CASE REPORT

Serous Cystic Neoplasms of the Whole Pancreas in a Patient with von Hippel-Lindau Disease

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Abstract

We describe here a case of von Hippel-Lindau (VHL) disease with a serous cystic neoplasm of the whole pancreas. The patient was a 35-year-old woman suffering from a palpable abdominal tumor. She had a history of hemangioblastomas of the cerebellum. CT revealed large solid tumors in the pancreatic head and body, and multiple cystic lesions in the whole pancreas as well as a right renal tumor. When endoscopic retrograde cholangiopancreatography (ERCP) was performed, bleeding from the duodenal papilla was detected. Since she had some distinguishing clinical features, the diagnosis of VHL disease was made. The preoperative diagnosis of the pancreatic lesion was serous cystic neoplasms with hemosuccus pancreaticus and total pancreatectomy was performed. Histological examination of the specimen revealed serous cystic neoplasms which occupied the entire pancreas. VHL cases operated on for serous cystic neoplasms of the entire pancreas are very rare.

Key words: von Hippel Lindau disease, serous cystic neoplasms, hemosuccus pancreaticus

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Introduction

Von Hippel-Lindau (VHL) disease is an autosomal dominant neoplasia syndrome that results from germline mutations in the VHL genes (1, 2). These mutations lead to the development of several benign or malignant tumors and cysts in many organs. VHL disease is characterized by the predisposition to develop hemangioblastomas of the retina and central nervous system (CNS) (3), renal cell carcinomas and renal cysts (4), pheochromocytomas (5), and endolymphatic sac tumors (6) with marked phenotypic variability.

Various pancreatic lesions, including pancreatic cysts, serous cystic neoplasms (SCN), neuroendocrine tumors, adenocarcinoma, hemangioblastomas, and metastasis of the renal cell carcinomas, have been described in patients with VHL (2, 7-14). In these previous reports, the frequency of pancreatic involvement in VHL disease was described to be from 0%-72%, with a mean of approximately 50% when the largest series are pooled.

SCNs are uncommon tumors which account for 1-2% of exocrine neoplasms of the pancreas (15). They present usually as single, unifocal, large, well-demarcated cystic tumors. Traditionally, SCNs have been regarded as essentially benign tumors compared with more commonly seen mucinous cystic neoplasms. Therefore, the SCN is monitored carefully but is not assumed to require (16, 17).

Here, we report a case of VHL complicated with SCNs of the whole pancreas. We could not avoid surgical resection of the whole pancreas because of the many symptoms. We also discuss the relation between SCNs and VHL.

Abbreviation: VHL: Von Hippel-Lindau, SCN: serous cystic neoplasm
Case Report

A 35-years old woman became aware of a tumor in the right hypochondriac region after the delivery of a live healthy male baby and visited a local hospital. In the hospital, she initially underwent an ultrasound of the abdomen, which identified giant masses in the whole pancreas and a tumor of the right kidney. She was referred to our hospital for evaluation of the pancreatic and renal tumor. She had a history of hemangioblastomas of the cerebellum that was treated by surgery 14 years previously. She had no relevant family history. Laboratory analysis showed no abnormal data. Though the patient had been suffering from lenteic stool during pregnancy, she left it untreated. Her blood glucose level was normal. B-mode ultrasonography (US) revealed the presence of large and hypoechoic nodules in the head and body of the pancreas as well as a right renal tumor (Fig. 1). The right kidney mass was regarded as renal cell carcinoma. Contrast-enhanced computed tomography (CT) revealed large solid tumors in the pancreatic head and body, and multiple cystic lesions in the whole pancreas. The solid masses showed weak enhancement in the early phase (Fig. 2). Magnetic resonance imaging (MRI) demonstrated multiple cystic lesions in the whole pancreas on both T1-weighted and T2-weighted images and MRCP (Fig. 3, 4). Solid tumors of the pancreatic body and tail appeared as low intensity lesions on the T1-weighted image and high intensity on the T2-weighted image. 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET) did not show uptake in the tumors of the pancreas (Fig. 5). Endoscopic retrograde cholangiopancreatography (ERCP) did not show the main pancreatic duct and the contrast media injected into the main pancreatic duct (MPD) exuded to the pancreatic parenchyma (Fig. 6). Additionally, the bleeding continued from the duodenal papilla. Endoscopic ultrasonography (EUS) revealed that the pancreas contained macrocystic areas and a solid portion with a honeycomb pattern (Fig. 7). We avoided the histological diagnosis by EUS-FNA because of the bleeding from the duodenal papilla. On the other hand, the renal tumor was diagnosed as renal cell carcinoma based on typical findings in various diagnostic imaging modalities. Since she had some distinguishing clinical features, the diagnosis of von Hippel-Lindau disease was made. The
Figure 3. Axial T1-weighted MR image shows a head tumor (arrow in Fig. 3a) and a tail tumor (arrowhead in Fig. 3a) with low intensity. Axial T2-weighted MR image shows a head tumor (arrow in Fig. 3b) and a tail tumor (arrowhead in Fig. 3b) with high intensity.

Figure 4. MRCP reveals innumerable cystic lesions of the whole pancreas.

Figure 6. Endoscopic retrograde cholangiopancreatography (ERCP) shows that the contrast media of ERCP exuded to the pancreatic parenchyma but does not depict the main pancreatic duct. Endoscopic finding shows bleeding from the duodenal papilla.

Figure 5. FDG-PET did not show uptake of the pancreas.

The patient had undergone genetic analysis for germline mutations and a mutation of exon 1 of VHL gene (233A>T) was identified. Thus, although some findings of the pancreas were consistent with SCN, laparotomy was performed because of the existence of RCC, bleeding from the duodenal papilla, insufficiency of the pancreas and suspicion that the solid lesion was a pancreatic neuroendocrine tumor. Laparotomy revealed a grayish-white tumor that occupied the whole pancreas. Total pancreatectomy and right nephrectomy were performed. The patient’s postoperative course was quite uneventful. Though she requires insulin and exocrine pancreatic enzyme replacement, she is now asymptomatic.

Macroscopically, the pancreas was diffusely involved and replaced by cystic and solid tumors with hemorrhage (Fig. 8). Microcysts, macrocysts and sponge-like areas were noted. Histological examination showed microcysts and macrocysts lined with cuboidal and flattened epithelium (Fig. 9). The solid portion was formed by a homogeneous population of polygonal cells with clear or pale eosinophilic cytoplasm and well-defined cell borders. The central nuclei were small and round to ovoid with smooth nuclear mem-
The solid tumors of the pancreatic head and tail were revealed to have a honeycomb pattern with a cystic component.

Gross photograph of serous cystic neoplasms. The lesion is well circumscribed and has a characteristic sponge-like appearance with hemorrhaging.

branes and showed dense chromatin. No pleomorphism, or mitotic activity was identified. The tumor cells contained large amounts of glycogen, demonstrated by the presence of large numbers of granules in the PAS stain. There were few acinar cells in the whole pancreas. Immunohistochemical investigation showed that the tumor was positive for epithelial membrane marker and CAM5.2, but negative for alpha1-antitrypsin and endocrine markers. As a result of the histological findings, we diagnosed this tumor as SCNs of the whole pancreas. On the other hand, the histological examination revealed that the tumor of the kidney was renal cell carcinoma.

Abbreviations: US: ultrasonography, CT: computed tomography, MRI: magnetic resonance imaging, FDG-PET: 18 F-fluorodeoxyglucose positron-emission tomography, ERCP: endoscopic retrograde cholangiopancreatography, EUS: endoscopic ultrasonography, FNA: fine needle aspiration

**Discussion**

Von Hippel Lindau disease, an autosomal dominant neoplasm syndrome, results from a germline mutation in the VHL gene (1, 2). Germline mutations in the VHL gene lead to the development of multiple benign or malignant tumors, and cysts in many organ systems. Affected individuals might develop CNS lesions including cerebellar, spinal cord, brainstem, nerve root, and supratentorial hemangioblastomas, as well as retinal hemangioblastomas and endolymphatic sac tumors. Visceral features of the disorder include renal cysts and carcinomas, pheochromocytomas, pancreatic cysts and neuroendocrine tumors, as well as epididymal and broad ligament cystadenomas (3-6). Although the present case did not have a family history of VHL, several signs suggestive of VHL and the germline mutation in the VHL gene appeared in this patient. Therefore, we speculated that this case is a de novo case of VHL.

Various types of pancreatic lesions have been described in VHL patients (13). Pancreatic neuroendocrine tumors arise in 8-17% of such patients and pancreatic cysts and SCNs occur with a prevalence of 17-56% in patients with von Hippel Lindau disease (7, 12, 13, 18). Overall, 35-70% of such patients have pancreatic neuroendocrine tumors, cysts, or SCNs (8, 9, 18). Differential diagnosis between benign SCNs and pancreatic neuroendocrine tumors is usually difficult. The mean age at presentation for neuroendocrine tumors is 35 years, and 37 years for pancreatic cysts in this disease (2).

Pancreatic SCNs are likely to show a benign biological and clinical course (17), and malignant cases are quite rare (16). The gross appearance of these tumors shows 3 types, microcystic, oligocystic and solid, with a frequency of 70, 25, and 5%, respectively (19-21). The correct differentiation of benign asymptomatic serous cystic tumors, from other cystic neoplasms of the pancreas with malignant potential is crucial. Laparotomy is frequently necessary for a definitive and complete histological diagnosis.

Though a growing number of SCNs of the pancreas are
being identified because of the frequent use of radiography and advances in imaging techniques (17), SCNs of the whole pancreas are very rare (22-31). In the present case, there were solid components in the head and body of the pancreas, and histological examination showed that this tumor was a solid variant of SCNs. Actually, the distinction of the solid type of SCNs from endocrine tumors is difficult preoperatively by radiological imaging. According to some reports, the heavily T2-weighted imaging is very useful for the differential diagnosis between SCNs and endocrine tumors (32). MRI is actually useful for differential diagnosis between SCNs and endocrine tumors, although it is still difficult to discriminate the cystic degeneration of endocrine tumors. Recently, 18-FDG-PET has attracted attention as a novel, noninvasive imaging procedure based on the principle of specific tissue metabolism. Since there is selective 18-FDG uptake and retention by malignant cells (33), the lack of uptake of 18-FDG may represent serous cystic neoplasms with a benign nature. Further investigation will be required for the differential diagnosis of SCNs and islet cell tumors by FDG-PET.

EUS-guided fine needle aspiration (EUS-FNA) has been increasingly utilized to differentiate malignant from benign or low malignant pancreatic cystic tumors (34). Although complication rates of EUS-FNAB are low, complications such as pancreatitis, hemorrhage, perforation, and dissemination can occur. In the present case, we did not perform EUS-FNA because of bleeding from the duodenal papilla.

Hemosuccus pancreaticus, defined as bleeding from the papilla of Vater, is rarely encountered. Hemosuccus pancreaticus is most commonly caused by the rupture of a pseudocyst on the main pancreatic duct leading to the anemia. To our knowledge, there are no cases of VHL with hemosuccus pancreaticus to date. In addition, there is only one case of SCN with hemosuccus pancreaticus (35). Since anemia caused by hemosuccus pancreaticus was not shown, most of the bleeding from the duodenal papilla might be from the vein of the SCN, even though the histological evidence of this finding was not demonstrated. This clinical finding of the present case is very rare.

Interestingly, the patient recognized the abdominal mass after her delivery. Pregnancy is known to promote hemangioblastoma symptoms by the development of new lesions (36). It is considered that the significant increase in blood volume and high estrogen state during pregnancy contributed to the growth of the hemangioblastoma. Thus, pregnancy may have had some role in the growth of the pancreatic tumor in this case, although the relation between serous cystic neoplasms and pregnancy is still unclear. Further information is required to clarify this issue.

In summary, a case of SCNs of the whole pancreas in a patient with VHL was presented. SCNs of the whole pancreas are very rare. Although SCNs should be generally followed up without surgery, surgical resection is sometimes necessary depending on the patient’s symptoms.

The authors state that they have no Conflict of Interest (COI).

References


