Somatostatinoma of the Pancreas Associated with von Hippel-Lindau Disease

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A 39-year-old man was admitted because of lumbago, vomiting and massive gastrointestinal bleeding. Oliguria developed a few days later, which was followed by hyperkalemia and cardiac arrest. Autopsy disclosed multiple renal cell carcinomas with diffuse metastasis to the liver, adrenal gland, psoas muscle and vertebrae. In addition, a somatostatinoma was found in the pancreas. From these findings and past history of cerebellar hemangioblastoma and spinal hemangioma he was diagnosed to have von Hippel-Lindau disease. Von Hippel-Lindau disease with islet cell tumor is very rare and is reported here with a review of literature.

Key words: renal cell carcinoma, islet cell tumor, liver metastasis, renal cyst

Introduction

Von Hippel-Lindau disease is a cancer syndrome causing predisposition to a variety of tumors such as hemangioblastoma of the central nervous system, cysts and carcinomas of the pancreas and kidneys, tumor of the epididymis, and pheochromocytoma (1). Although these tumors affect a patient in any sequence or combination, the sequential occurrence of hemangioma of the central nervous system and renal cell carcinoma is most frequent (2, 3). Pheochromocytoma also develops frequently in this disease, while neuroendocrine tumor of the pancreas is rare in spite of the frequent occurrence of pancreas cysts and carcinomas (1, 2). Recently, we treated a patient who died due to acute renal failure caused by massive gastrointestinal hemorrhage. Postmortem pathological studies disclosed that he had von Hippel-Lindau disease. In this case, diffuse infiltration of renal cell carcinoma into the liver and retroperitoneal space was remarkable. In addition, a tumor was found in the pancreas which was immunohistologically positive for somatostatin (4, 5). As far as we know, this is the first case of somatostatinoma associated with von Hippel-Lindau disease. Here, we report this case along with a review of the literature.

Case Report

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Introduction

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Case Report

A 39-year-old man was admitted because of low back pain, edema of the lower extremities, dyspnea and tarry stool. One month previously, kyphosis without pain was noticed. Three weeks previously, lumbago appeared and he was unable to walk because of severe low back pain. Three days earlier, he vomited dark fluid and tarry stool was recognized. Thereafter, anemia, dyspnea and marked edema in the lower extremities appeared. He had undergone surgical operations to remove cerebellar hemangioblastoma at the age of 17, and spinal hemangioma at ages of 19 and 36.

On emergency admission, his blood pressure (BP) was 100/60 mmHg and his pulse was 128 beats/min. Laboratory data were: red blood cell (RBC) 235x10^4/µl, hemoglobin (Hb) 4.5 g/dl, hematocrit (Ht) 16.2%, white blood cell (WBC) 24,900/µl, platelet 52.9x10^4/µl, total protein (TP) 4.8 g/dl, albumin (Alb) 2.9 g/dl, aspartate aminotransferase (AST) 52 IU/l, alanine aminotransferase (ALT) 73 IU/l, γ-glutamyl transpeptidase (γ-GTP) 168 IU/l, alkaline phosphatase (Alp) 247 IU/l, lactate dehydrogenase (LDH) 396 IU/l, blood urea nitrogen (BUN) 51 mg/dl, creatinine (Crea) 1.2 mg/dl, sodium (Na) 138 mEq/l, potassium (K) 4.5 mEq/l, chloride (Cl) 101 mEq/l, and C-reactive protein (CRP) 13.8 mg/dl. Lumbar spine X-ray photographs demonstrated marked kyphosis (Fig. 1). Emergency gastroendoscopy revealed large ulcers in the stomach. Abdominal ultrasonography disclosed ascites. Multiple space occupying lesions (SOLs) were found in the kidney, which were hyperechoic and were compatible with renal cysts. However, the study of the SOLs was limited because of severe back pain (Fig.
Figure 1. Lumbar spine X-ray photographs showing kyphosis. Left, posterior-anterior view. Right, lateral view.

Figure 2. Abdominal ultrasonography performed on admission. Multiple hypoechoic SOLs were seen in the right kidney (left), while SOLs were not detected in the left kidney (right).

Figure 3. Macroscopic appearance of kidney fixed with formalin (A), liver (B), and pancreas (C) on autopsy. Arrow in C indicates somatostatinoma.

Figure 4. Microscopic appearance of renal cell carcinoma and renal cysts. A) Renal cell carcinoma of clear cell type (×70). B) Undifferentiated cells intermingled with the clear cell type (×70). C) Papillary lesions of renal cysts in which a sheet of columnar, epithelial or clear cells were seen (×175).
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2). Blood transfusion was started. His general condition improved transiently, but disorientation appeared on the 3rd day of admission. On the 4th day, a large amount of crystals of uric acid was excreted with the urine, which was followed by oliguria. On the 5th day, BP dropped suddenly. The laboratory data were: TP 5.3 g/dl, Alb 2.4 g/dl, AST 269 IU/l, ALT 186 IU/l, γGTP 437 IU/l, Alp 899 IU/l, Na 131 mEq/l, K 5.3 mEq/l, BUN 31 mg/dl, Crea 2.8 mg/dl and uric acid (UA) 12.6 mg/dl. A sharp T wave indicating high serum potassium appeared on ECG and cardiac arrest followed.

On autopsy, acute gastric ulcers, 1.5×1.0 cm, 2.5×1.5 cm, and 4.5×2.5 cm in size, were found at the antrum, which were histologically benign. Multiple yellowish-white, necrotic and hemorrhagic tumors, up to 3.5 cm in diameter, were seen in the cortices of bilateral kidneys (Fig. 3A). They were histologically renal cell carcinoma, common type, in which clear cells formed cystic structures. Cells of undifferentiated phenotype intermingled with clear cells were seen in some of the cancer nodules (Fig. 4A and B). In addition, multiple cysts up to 3 cm in diameter were seen which contained greenish gelatinous material (Fig. 3A). The inner surface of renal cysts was covered with a sheet of columnar cells, epithelial cells or clear cells forming papillary structures (Fig. 4C). Renal cell carcinoma metastasized extensively to the liver, lung, adrenal glands, psoas muscles, and vertebrae (L1 to L5). Macroscopic appearance of the liver metastasis is shown in Fig. 3B. Cancer cells with sarcomatous change infiltrated diffusely in the portal area and sinusoids of the liver (Fig. 5A). Diffusely infiltrated cancer cells were found in the psoas muscle (Fig. 5B) and vertebrae and around the right ureter. Lymph node metastasis was seen in the axilla, mediastinum, pulmonary hilus, carina, and paraaorta. Lymph nodes in the retroperitoneal space were swollen, conglomerated, and formed a mass of 12×8×3.5 cm in size along the abdominal aorta. In the pancreas, a few small cysts up to 0.5 cm in diameter were observed. In addition, a yellowish tumor of 1 cm in diameter was found (Fig. 3C), which was immunologically

Figure 5. Histological appearance of renal cell carcinoma metastasized to the liver (A) or psoas muscle (B). A) Microscopic appearance showing diffuse infiltration of sarcomatous cells in the liver (x70). B) Renal cell carcinoma infiltrated into the psoas muscle (x175).

Figure 6. Somatostatinoma of the pancreas. A) Microscopic appearance of the somatostatinoma (HE stain, x175). B) Immunohistochemical study using anti-somatostatin antibody (x175). C) Chromogranin A was visualized immunohistochemically using specific antibody (x175).
positive for somatostatin, chromogranin A, and neuron-specific enolase (NSE) but negative for glucagon and insulin (Fig. 6). Other findings related to von Hippel-Lindau disease were; cystic tissue defect at the left and right cerebellar hemispheres (2x1x1 cm and 3x1.5x1.0 cm in size) and dish-like tissue defect at the Th 12 of spinal cord (2x0.5x0.3 cm in size), both of which were due to past surgical operations. A small residual focus of the hemangioblastoma was also found at the spinal cord.

**Discussion**

The urologic lesions of von Hippel-Lindau disease may present as renal cysts, renal angiomas, or adenocarcinomas (3). Renal cysts appear to be premalignant lesions, since they have clear cells from which renal cell carcinoma is considered to develop (3, 6, 7). Renal cell carcinoma is now the most frequent cause of death in patients with von Hippel-Lindau disease, and all patients and relatives at risk for this disease must be screened for renal cell carcinoma. Renal cell carcinoma with the same echogenicity as surrounding parenchyma may not be readily identifiable with abdominal ultrasonography, and a close surveillance program including annual abdominal computerized tomography (CT) may be recommended. Selective renal angiography still seems to be most definitive for distinguishing renal adenocarcinoma from benign cysts, and may be used to monitor any von Hippel-Lindau patients with a renal abnormality (8). Inasmuch as the lesions can be found early, are small and arise de novo, metastasis is rare and treatment of the primary lesions is clearly indicated (8).

Renal cell carcinoma metastasizes to the liver, usually forming multiple hypervascular masses. In the present case, however, renal cell carcinoma diffusely infiltrated into the portal area and sinusoid, which was atypical for its metastasis (Fig. 2). As shown in Fig. 5, the metastasized cancer cells were phenotypically sarcomatous, which may be the reason for the diffuse infiltration (4). The metastasis to retroperitoneal space was also remarkable in this case. Diffuse infiltrations into vertebrae, right ureter, adrenal gland and psoas muscles, and a large mass of conglomerated retroperitoneal lymph nodes along the abdominal aorta appeared to be the cause of kyphosis, back pain and edema in the lower extremities.

Pancreatic cysts and carcinomas are not uncommon in von Hippel-Lindau disease. Unlike renal cysts, however, there is little evidence that pancreatic cysts are premalignant (2). Pancreatic neuroendocrine tumors associated with von Hippel-Lindau disease are very rare in contrast to pheochromocytoma. Only eleven cases of von Hippel-Lindau disease with neuroendocrine tumors of the pancreas (listed in Table 1) have been reported in the literatures (1, 9–17). Among them, three cases have functioning tumors producing insulin, glucagon, pancreatic polypeptide, vasoactive intestinal peptide (VIP), and/or calcitonin (11, 13, 14). Somatostatin production was not reported in these cases, indicating that our patient is likely the first case of von Hippel-Lindau disease with somatostatinoma. Somatostatinoma is the least common pancreatic endocrine tumor; to date, approximately 50 cases have been described (5). Excessive production of somatostatin causes diabetes mellitus, gallbladder disease, diarrhea, weight loss, steatorrhea and hypochlorhydria (5). In the present case no evidence of such islet cell dysfunction was noticed during the life. Although multiple giant gastric ulcers which caused massive bleeding were found, gastrin production was ruled out immunohistologically (5).

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**Table 1. Neuroendocrine Tumors of the Pancreas in Patients with von Hippel-Lindau Disease**

<table>
<thead>
<tr>
<th>Case</th>
<th>von Hippel-Lindau disease</th>
<th>Hormone production by neuroendocrine tumor of the pancreas</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 F</td>
<td>Cerebellar hemangioma, visual defect</td>
<td>None</td>
<td>Cubilla 1975 (9)</td>
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<tr>
<td>33 M</td>
<td>Cerebellar hemangioma, renal adenoma, pheochromocytoma</td>
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<td>Andersson 1976 (10)</td>
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<td>20 F</td>
<td>Retinal hemangiblastoma, renal cell carcinoma, cerebellar hemangioma</td>
<td>None</td>
<td>Horton 1976 (1)</td>
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<tr>
<td>41 M</td>
<td>Retinal hemangiblastoma, pheochromocytoma, cerebellar hemangioma</td>
<td>Insulin, glucagon, pancreatic polypeptide</td>
<td>Probst 1978 (11)</td>
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<tr>
<td>23 F</td>
<td>Pheochromocytoma, cerebellar hemangioma</td>
<td>None</td>
<td>Hull 1979 (12)</td>
</tr>
<tr>
<td>17 M</td>
<td>Pheochromocytoma, cerebellar hemangioma</td>
<td>None</td>
<td>Hull 1979 (12)</td>
</tr>
<tr>
<td>27 M</td>
<td>Retinal hemangiblastoma, pheochromocytoma</td>
<td>VIP</td>
<td>Mulshine 1984 (13)</td>
</tr>
<tr>
<td>56 F</td>
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<td>Calcitonin, VIP</td>
<td>Cornish 1984 (14)</td>
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<td>18 F</td>
<td>Spinal cord hemangiblastoma</td>
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<tr>
<td>42 F</td>
<td>Cerebellar hemangioma, renal cell carcinoma, retinal hemangiblastoma</td>
<td>None</td>
<td>Clelland 1989 (16)</td>
</tr>
<tr>
<td>41 F</td>
<td>Retinal hemangiblastoma, renal cysts</td>
<td>None</td>
<td>Lamiell 1989 (17)</td>
</tr>
</tbody>
</table>

F: female, M: male, VIP: vasoactive intestinal peptide.
However, endocrine tumors of the pancreas may be ulcerogenic, and the possibility that the giant ulcers may have been caused by some unknown hormones produced by this neuroendocrine tumor cannot be ruled out completely (18, 19).

Genetic abnormalities which cause von Hippel-Lindau disease have become clear. Specific loss of alleles from chromosome 3p has been detected in many of the renal cell carcinomas, pheochromocytoma, and spinal hemangioblastomas of patients of this disease (1–3, 20). Recently, the von Hippel-Lindau disease gene was identified, which was a tumor suppressor (20). Detailed analysis of this gene will clarify the mechanism of development of neuroendocrine tumors in von Hippel-Lindau disease.

References