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Clinical Characteristics of Renal Cell Carcinoma in Korean Patients with von Hippel-Lindau Disease Compared to Sporadic Bilateral or Multifocal Renal Cell Carcinoma

This study was done to analyze the clinical characteristics of renal cell carcinoma (RCC) in Korean patients with von Hippel-Lindau (VHL) disease. Between January 1996 and July 2008, 1,514 patients were diagnosed with RCC and 24 patients were diagnosed with VHL disease at our institute. We analyzed the clinical characteristics of the 24 patients diagnosed with VHL. The mean age of patients with VHL was 39.2±12.6 yr; the mean age of patients with both VHL and RCC was 42.5±10.3 yr. Among the 24 patients with VHL, 7 patients had retinal angiomas, 11 had RCC, 16 had renal lesions, 18 had pancreatic lesions and 21 had cerebellar hemangioblastomas. There was no significant difference between survival rates of patients with VHL alone and those with VHL and RCC. However, cancer-specific survival rates were significantly different between patients with both VHL and RCC and patients with sporadic bilateral or multifocal RCC. In our Korean study, the incidence of RCC in patients with VHL disease is 45.8% and the incidence of VHL disease in patients with RCC is 0.73%. Due to the low overall incidence of VHL in Korea, extended multi-institutional studies are needed to establish the true characteristics of VHL disease.

Key Words : *Von Hippel-Lindau Disease; Carcinoma, Renal Cell; Incidence*

Won Tae Kim[1,*], Won Sik Ham[1], Hee Jeong Ju[1], Jin Sun Lee[1], Jin Sung Lee[2], and Young Deuk Choi[1]

Department of Urology & Urological Science Institute[1], Department of Clinical Genetics[2], Yonsei University College of Medicine, Seoul, Korea

*Current address: Department of Urology, Chungbuk National University College of Medicine, Cheongju, Korea

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Address for correspondence
Young Deuk Choi, M.D.
Department of Urology and Urological Science Institute, Yonsei University College of Medicine, 250 Seongsan-ro, Seodaemun-gu, Seoul 120-752, Korea
Tel : +82.2-2228-2317, Fax : +82.2-312-2538
E-mail : youngd74@yuhs.ac

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INTRODUCTION

Von Hippel Lindau (VHL) disease is an autosomal dominant disease that produces a variety of tumors and cysts in the central nervous system (CNS) and visceral organs (1). Tumor types seen in VHL include hemangioblastoma in the CNS and retina, renal cell carcinoma (RCC), pheochromocytoma, and pancreatic neuroendocrine tumors. VHL is associated with the inactivation of a tumor suppressor gene located on chromosome 3p25-26 (2).

The global prevalence of patients with VHL has been reported to be between 1 in 30,000 and 1 in 100,000 (3). However, VHL is very rare in Korea; there are only three reports of patients with VHL and RCC (4-6). In this report, we examine Korean patients with VHL to characterize the types of benign and malignant tumors that develop and the clinical characteristics of concomitant RCC.

MATERIALS AND METHODS

Patients

Between January 1996 and July 2008, 24 patients were diagnosed with VHL and 1,514 patients were diagnosed with RCC in our institute. In patients with VHL, we examined clinical manifestations and accompanying lesions including CNS hemangioblastoma, retinal angioma, RCC, renal cyst, pancreatic tumor, pancreatic cyst, pheochromocytoma, and epididymal cyst. These conditions were diagnosed as follows. Retinal angiomas were diagnosed by ophthalmoscope in the department of ophthalmology, pancreatic lesions were diagnosed by computed tomography (CT) or ultrasonography (US), CNS hemangioblastomas and pheochromocytomas were diagnosed by CT and magnetic resonance imaging (MRI), and renal cysts and RCCs were diagnosed by CT or US and their size, characteristics and metastasis were evaluated by CT. Genetic testing was performed in the department of clin-

ical genetics. The diagnostic criteria for VHL include the following: 1) one CNS hemangioblastoma and visceral manifestations of VHL, or 2) any manifestation and possession of a known VHL gene or a family history of VHL.

Data analysis

We studied patients diagnosed with RCC during the same time period in our institute and compared this information with the incidence of RCC in Korean patients with VHL. In patients with RCC related to VHL disease, we examined age, clinical characteristics of the tumor, symptoms, metastasis, type of pathology, and survival. We also documented the management of patients with RCC, which included partial nephrectomy, radical nephrectomy, immunotherapy, and target therapy.

We examined mean age, histological type, pathologic tumor grade and mean size of sporadic bilateral or multifocal RCC and compared the survival rates of 11 VHL patients with RCC to those of 54 patients with sporadic bilateral RCC or sporadic multifocal RCC.

Survival rates of patients with VHL with and without RCC, and VHL patients with RCC and patients with sporadic bilateral or multifocal RCC were analyzed using the Kaplan-Meier log-rank test. A value of $P<0.05$ was considered statistically significant. Analyses were performed using SPSS 12.0 software (SPSS, Inc. Chicago, IL, U.S.A.).

RESULTS

Incidence

Between January 1996 and July 2008, 1,514 patients were diagnosed with RCC, 24 patients were diagnosed with VHL, and 11 patients were diagnosed with both RCC and VHL in our institute. In Korean patients, the incidence of RCC in patients with VHL is 45.8% and the incidence of VHL in patients with RCC is 0.73%.

Clinical manifestations of VHL disease

The mean age at diagnosis was 39.2±12.6 yr for VHL. In these patients, the distribution of tumor manifestations was as follows: 5 had pheochromocytomas, 7 (29.1%) had retinal angiomas, 16 (66.7%) had renal cysts or RCCs, 18 (75.0%) had pancreatic cysts or tumors, and 21 (87.5%) had hemangioblastomas of the cerebellum or spinal cord (Table 1). One pheochromocytoma patient had hypertension while three had normal blood pressure. No patient had diabetes mellitus (DM), including those with pancreatic islet cell tumors and pancreatic cysts.

Table 1. Profiles of 24 patients with von Hippel-Lindau disease

No.	Age (yr)	Sex	Family Hx.	Retinal angioma	Pancreatic cyst or mass	Cerebellar or spinal hemangioblastoma	Adrenal mass	Renal cyst	RCC
1	42	M	+	−	+	+	−	+	−
2	22	F	−	−	+	+	−	−	−
3	29	M	−	+	−	+	−	−	−
4	47	F	−	−	−	+	−	−	−
5	47	M	−	−	+	+	−	+	+
6	54	F	−	+	−	+	−	−	−
7	18	M	+	−	+	+	−	−	−
8	43	M	−	−	−	+	−	+	−
9	33	M	−	−	+	+	−	−	+
10	65	M	−	−	+	+	−	+	+
11	49	F	+	−	+	+	+	+	+
12	42	M	−	−	+	+	−	+	+
13	27	F	−	+	+	−	−	+	+
14	22	M	−	−	+	+	−	−	−
15	60	F	−	−	+	+	−	+	−
16	34	M	−	−	+	+	−	−	+
17	36	M	−	−	+	+	−	+	+
18	51	M	+	+	+	+	+	−	−
19	29	M	−	+	−	−	+	−	−
20	50	M	−	+	−	+	+	+	+
21	21	M	+	−	+	−	+	+	−
22	43	F	−	+	+	+	−	+	+
23	42	M	−	−	+	+	−	−	+
24	34	F	−	−	+	+	−	+	−

No., number; Hx., history; RCC, renal cell carcinoma; M, male; F, female.

VHL gene analysis

We performed genetic testing on 12 patients for VHL gene mutations. Of them, 7 patients had mutations (Table 2). Two patients with mutations were mother and son. Twelve patients did not undergo genetic testing.

Clinical characteristics of RCC in VHL disease

Of the 24 patients with VHL, 16 had renal lesions: 11 (45.8%) had RCC and 5 had renal cysts without RCC. Thus in this study, the incidence of VHL disease in patients with RCC was 0.73% (11 patients). The mean age of VHL patients with RCC was 42.5±10.3 yr. The tumor characteristics were as follows: five patients had unilateral RCCs and six had bilateral RCCs; nine patients had multiple RCCs; the largest tumor was 8-9 cm and the smallest was 1.8 cm; symptoms included one patient with flank pain and one with gross hematuria; nine patients were asymptomatic; two patients had lung metastasis, and one had brain metastasis.

Management

Of the 11 patients who received treatment, 3 underwent radical nephrectomies, 1 received target therapy with sorafenib after a radical nephrectomy, 2 underwent partial nephrectomies, 2 received IL-2 immunotherapy, and 1 with lung metastases received target therapy with sunitinib. The stage of the two patients who underwent partial nephrectomies was pT1a. The stages of the four patients who underwent radical nephrectomy and target therapy after a radical nephrectomy were 2 pT2, 1 pT1b and 1 pT1a with multiple RCCs. Two patients received no treatment due to severe complications associated with cerebellar hemangioblastomas.

Table 2. Mutations of the von Hippel-Lindau (VHL) gene

No.	VHL gene
1	3 bp deletion (TCT, codon 76-77) (7)
2	His115Gln (CAC>CAA) (8)
3	Arg167Gln (50DSUB G>A) (9)
4	Trp88Arg (262T>C) (10)
5	Arg167Trp (499C>T) (9)
6	Trp88Arg (TGG>CGG) (10)
7	Asn78Ser (8)

T, thymine; C, cytosine; A, adenine; G, guanine; His, histidine; Gln, glutamine; Arg, arginine; Trp, tryptophan; Asn, asparagine; Ser, serine.

Pathology of RCC

Three patients who received immunotherapy or target therapy underwent needle biopsies and six patients underwent surgery. All nine patients who underwent biopsies were shown to have conventional RCC pathology (Table 3). Pathologic tumor grade was 1 in 1 patient, 2 in 5 patients and 3 in 3 patients.

Characteristics of sporadic bilateral or multifocal RCC

We analyzed 54 patients with sporadic bilateral or multifocal RCC. 17 patients were sporadic bilateral RCC and 37 patients were sporadic multifocal RCC. The mean tumor size of sporadic bilateral or multifocal RCC was 6.59±3.34 cm. Histology types in these patients were conventional RCC in 47 patients, papillary RCC in 4 patients and chromophobe RCC in 3 patients. Pathologic tumor grades in these patients were 1 in 4 patients, 2 in 21 patients, 3 in 19 patients, 4 in 6 patients and unknown in 4 patients.

Follow-up and prognosis

The mean follow-up period of patients with VHL was 37.3 ±7.5 months. At follow-up, 7 of 24 patients with VHL had

Table 3. Description of renal cell carcinoma in nine patients with von Hippel-Lindau disease

Case No.	Age (yr)	Site	Max. diameter (cm)	Single or multiple	Pathology	Symptom	RCC stage	Treatment	Distant metastasis	Survival
1	47	B	2.7	Multiple	No	No	cT1acN0cM0	Refuse	-	-
2	33	R	8	Multiple	C	No	pT2pN0cM0	Nephrec	-	+
3	65	B	8	Multiple	C	GH	pT2pN0cM0	Nephrec+ Sorafenib	+	+
4	49	B	9	Multiple	C	FP	cT2cN1cM1	Sunitinib	-	+
5	42	R	2	Single	C	No	pT1acN0cM0	Partial	-	+
6	27	L	3	Single	C	No	pT1acN0cM0	Partial	-	+
7	34	B	5.1	Multiple	No	No	pT1bcN0cM0	Observ	-	+
8	36	L	1.8	Multiple	C	No	pT1acN0cM0	Nephrec	-	+
9	50	B	4.3	Multiple	C	No	cT1bcN0cM0	IL-2	-	+
10	43	B	3.5	Multiple	C	No	cT1acN0cM0	IL-2	-	+
11	42	R	6.5	Multiple	C	No	cT1bcN0cM0	Nephrec	-	+

B, bilateral; R, right; L, left; C, conventional renal cell carcinoma; RCC, renal cell carcinoma; GH, gross hematuria; FP, flank pain; Nephrec, nephrectomy; Partial, partial nephrectomy; Observ, observation only; IL-2, IL-2 based immunotherapy.

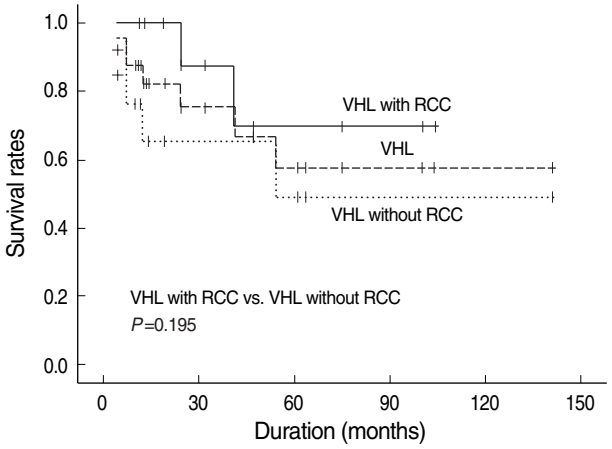

Fig. 1. Overall disease-specific survival rates for patients with von Hippel-Lindau (VHL) disease only, and VHL with and without renal cell carcinoma (RCC).

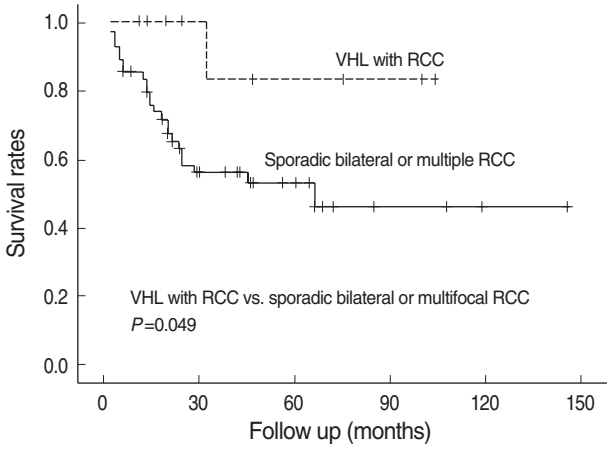

Fig. 2. Cancer-specific survival rates of patients with both von Hippel-Lindau (VHL) disease and RCC, versus patients with sporadic bilateral or multifocal RCC.

died and 2 VHL patients with RCC had died, one from complications of a cerebellar hemangioblastoma and one from lung and brain metastases. There was no significant difference in overall survival rates between patients with VHL with and without RCC (P=0.195) (Fig. 1). However, the cancer-specific survival rate was significantly different between VHL with RCC and sporadic bilateral or multifocal RCC (P<0.05) (Fig. 2).

DISCUSSION

The global prevalence of patients with VHL disease has been reported to be between 1 in 30,000 and 1 in 100,000 (3, 11, 12). It has been reported that 40-70% of patients with VHL have concomitant RCC and that the mean age of patients diagnosed with both disorders is 37 yr old (13). This is the first report that analyzes the clinical characteristics of RCC in a group of Korean patients with VHL. In this study, 45.8% of patients with VHL had concurrent RCC and their mean age was 42.5±10.3 yr old.

Renal cysts commonly occur in VHL disease and can give rise to RCC (13). In this study, a total of 13 patients had renal cysts and 5 patients had renal cysts without RCC. If the latter were followed-up, RCC may have developed. For this reason, serial imaging is important to detect malignant transformation of benign cysts.

Before modern screening tests were established, many patients with VHL died before reaching 50 yr of age, mostly due to complications of CNS hemangioblastoma or RCC (14, 15). Today, modern diagnostic and treatment techniques allow earlier detection and improved prognosis. For example, retinal angiomas can lead to retinal detachment and blindness, but if detected early these lesions respond well to laser photocoagulation or cryotherapy (13).

Early detection of RCCs enables kidney-preserving rather than radical nephrectomy. RCCs in VHL disease grow slowly, usually less than 0.3 cm per year (16, 17). Therefore, after diagnosis, follow-up CTs are indicated. If the tumor is larger than 3 cm, nephron-sparing surgery (NSS) is performed to preserve renal function (18-20). NSS is effective and safe in patients with VHL disease and renal function is preserved without increasing the risk of metastasis (21). In this study, two patients with RCC smaller than 3 cm underwent partial nephrectomies and there was no recurrence or metastasis during follow-up.

Compared with its sporadic counterpart, RCC in VHL is associated with a less aggressive course, demonstrating slower growth, a lower rate of metastasis, and most importantly, improved cancer-specific survival (17). In this study, there was no significant difference in survival rates between VHL patients with and without RCC. Of the VHL patients with RCC, one died of RCC during follow-up and six died from complications of CNS hemangioblastomas. This implies that careful management of complications of CNS hemangioblastoma in Korean patients with VHL may improve survival. Furthermore, cancer-specific survival of VHL patients with RCC was significantly better than that of patients with sporadic bilateral or multifocal RCC.

Given that the diagnostic criteria for VHL disease include any disease manifestation and a family history or known VHL gene, over 50% of VHL patients have only one manifestation (11, 15). One limitation of this retrospective study is failure to enroll patients with only one manifestation with a family history of VHL disease or with a positive genetic test. VHL genetic testing and asking family history was not performed on patients with only one manifestation of VHL disease.

In conclusion, the results of this study show that in a Korean population, 0.73% of patients with RCC have associated VHL disease and 45.8% of patients with VHL disease have concomitant RCC. However, due to the relatively small study size and the fact that VHL disease is rare in Korea, further

multi-institutional studies are needed to establish the characteristics of VHL disease in Korea.

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