugs (hematoxylin-eosin x 400).

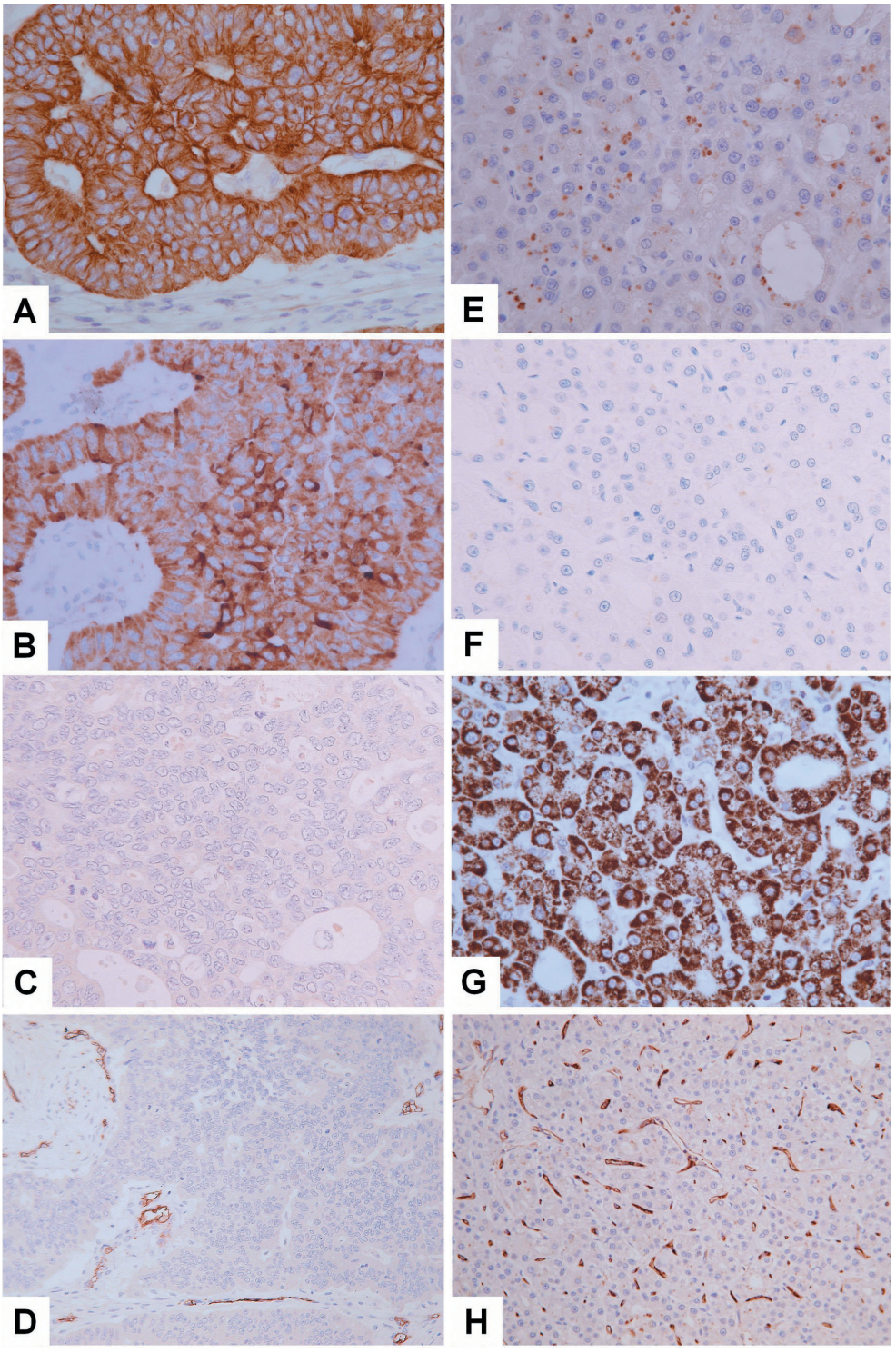

Fig. 3 The results of immunohistochemical studies. (A) to (D) is the ampullary large cell neuroendocrine carcinoma, and (E) to (H) is the pancreatic hepatoid microcarcinoma. (A) (E) cytokeratin 7 (x 400). (B) (F) chromogranin A (x 400). (C) (G) hepatocyte-paraffin-1 (x 400). (D) (H) CD34 (x 100).

Microscopic examination of the pancreatic nodule revealed a tonguelike invasion into the surrounding pancreatic lobules (Fig. 2C). The nodule consisted of bile-producing hepatoid tumor cells arranged in thick trabeculae (2–3 cells in thickness) or tubules with intervening sinusoid-like vascular spaces (Fig. 2D). The neoplastic cells had eosinophilic granular cytoplasms and central rounded or oval nuclei with single prominent nucleoli. Occasional binucleation and mild nuclear pleomorphism could be observed. No ectopic normal liver tissue was noted around the nodule. Immunohistochemically, the tumor cells showed strong cytoplasmic positivity for hepatocyte-paraffin-1 (Fig. 3G) with completely CD34-positive sinusoids (Fig. 3H). Membranous staining of CAM 5.2 was noted, along with negativity for CK 7/20 (Fig. 3E), chromogranin A (Fig. 3F), synaptophysin, glypican-3, α-fetoprotein, and CD 117. The nodule was diagnosed as a pancreatic hepatoid microcarcinoma because of the lack of a hepatic mass in this patient.

All regional lymph nodes were negative for metastatic carcinoma initially. The postoperative course of this patient was uneventful until the 11th month, at which time he had recurrence of the tumor at the anastomosis site; neuroendocrine carcinoma metastasis was observed in the liver. Thereafter, he received oral sunitinib and was still alive at the time of writing, 4 months after the recurrence and metastasis were identified.

DISCUSSION

In addition to an ampullary large cell neuroendocrine carcinoma, we found an unusual intrapancreatic nodule with a combination of hepatocytic differentiation and malignant features in this patient. We made a diagnosis of pure hepatoid carcinoma because stromal invasion and neovascularization are early signs of hepatocellular carcinoma.[11] Furthermore, this diagnosis was also supported by the dysplastic cytology, abnormal architecture, and absence of residual normal liver tissue and other neoplastic components.[3,9,10] While 10.9% of ampullary carcinomas are associated synchronously with other primary malignancies, no previous report has described ampullary carcinoma occurring simultaneously with pancreatic carcinoma.[12] Thus, this is the first reported case of concurrent ampullary large cell neuroendocrine carcinoma and pancreatic pure hepatoid carcinoma.

Pancreatic hepatoid carcinoma can arise with neuroendocrine neoplasms. In the literature, one case with malignant glucagonoma, one with malignant insulinoma, and three with neuroendocrine carcinoma have been reported.[2,3,13-15] The neuroendocrine components in these cases were all intermingled intimately with hepatoid areas. In contrast, our case contained two separate lesions exhibiting different morphological and immunohistochemical profiles.

Pancreatic carcinoma with solely hepatocellular features is reminiscent of ectopic hepatocellular carcinoma or metastatic hepatocellular carcinoma.[9,10,16] The latter occurs rarely and as a late event, so the original hepatic tumor is usually obvious at presentation.[16] Thorough clinical evaluation and imaging excluded this possibility in the current case. Ectopic hepatocellular carcinoma is identical to pure hepatoid carcinoma in both morphology and immunophenotype. The crucial distinguishable feature is whether the tumor has residual normal liver tissue.[9,10] However, there was no normal liver tissue in both cases classified as pancreatic ectopic hepatocellular carcinoma in the literature. Therefore, the distinction between hepatoid carcinoma and ectopic hepatocellular carcinoma remains somewhat arbitrary. In our case, the pancreatic hepatoid carcinoma was less than 1 cm, which allowed us to observe the tumorigenesis of pure hepatoid carcinoma at an early stage. Although there was no solid evidence, the lack of normal liver tissue around the microcarcinoma favors the possibility of a malignant change of metaplastic cells from uncommitted stem cells rather than from handicapped ectopic liver tissue.[2,9,10] Because of the obscurity of the difference between pancreatic pure hepatoid carcinoma and ectopic hepatocellular carcinoma, pancreatic carcinomas with pure hepatoid features might be regarded as the same group.

To the best of our knowledge, only eight cases of pancreatic carcinoma with exclusive hepatocytic features have been reported in the literature.[2,4-10] The clinical and pathological features of these cases and our present case are summarized in the Table.[2,4-10] The ages of the patients ranged from 28 to 80 years. The clinical manifestations included lesions found incidentally, abdominal pain, back pain, emesis, gastrointestinal bleeding, diarrhea, weight loss, and fever. Elevation of the alpha-fetoprotein level was

Table Clinicopathologic Features in Reported Cases of Pancreatic Carcinoma with Pure Hepatocytic Differentiation

Authors	Age (year)	Sex	Presentation	AFP (ng/mL)	Location	Size (cm)	Diagnosis and differentiation	Metastasis	Follow up (months)	Out-come
Yano et al.[4]	57	M	Epigastric pain, vomiting, fever	177.6	Head	9	Hepatoid carcinoma, unspecified	Liver, peritoneum	3	Died
Paner et al.[2]	28	M	Severe abdominal and back pain	NA	Diffuse	8	Hepatoid carcinoma, poorly differentiated	Gastric, ileal, colonic serosa	14	Died
Hughes et al.[5]	51	M	Gastrointestinal bleeding	NA	Body	6	Hepatoid carcinoma, unspecified	none	14	ANED
Shih NN et al.[6]	32	M	Incidental finding	Normal	Tail	7	Hepatoid carcinoma, unspecified	none	18	ANED
Matsueda et al.[7]	29	F	Asymptomatic with weight loss	623	Tail	NA	Hepatoid carcinoma, unspecified	Liver (at 12 months)	48	Alive
Liu CZ et al.[8]	80	M	Nausea, emesis, diarrhea, weight loss	normal	Head	6	Hepatoid carcinoma, poorly differentiated	Invasion to colon	8	ANED
Cardona et al.[9]	58	M	Back and flank pain	NA	Body	3.3	Ectopic HCC, well differentiated	none	15	ANED
Kubota et al.[10]	56	M	Incidental finding	NA	Tail	6.3	Ectopic HCC, moderately differentiated	none	36	ANED
Current case	52	M	Incidental finding	NA	Head	0.5	Hepatoid carcinoma, well differentiated	none	16	Alive

Abbreviations: AFP: alpha-fetoprotein; M: male; F: female; NA: not available; HCC: hepatocellular carcinoma; ANED: alive with no evidence of disease.

noted in two out of four cases. Pancreatic carcinoma with exclusive hepatocytic features had no predilection for location in the pancreas and ranged from 0.5 to 9 cm. Morphologically, these tumors were usually well circumscribed with capsule formation and were composed of hepatoid tumor cells arranged in trabecular, pseudoacinar, or solid patterns with sinusoids and bile plugs, depending on their level of differentiation. Of the 5 tumors with information on differentiation, only two were well differentiated (including the current one), one was moderately differentiated, and two were poorly differentiated. The degree of diffentiation seemed to be almost equally distributed. All reported cases had the same immunophenotype as real hepatocellular carcinoma with respect to staining for hepatocyte-paraffin-1 and polyclonal carcinoembryonic antigen in a bile canalicular pattern. Three of the nine cases developed metastatic foci in the liver or peritoneum. Two patients died of the disease at 3 and 14 months. Patients with pure hepatoid carcinoma had a median survival period of 14 months, with a mean survival period of 18.9 months. However, conclusions on prognosis are premature and more cases are needed to define the behavior of this lesion. Complete surgical resection is still the first choice for treatment.

In conclusion, we present the first case of ampullary large cell neuroendocrine carcinoma coexisting with a pancreatic hepatoid microcarcinoma. When diagnosing primary pancreatic hepatoid carcinoma, it is important to exclude metastatic hepatocellular carcinoma and ectopic hepatocellular carcinoma by clinical and pathological examination. The existence of a hepatoid microcarcinoma suggests that a metaplastic change is the possible histogenesis of the hepatocytic differentiation. Because of the limited number of cases and short follow-up times, the prognosis of pure hepatoid carcinoma is still unclear.

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REFERENCES

1. Metzgeroth G, Ströbel P, Baumbusch T, Reiter A, Hastka J. Hepatoid adenocarcinoma-review of the literature illustrated by a rare case originating in the peritoneal cavity. Onkologie 2010;33:263-9.
2. Paner GP, Thompson KS, Reyes CV. Hepatoid carcinoma of the pancreas. Cancer 2000;88:1582-9.
3. Hameed O, Xu H, Saddeghi S, Maluf H. Hepatoid carcinoma of the pancreas: a case report and literature review of a heterogeneous group of tumors. Am J Surg Pathol 2007;31:146-52.
4. Yano T, Ishikura H, Wada T, Kishimoto T, Kondo S, Katoh H, Yoshiki T. Hepatoid adenocarcinoma of the pancreas. Histopathology 1999;35:90-2.
5. Hughes K, Kelty S, Martin R. Hepatoid carcinoma of the pancreas. Am Surg 2004;70:1030-3.
6. Shih NN, Tsung JS, Yang AH, Tsou MH, Cheng TY. A unique pancreatic tumor with exclusive hepatocytic differentiation. Ann Clin Lab Sci 2006;36:216-21.
7. Matsueda K, Yamamoto H, Yoshida Y, Notohara K. Hepatoid carcinoma of the pancreas producing protein induced by vitamin K absence or antagonist II (PIVKA-II) and alpha-fetoprotein (AFP). J Gastroenterol 2006;41:1011-9.
8. Liu CZ, Hu SY, Wang L, Zhi XT, Jin B, Zhu M, Wachtel MS, Frezza EE. Hepatoid carcinoma of the pancreas: a case report. Chin Med J 2007;120:1850-2.
9. Cardona D, Grobmyer S, Crawford JM, Liu C. Hepatocellular carcinoma arising from ectopic liver tissue in the pancreas. Virchows Arch 2007;450:225-9.
10. Kubota K, Kita J, Rokkaku K, Iwasaki Y, Sawada T, Imura J, Fujimori T. Ectopic hepatocellular carcinoma arising from pancreas: a case report and review of the literature. World J Gastroenterol 2007;13:4270-3.
11. Kojiro M, Roskams T. Early hepatocellular carcinoma and dysplastic nodules. Semin Liver Dis 2005;25:133-42.
12. Kamisawa T, Egawa N, Tsuruta K, Okamoto A, Horiguchi S, Funata N. An investigation of primary malignancies associated with ampullary carcinoma. Hepatogastroenterology 2005;52:22-4.
13. Lam K, Lo C, Wat M, Fan ST. Malignant insulinoma with hepatoid differentiation: a unique case with alpha-fetoprotein production. Endocr Pathol 2001;12:351-4.
14. Oh HJ, Cheung DY, Kim TH, Kim SS, Kim MS, Kim JI, Park SH, Han JY, Han NI, Kim JK, Lee YS, Kim EK, Jung ES. A case of hepatoid carcinoma of the pancreas. Korean J Gastroenterol 2006;47:389-93.
15. Jung JY, Kim YJ, Kim HM, Kim HJ, Park SW, Song SY, Chung JB, Kang CM, Pyo JY, Yang WI, Bang S. Hepatoid carcinoma of the pancreas combined with neuroendocrine carcinoma. Gut Liver 2010;4:98-102.
16. Lowe CJ Jr, Riepe SP, Wood WC. Hepatocellular carcinoma presenting as a pancreatic head mass: report of an unusual case. Am J Clin Oncol 1997;20:509-10.

胰臟微小類肝細胞癌：案例報告與文獻回顧

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類肝細胞分化發生在胰臟癌是很罕見的。它可以單獨出現或與其他類型的癌合併出現。在本文中，我們發表一名五十二歲的男性因罹患腹壺大細胞神經內分泌細胞癌而表現出爲期二個月的黃膽。除此之外，在胰臟頭部發現一顆 0.5 公分大的結節。病理檢查下，此結節呈現單純的類肝細胞分化，合伴細胞多形性以及包囊浸潤。在此病人沒有發現肝腫瘤或異位性的肝細胞組織。此案例爲第一例腹壺大細胞神經內分泌細胞癌合併胰臟單純類肝細胞癌。在此，我們就胰臟類肝細胞癌的臨床病理特徵與組織發生學加以討論。(長庚醫誌 2012;35:285-91)

關鍵詞：大細胞神經內分泌細胞癌，維氏腹壺，類肝細胞癌，胰臟，異位肝細胞癌

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