Islet Cell Tumor in von Hippel-Lindau Disease

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We describe a 42-year-old man with von Hippel-Lindau disease and islet cell tumor of the pancreas. He had retinal and cerebellar hemangioblastomas. His sister had pheochromocytoma. A pancreatic tumor was detected by ultrasonography at his periodical medical checkup. Contrast enhanced computed tomography and abdominal angiography revealed a hypervascular tumor in the pancreatic head. Histological examination of the resected tumor revealed characteristics of islet cell tumor of the pancreas, which was positive for chromogranin-A, S-100 protein, and pancreatic polypeptide, but was negative for insulin, gastrin, glucagon, somatostatin, vasoactive intestinal peptide, serotonin, and adrenocorticotrophic hormone. (Internal Medicine 37: 295–299, 1998)

Key words: pancreatic polypeptide producing tumor, hemangioblastoma

Introduction

Von Hippel-Lindau (VHL) disease is an autosomal dominant disorder that causes a variety of neoplastic diseases such as hemangioblastomas of the central nervous system (CNS), retinal hemangioblastomas, renal cell carcinomas, pheochromocytomas, renal and pancreatic cysts, and epididymal cystadenomas (1, 2). In 1964, Melmon and Rosen (3) reported a large number of families with VHL disease and proposed a diagnostic criteria: two or more hemangioblastomas, or a single hemangioblastoma in association with a visceral manifestation. When there is a family history of retinal or CNS hemangioblastoma, only one hemangioblastoma or visceral manifestation is required. In VHL disease, pancreatic cysts are common, but islet cell tumor of the pancreas is very rare (1, 2, 4). We describe a patient with VHL disease who had pancreatic polypeptide (PP) producing tumor of the pancreas.

Case Report

A 42-year-old man was admitted to our hospital because of a pancreatic tumor detected by ultrasonography at his periodical medical checkup. Retinal hemangioblastoma was noted at the age of 13 and his left eye was removed at the age of 15. He had no symptom except for progressive impairment of vision. His elder sister died of pheochromocytoma at the age of 27.

On physical examination, his blood pressure and pulse were 110/64 mmHg and 60/min. His right visual acuity was 0.1. The abdomen was soft and flat, and the tumor was not palpable. Dermatological and neurological examinations revealed no abnormalities.

Laboratory examinations were normal, including complete blood counts, blood chemistry, endocrine tests and tumor markers. Plasma levels of insulin, gastrin, glucagon, pituitary hormones, thyroid hormones, and parathyroid hormone were normal. Urinary levels of catecholamines and their metabolites were normal. Exocrine and endocrine pancreatic function test were normal (Table 1). Ultrasonography (US) showed a round and hypoechoic mass (4.0 × 4.0 cm) in the pancreatic head. Endoscopic ultrasonography showed a well-defined hyperechoic mass with hypoechoic spots. Computed tomography (CT) showed a hypodense mass, and dynamic contrast enhanced study showed a hypervascular mass with a central necrosis (Fig. 1). Imaging studies of kidneys and adrenal glands revealed only a renal cyst on the right. Axial magnetic resonance imaging (MRI) showed a mass which was hypointense on T1-weighted images and hyperintense on T2-weighted images. Endoscopic retrograde cholangiopancreatography showed displacement of the main pancreatic duct without stenosis and irregularities of branches. Celiac and superior mesenteric arteriography revealed hypervascular masses in the pancreatic head (Fig. 2). Fluorescein angiography demonstrated a retinal hemangio-

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Table 1. Laboratory Findings on Admission

Aspartate amino transferase	13 IU//	Adrenocorticotrophic hormone	46.1 ng/ml
Alanine amino transferase	15 IU//	Growth hormone	0.6 ng/ml
Lactate dehydrogenase	128 IU//	Prolactin	21.7 ng/ml
Alkaline phosphatase	210 IU//	Thyroid-stimulating hormone	1.54 mU/ml
Total bilirubin	0.7 mg/dl	Free triiodothyronine	2.84 ng/ml
Total amylase	79 IU//	Free thyroxine	1.25 ng/dl
Pancreatic amylase	50 IU//	Intact parathyroid hormone	22.6 ng/ml
Salivary amylase	29 IU//	Insulin	6 mU/ml
Lipase	21 IU//	Gastrin	47.2 pg/dl
Elastase-1	10.8 ng/dl	Glucagon	95 pg/dl
Trypsin	185 ng/ml	Urinary adrenaline	1.8 mg/day
PSTI	8.4 ng/ml	Urinary noradrenaline	6.2 mg/day
PLA ₂	298.9 ng/dl	Urinary dopamine	52 mg/day
CEA	1.7 ng/ml	Urinary VMA	3.1 mg/day
CA19-9	<5 U/ml	Urinary HMA	3.0 mg/day
NBT-PABA test	74.7%	Urinary 5-HIAA	2.9 mg/day
Fecal chymotrypsin	23.6 U/g	75g OGTT	Glucose
Secretin test			0' 95 mg/day
MBC	88.6 mEq/l		60' 163
Volume	385 ml		120' 119
Amylase output	15.2 × 10 ⁴ U		

PSTI: pancreatic secretory trypsin inhibitor, PLA₂: phospholipase A₂, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, NBT-PABA: N-benzoyl-L-tyrosyl-p-aminobenzoic acid, MBC: maximal bicarbonate concentration, VMA: vanillylmandelic acid, HMA: homovanillic acid, 5-HIAA: 5-hydroxyindoleacetic acid, OGTT: oral glucose tolerance test.

Figure 2. Superior mesenteric arteriography shows hypervascular masses.

Figure 1. Upper: Unenhanced CT shows a hypodense mass in the pancreatic head. Lower: Contrast enhanced CT shows a hyperdense mass with hypodense spots.

blastoma on the right (Fig. 3). Gadolinium-enhanced T2-weighted axial MRI showed a hemangioblastoma on the left cerebellum (Fig. 4). Pituitary gland was normal.

Based on these findings, we diagnosed him as a VHL disease and an islet cell tumor of the pancreas. The patient underwent pylorus-preserving pancreaticoduodenectomy. During the operation, there was no evidence of metastasis in the liver or lymph nodes.

Macroscopically, the resected tumor (4.5×4.0×2.5cm) was elastic hard and well defined with a fibrous capsule. The cut

surface of the tumor showed a solid mass with necrosis. Three other small tumors were detected in the resected pancreas. Microscopically, the tumor cells were arranged in a trabecular pattern, and had clear granular, eosinophilic cytoplasm, and round nuclei. Mitoses were rare. The small tumors were compatible with islet hyperplasia. Immunohistochemically, the tumor cells were positive for chromogranin-A, S-100 protein, and PP. No immunoreactivity was demonstrated for gastrin, insulin, glucagon, somatostatin, vasoactive intestinal peptide (VIP), serotonin and adrenocorticotrophic hormone.

Discussion

VHL disease is categorized as neurocutaneous syndromes or phacomatoses together with neurofibromatosis (von Recklinghausen's disease), tuberous sclerosis (Bourneville's disease), encephalotrigeminal syndrome (Sturge-Weber disease),

Figure 3. Fluorescein angiography shows a retinal hemangioblastoma on the right.

Figure 4. T2-weighted axial MRI shows a hemangioblastoma in the left cerebellum (arrow).

Figure 5. The tumor cells show a trabecular pattern. Most of tumor cells have clear granular and eosinophilic cytoplasm, and round nuclei (HE stain, ×50).

Figure 6. Immunohistochemical staining for pancreatic polypeptide (×200).

and ataxia telangiectasis (Louis-Bar syndrome), but skin lesions are not common in VHL disease (5, 6). The gene of VHL disease was identified and mapped to the short arm of chromosome 3p25–26 (7). The present case had a retinal hemangioblastoma, a pancreatic tumor, and probably a cerebellar hemangioblastoma revealed by MRI. He had a definite VHL disease. His sister is also assumed to have had a VHL disease according to Melmon's criteria (3), because she had a family history of VHL disease and died of pheochromocytoma.

Retinal hemangioblastomas may be the earliest manifestation of VHL disease. The mean age at diagnosis is 21–28 years. Multiple or bilateral lesions occur in 20%–58% of patients, and 16%–36% of those with retinal lesions have diminished vision (1). In this case, retinal hemangioblastoma in the left eye was noted at the age of 13, and impaired vision appeared gradually in the right eye.

Hemangioblastomas of CNS in VHL disease are usually benign, and associated morbidity is due to space-occupying effects. Renal cell carcinoma is a major cause of death (1). Renal cysts, hemangioblastomas and benign adenomas are usually asymptomatic in VHL disease. The present case had hemangioblastomas and renal cyst without neurological abnormalities and abdominal symptoms.

The common pancreatic diseases in VHL disease include pancreatic cyst, cystadenoma and cystadenocarcinoma (8, 9). Pancreatic cysts were found in 72% of patients with VHL

disease at autopsy (10). The prevalence of islet cell tumors of the pancreas in VHL disease was difficult to assess accurately, because most of the published reports were the case reports of a few patients or limited to kindred studies (2, 9–24). Binkovitz et al reported that 6 of 43 patients from 25 kindreds with VHL disease had islet cell tumor of the pancreas (4). Table 2 reviews 25 patients with an islet cell tumor of the pancreas in VHL disease. Most of the patients were asymptomatic. Four patients had abdominal pain, two had metastatic diseases and one had abdominal tumor. Immunohistochemical examination for gastrointestinal hormones was performed in 10 of 24 cases. Two tumors were positive for either PP or somatostatin, one for insulin, glucagon and PP, one for both calcitonin and VIP, both gastrin and VIP, or VIP alone. Most of the patients had no endocrinological symptoms. Only two patients complained of watery diarrhea due to oversecretion of VIP. In our case, tumor cells were positive for PP, but he was asymptomatic. The physiological role of PP is the inhibition of pancreatic secretion and biliary tract motility (25). No typical clinical presentation was, however, seen in the reported cases of PP producing tumors (26–29). The present case had no endocrinological abnormalities and no abdominal symptoms. Pancreatic tumor was detected at his periodical medical checkup incidentally. His exocrine and endocrine functions were also normal.

Pheochromocytomas are relatively common in familial cancer diseases. The incidence of the association of pheochromo-

Table 2. Islet Cell Tumors of the Pancreas in von Hippel-Lindau Disease

Case No.	Age/Sex	Family history of VHL	Initial symptoms or signs	Diagnosis	Number of lesions in pancreas	Immunohistological study	Associated tumors	References
1	27/F	Yes	Not described	ICC	1	Not performed	HBC	Cubilla et al (11)
2	20/F	Yes	None	Not described	Not described	None	RH, HBC, RCC	Horton et al (10)
3	33/M	Not described	Not described	ICA	Not described	Not performed	HBC, Pheo.	Andersson et al (12)
4	41/M	Not described	None	ICA	1	Insulin, glucagon, PP	RH, HBC, Pheo., syringomyelia	Probst et al (13)
5	23/F	Yes	None	ICC	1	Not performed	HBC, Pheo.	Hull et al (14)
6	17/M	Yes	None	ICC	4	Not performed	HBC, Pheo.	Hull et al (14)
7	56/F	Yes	Watery diarrhea, liver metastasis	ICC	1	Calcitonin, VIP	Pheo., RCC, pancreatic cyst	Cornish et al (15)
8	27/M	Yes	Watery diarrhea	ICA	2	VIP	RH, Pheo.	Mulshine et al (16)
9	26/F	Yes	None	Not described	1	Not performed	RH, HBC, RCC, renal cyst	Hardwig et al (17)
10	38/F	Yes	None	Not described	1	PP	Pancreatic cyst RH, HBC, pancreatic cyst Renal cyst	Jennings et al (18)
11	41/F	Yes	Liver metastasis	ICC	1	Not performed	RH, renal cyst	Lamiell et al (19)
12	42/F	Not described	None	Not described	1	None	RH, HBC, RCC, renal cyst	Clelland et al (20)
13	43/F	Yes	None	ICA	Not described	Not performed	RH, RCC	Binkovitz et al (4)
14	26/F	No	None	ICA	Not described	Not performed	RH, HBC, RCC Pancreatic cyst	Binkovitz et al (4)
15	28/F	Yes	None	ICA	1	Not performed	HBC, Pheo., RCC Pancreatic cyst	Binkovitz et al (4)
16	29/F	Yes	None	ICC	1	Not performed	Pheo., RCC, pituitary adenoma	Binkovitz et al (4)
17	36/M	Yes	Abdominal pain	ICC	5	Not performed	Liver cyst	Binkovitz et al (4)
18	57/M	Yes	Palpable mass	ICC	Not described	Not performed	RH, HBC	Binkovitz et al (4)
19	28/F	Yes	Abdominal pain	ICC	2	Not performed	RH	Ikami et al (21)
20	50/F	Not described	Abdominal pain, BW loss	ICC	2	Not performed	RH, RCC, renal cyst	Neumann et al (9)
21	59/M	Yes	Not described	Not described	Not described	Gastrin, VIP	HBC, Pheo., RCC, liver cyst Pancreatic cyst	Karsdorp et al (2)
22	Not described	Yes	Not described	Not described	Not described	Not performed	RCC	Walther et al (22)
23	21/F	Yes	Abdominal pain	ICA	1	Somatostatin	None	Moynot et al (23)
24	39/M	Not described	None	ICA	1	Somatostatin	HBC, RCC	Maki et al (24)
25	42/M	Yes	None	ICA	4	PP	RH, HBC, renal cyst	Our case

VHLD: von Hippel-Lindau disease, ICA: islet cell adenoma, ICC: islet cell carcinoma, PP: pancreatic polypeptide, VIP: vasoactive intestinal peptide, RH: retinal hemangioblastoma, HBC: hemangioblastoma of the central nervous system, Pheo.: pheochromocytoma, RCC: renal cell carcinoma.

cytomas with the multiple endocrine neoplasia type 2, neurofibromatosis type 1, and VHL disease are reported to be 50%, 1%, and 15%, respectively (2). The frequency of VHL disease in unselected patients with pheochromocytoma is 19% (30). His sister had pheochromocytoma, but he had no clinical evidence of pheochromocytoma. His endocrinological examinations, such as blood levels of pituitary, thyroid, parathyroid and adrenal hormones and urinary levels of catecholamines and their metabolites, showed no abnormalities. Imaging studies showed no tumors in endocrine glands.

Table 2 summarizes the case reports of islet cell tumors associated with VHL disease. This shows that 10 of 19 patients (53%) had a malignant tumor. Therefore, patients with a hemangioblastoma should have a careful review of the family history, brain CT or MRI, and abdominal CT or ultrasonography. Periodical medical checkup using ultrasonography would be very useful to detect a tumor in the liver, gall bladder, pancreas, kidney and adrenal gland.

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