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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Pancreatic involvement in Korean patients with von Hippel-Lindau disease

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Abstract
Purpose The aim of this study was to describe pancreatic involvement in von Hippel-Lindau (VHL) disease and to document the changes that occur in pancreatic lesions.
Methods We retrospectively analyzed the medical records and CT scans of 18 VHL patients who were diagnosed between 1994 and 2007 at the Samsung Medical Center. The clinical history with a detailed family history, biochemical test results, and imaging studies of the pancreas, adrenal glands, and kidneys were reviewed. Genetic analysis was performed in 12 patients. The changes in pancreatic lesions, such as an increase in cystic lesions, calcifications, and dilatation of the pancreatic duct, were analyzed in patients who had CT scans at least 1 year apart.
Results Pancreatic lesions existed in 89% (16/18) of the patients. All 16 patients had multiple cystic lesions. Two patients had co-existing neuroendocrine tumors (NET), and two patients had co-existing serous cystadenomas (SCA). At least one of three features of pancreatic lesions (cystic lesions, calcifications, and dilatation of the pancreatic duct) progressed in all nine patients who had CT scans 1 year apart.
Conclusion Pancreatic involvement in VHL disease was relatively common in Korean patients. The most common type of pancreatic involvement was a multiple cystic lesion. NET and SCA existed in approximately 10% of VHL patients with pancreatic involvement. Pancreatic lesions in VHL disease progressed, at least according to radiological images.

Keywords Pancreas · Von Hippel-Lindau disease · Cyst · Calcification

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Introduction

Von Hippel-Lindau syndrome is an autosomal-dominant disorder with a predisposition for multiple tumors and cysts, such as retinal or cerebellar hemangioblastomas, clear cell renal cell carcinomas (RCC), endolymphatic sac tumors, pheochromocytomas, pancreatic neuroendocrine tumors (NET), and cysts of the kidney, epididymis, and pancreas. CNS lesions, RCC, and pheochromocytomas are well known for important prognostic factors and managed according to well-established guidelines [1]. Pancreatic cystic lesions are very common [2] and considered clinically indolent in VHL disease [3, 4]. In contrast, some reported pancreatic cysts cause obstructive jaundice because of mechanical compression of the bile ducts [5, 6]. In some patients with VHL disease, the number and size of cysts increase [3, 7].

There is a report of a VHL germline mutation that resulted in three novel mutations in Korean patients with VHL disease [8]. However, there have been no studies about the pancreatic involvement of VHL disease in Korean patients.

The aims of this study were to determine if pancreatic lesions in VHL disease progress and to assess the pancreatic manifestations of VHL disease in Korean

Table 1 Patient profiles and types of VHL disease

No.	Sex age (years)	Presenting symptoms	Type [28]	CNS[a]	Retina[a]/ adrenal gland[b]	Kidney	Genetic testing	Pancreatic involvement
1	F/26	Paraplegia, numbness	Type I	Cerebellum, C7, C8	Yes/no	No	c.223_224insT (p.Ile75TyrfsX57)	Yes
2	M/38	Incidental renal mass	Type I	Cerebellum	No/no	RCC cyst	Negative	Yes
3	F/29	Headache nausea	Type I	Cerebellum	No/no	Cyst	Not done	Yes
4	F/30	Epigastric palpable mass	Type I	Cerebellum, spine	No/no	Cyst	Deletion exon 2 and 3	Yes
5	F/40	Numbness	Type IIa	Medulla, spine	No/yes	RCC cyst	Negative	Yes
6	M/37	Incidental renal mass	Type I	Cerebellum	No/no	RCC cyst	Not done	Yes
7	M/50	Tingling sense	Type I	Cerebellum	No/no	RCC cyst	Negative	Yes
8	F/24	Neck pain, tingling sense,	Type I	Cerebellum, spine	No/no	RCC cyst	c.586A > T (p.K196X)	Yes
9	F/33	Bilateral renal mass	Type I	Cerebellum	Yes/no	RCC cyst	c.484T > C (p.C162R)	Yes
10	M/39	Bilateral renal mass	Type I	Cerebellum	No/no	RCC cyst	Not done	Yes
11	F/46	Quadriparesis numbness	Type I	Spine	Yes/no	Cyst	Negative	Yes
12	F/32	Genetic screening	Type I	Cerebellum, spine	No/no	Cyst	Deletion exon 2 and 3	Yes
13	M/51	Radiating pain, left flank pain	Type I	Cerebellum, spine	No/no	RCC cyst	Negative	Yes
14	M/27	Headache nausea vomiting	Type I	Cerebellum	No/no	RCC cyst	Not done	Yes
15	M/36	Decreased visual acuity	Type iIa	Cerebellum	No/yes	RCC cyst	Negative	Yes
16	M/41	Headache	Type I	Cerebellum, medulla	No/no	Cyst	c.486C > G (p.C162 W)	Yes
17	M/50	Bilateral renal mass	Type I	Cerebellum, spine	No/no	RCC cyst	Not done	Yes
18	M/21	Visual disturbance	Type I	No	Yes/no	Cyst	Not done	No

[a] Hemangioblastoma in the CNS or retina

[b] Pheochromocytoma of the adrenal glands diagnosed by CT and MIBG scan

F female, *M* male, *RCC* renal cell carcinoma

patients. We retrospectively analyzed the pancreatic CT scans and clinical histories of VHL patients in our hospital.

Materials and methods

Patient selection and retrospective analysis

All patients with VHL disease who were diagnosed between 1994 and 2007 at the Samsung Medical Center were included in the analysis. In 1964, Melmon and Rosen proposed the clinical diagnostic criteria for VHL disease as follows: (1) two or more hemangioblastomas, (2) a haemangioblastoma and another visceral lesion, or (3) a hemangioblastoma or another visceral lesion and a family history of hemangioblastoma. These criteria are still used for clinical diagnosis of VHL disease [9], and our patients were diagnosed according to these criteria.

The medical records were retrospectively analyzed for clinical history, detailed family history, biochemical test results, and imaging studies of the adrenal glands, kidneys, and pancreas. Genetic analysis was performed in 12 patients.

Analysis of images of the pancreas

All CT scans were reviewed by two radiologists who were experienced in imaging of the pancreas and blind to the patient's clinical data. The morphologic characteristics of the pancreas, as well as the location, number, type, size, calcification, and enhancement pattern of the pancreatic lesion, pancreatic duct and parenchymal changes, and peri-pancreatic organ compression were recorded.

According to the criteria suggested by Johnson et al. [10], true cysts and serous cystadenomas(SCA) were diagnosed. A NET was diagnosed by CT scan when a well-circumscribed lesion was homogenously enhanced after contrast injection.

The changes of the pancreatic lesions were analyzed in patients who had two separate CT scans at least 1 year apart. The changes of the cystic lesions, calcifications, and pancreatic duct were reviewed in detail. In addition to these radiologic changes, we also reviewed symptomatic changes related to chronic pancreatitis.

Table 2 Description of pancreatic lesions in patients with VHL disease

Case no.	Cyst location	Cystic wall enhancement	Calcification	Adjacent organ compression	Other pancreatic lesions
1	Diffuse	Yes	Yes	Yes	Serous cystadenoma
2	Diffuse	Yes	Yes	Yes	
3	Diffuse	Yes	No	Yes	
4	Diffuse	Yes	Yes	No	
5	Diffuse	Yes	Yes	Yes	
6	Diffuse	Yes	Yes	Yes	
7	Diffuse	Yes	Yes	No	
8	Diffuse	No	No	No	Neuroendocrine tumor
9	Diffuse	Yes	Yes	No	Serous cystadenoma
10	Diffuse	Yes	Yes	Yes	
11	Diffuse	Yes	Yes	No	
12	Diffuse	Yes	No	Yes	
13	Diffuse	Yes	No	No	
14	Diffuse	Yes	No	Yes	Neuroendocrine tumor
15	Diffuse	Yes	Yes	No	
16	Diffuse	No	No	No	
17	No cyst	No cyst			No pancreatic lesion
18	No cyst	No cyst			No pancreatic lesion

Results

Patient characteristics

A total of 18 patients from 16 families were studied (Table 1). The mean age was 36.1 years (range, 21–51 years), and the male-to-female ratio was 10:8. VHL type I and IIa lesions existed in 88.8% (16/18) and 12.2% (2/18) of the patients, respectively. There was a family history of VHL in 44.4% of the patients (8/18), but only one patient was diagnosed by a screening test. Patients sought evaluation at the hospital for the following reasons: neurologic symptoms ($n = 11$), an incidental renal mass ($n = 5$), and epigastric palpable mass ($n = 1$). Genetic tests were done in 12 patients, and 6 mutations were identified.

Pancreatic involvement

Pancreatic involvement was noted in 16 of 18 patients (Table 2). Sixteen patients had multiple cysts diffusely distributed in the pancreas; patients also had SCAs, and another two patients had NETs (Fig. 1). In one case (case 8) with a NET, the pathologic diagnosis was made by surgical resection during a nephrectomry for renal cell cancer (Fig. 1).

Cystic wall enhancement and calcifications were demonstrated in 14 and 11 of 16 patients, respectively. The two patients without cystic wall enhancement also had no calcifications. The CT scans of five patients with pancreatic cysts compressed the stomach or duodenum slightly, but none required decompression.

The course of the pancreatic lesion

Two CT scans done at least 1 year apart were available in nine patients with an average of 30 months (SD, 14.0 months) of follow-up. At least one of the three pancreatic features (changes of cystic lesions, calcifications, and pancreatic duct) progressed in all nine patients (Table 3). Seven of nine patients had calcifications. In seven patients, calcifications were newly developed, and calcifications increased in three patients (Fig. 2). One patient without any change in calcifications had slightly increasing cystic lesions. Two patients with no calcifications had an increase in pancreatic cystic lesions and one patient had a dilatation of the pancreatic duct. In spite of these radiological changes, there were no symptoms related to chronic pancreatitis during the follow-up period.

Discussion

In this study, the frequency of pancreatic involvement in VHL patients was higher than reported in previous studies, and all of the cystic lesions were distributed diffusely. In some studies, the frequency of pancreatic involvement has been reported from 15 to 77.2% with a mean of 53% [1–4,

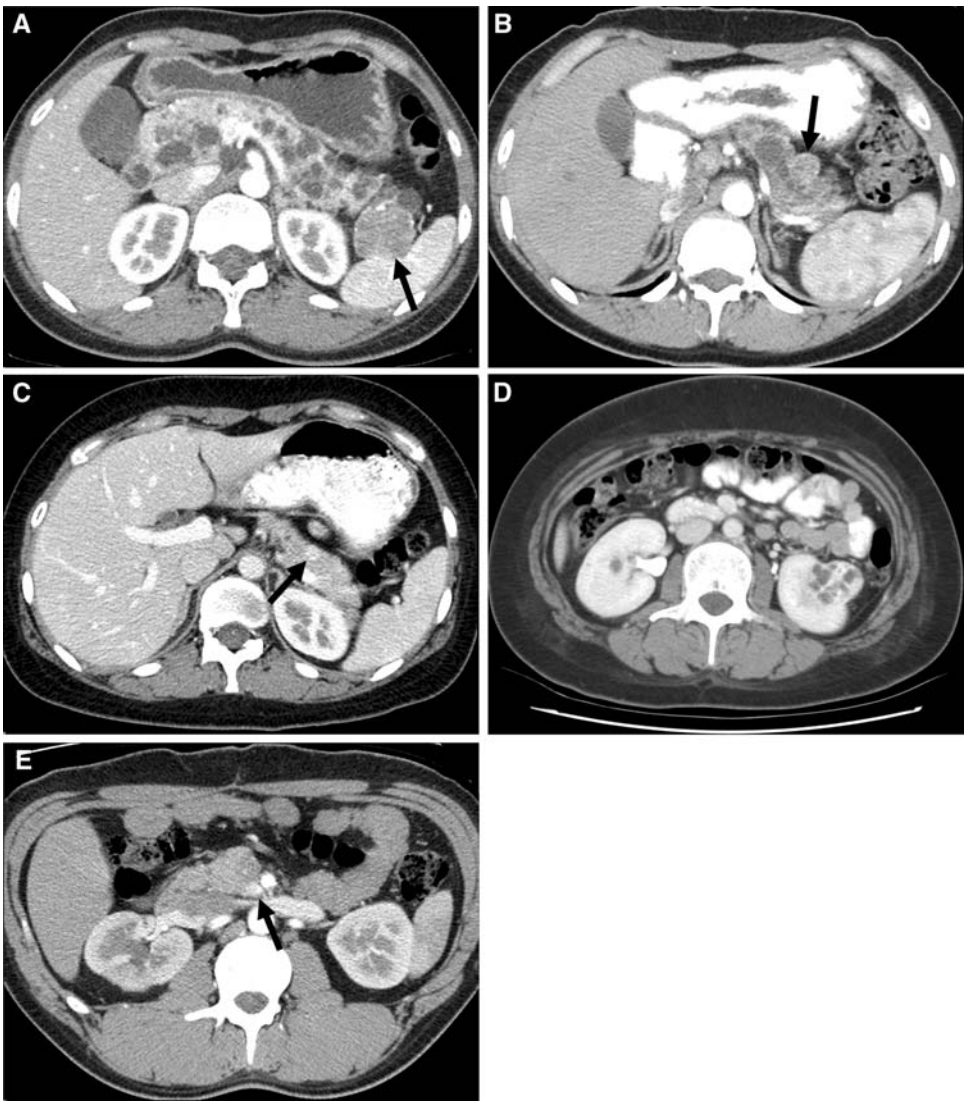

Fig. 1 Pancreatic serous cystadenomas and neuroendocrine tumors in patients with von Hippel-Lindau syndrome. Pancreatic CT scans of case 1 (**a**) and case 9 (**b**) showed relatively well-defined solid mass-like lesions (*arrows* in **a** and **b**). Enhancing nodules (*arrows* in **c** and **e**), which are characteristic findings for neuroendocrine tumors, were noted in the CT scans of two patients—case 8 (**c**) and case 14 (**e**). Surgical pathologic diagnosis was made in case 8 during a nephrectomy for a renal cell carcinoma (**d**)

11–13]. In the current study, the frequency of pancreatic involvement was 94%. The higher frequency may be due to more commonly used abdominal CT or genetic differences. The frequency of pancreatic lesions in VHL disease has been reported to range from 0% in two families to 92% in another family [11, 14]. These big differences according to families showed that genetic differences influenced the phenotype of the pancreas. The possibility of selection bias was negligible because only 10 of 18 patients visited a gastroenterologist, and many patients from all over the country visit other departments in our hospital.

The frequency of NET and SCA was similar to other reports. Among patients with pancreatic lesions, 94% had multiple cystic lesions, 12% had serous cystic adenomas, and 12% had neuroendocrine tumors. It was similar to previous reports in which about 90% of pancreatic lesions were single or multiple cysts, and the others were NET or SCA [3, 15, 16]. Thus, asymptomatic patients with multiple cysts in the pancreas should be carefully evaluated for VHL disease.

It is impossible to make a diagnosis of SCA based only on CT. However, EUS-FNA was not available at the time of the first study, follow-up CT scans showed no change of semi-solid lesions, it has been reported that SCA and VHL disease were related, and the pathologic diagnosis of SCA is of less clinical significance. We made presumptive diagnosis of SCA in two patients.

Two patients with NET also had RCC. In case of pancreatic metastasis of RCC, it can show a hypervascular mass like NET. One NET was confirmed by surgical resection during nephrectomy of coexisting RCC. The other patient presented because of recurring RCC. He had had a bilateral partial nephrectomy 1 1/2 years before and was treated with bilateral radiofrequency catheter ablation. For 6 months, there were no changes in the pancreatic hypervascular mass, and we made a presumptive diagnosis

Table 3 Changes of pancreatic lesions in VHL patients

Case No	F/U (Mon[a])	Cystic lesions	Calcification	Main duct change
1	29	Increase	Newly developed	No
2	56	Increase	Increase	No
3	32	Increase	No calcification	Mild dilatation developed
4	18	Increase	Newly develop	No
5	14	Increase	Increase	Mild dilatation developed
6	17	Increase	Persistent and no change	No
7	28	Increase	Increase	No
8	32	Increase	No calcification	No
9	47	Decrease	Newly developed	No

[a] Follow-up period is expressed in months

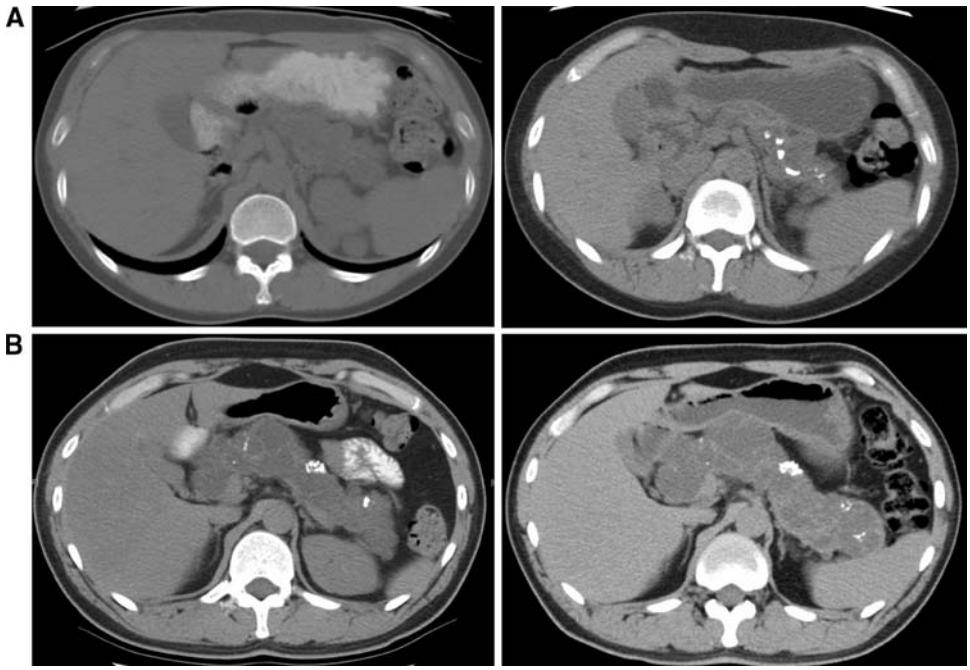

Fig. 2 Changes of pancreatic lesions. **a** New calcifications were observed in CT scan of case 9 after 3 years. **b** Increasing calcifications were noted in the CT scan of case 2 after 5 years

of NET for a pancreatic lesion. Some reported that pancreatic NET was associated with pheochromocytoma [17]. In our cases, two NET and two pheochromocytomas were detected separately.

It is well known that the VHL tumor suppressor gene product leads to HIF-1 alpha inactivation by making an E3 ubiquitin ligase complex [18]. In addition, other functions of the VHL protein, such as extracellular matrix assembly, microtubule stabilization [19], p53 [20], and junB [21], have been suggested. All of these functions might explain the predisposition of a person with a mutant allele of VHL gene to development of various types of tumors [22]. Among patients with VHL disease, 40% of the mutations are due to genomic deletions. Other mutations, such as truncating or missense mutations, have been identified [23]. Recently, some correlation of metastasis of pancreatic NET with exon 3 mutation in the VHL gene was suggested [24]. In this study, one patient with a NET had heterozygous A to T transversion in exon 3 of the VHL gene (c.586A > T). NET was removed by surgical resection, and no metastasis of NET was found.

We observed radiological progression of pancreatic lesions in nine patients who had CT scans 1 year apart. The prognosis of VHL disease was improved as the management of CNS and renal lesions advanced. The prognosis was determined largely by treatment of a hemangioblastoma in an earlier stage and RCC at a later stage [25]. In addition to the development of the surgical technique, including emergence of nephron-sparing surgery, radiofrequency ablation of RCC, and gamma knife

treatment of CNS, hemangioblastomas improved the management and result in longer survival of patients with VHL disease [26]. Most of the pancreatic lesions are less important in view of clinical features unless malignant NET or compression of adjacent exists. It is also well known that some pancreatic lesions show increasing calcifications around the cysts [3, 4, 7, 27]. In our study, radiologic compression by pancreatic cysts was observed in five patients on CT scan, but they did not have any symptoms related to the compression. Interestingly, all of patients who had CT scans 1 year apart showed progression of pancreatic lesions with respect to one of three features (increase of cystic lesion, increase of calcifications, and dilatation of main pancreatic duct). Although no patient required specific treatment for pancreatic changes, the pancreatic lesions might progress and some patients might need treatment in the future.

In summary, pancreatic involvement in VHL disease is more common in Korean patients. The most common type of pancreatic involvement was a multiple cystic lesion. NET and SCA were found in around 10% of VHL patients with pancreatic involvement. During follow-up of VHL disease patients, it should be considered that pancreatic lesions may progress.

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