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Von Hippel-Lindau Disease–A Case Report and Review of Literature

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ABSTRACT

Von Hippel-Lindau disease is a dominantly inherited familial cancer syndrome with variable expression. Here we are reporting a case of von Hippel-Lindau disease in a family.

INTRODUCTION

The familial form of the common clear-cell variant of RCC is von Hippel-Lindau disease. Major manifestations include the development of RCC, pheochromocytoma, retinal angiomas, and hemangioblastomas of the brain stem, cerebellum, or spinal cord [1]. All these tumor types are vascular and can lead to substantial morbidity, much of which can be avoided with prompt recognition and careful, skilled management. With improved management of the central nervous system manifestations of the disease, RCC has now become the most common cause of mortality in patients with von Hippel-Lindau disease [1].

CASE REPORT

A 32-year-old male presented with a sudden onset of blurry vision in his left eye in 2002. On investigation, he was found to have bilateral retinal angiomas and bilateral renal tumors. He was treated with laser therapy for retinal angiomas. A CECT scan of the abdomen revealed bilateral renal tumors (4 cm on the right side and 1 cm on the left side) and multiple pancreatic cysts (Figure 1). He underwent a right partial nephrectomy and later, the patient was on regular follow-up. A twin brother was also affected and underwent surgery for bleeding from cerebellar hemangioblastoma. The patient's wife conceived, and chorionic villous sampling revealed the VHL gene was positive, and aborted. A CECT scan of the abdomen in 2007 revealed a left, lower pole renal tumor of about 4.3 cm with

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Abbreviations and Acronyms
RCC, renal cell carcinoma
VHL, von Hippel-Lindau
VEGF, vascular endothelial growth factor
HIF, hypoxia induced factor
PDGF, platelet derived growth factor

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case report

Figure 1. CECT scan of the abdomen revealed bilateral renal tumors (4 cm on right side and 1 cm on left side) and multiple pancreatic cysts.

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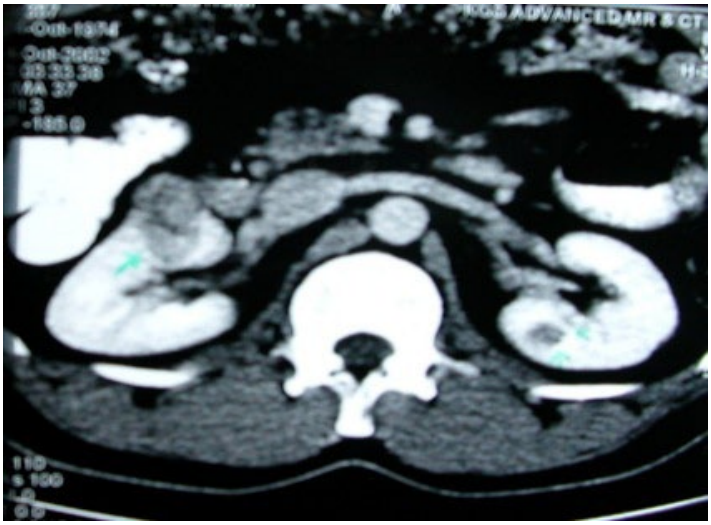

Figure 2. CECT scan of the abdomen revealed a left lower pole renal tumor of about 4.3 cm with multiple pancreatic cysts.

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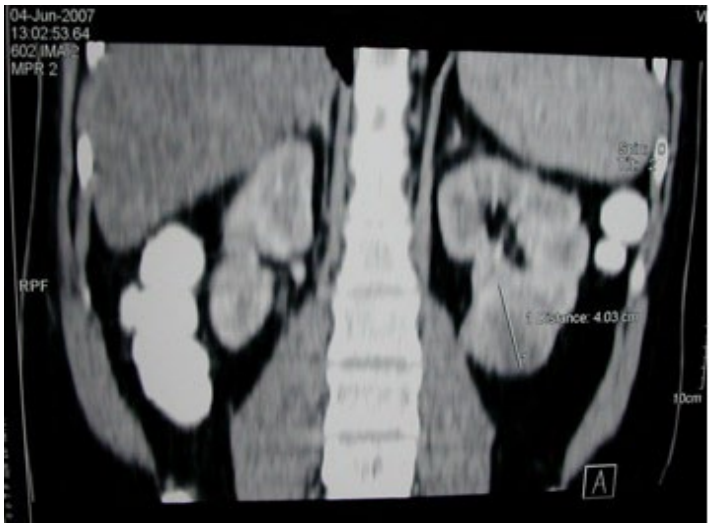

multiple pancreatic cysts (Figure 2). A DTPA renogram showed a normally functioning right kidney and a space-occupying lesion (SOL) in the left lower pole renal parenchyma. A brain CT showed a normal study. After a preoperative workup, a left partial nephrectomy was done. A frozen section revealed the margins were tumor free. A histopathology revealed a clear cell variant of low-grade renal cell carcinoma. The patient is now in follow-up.

DISCUSSION

The familial form of the common clear cell variant of RCC is von Hippel-Lindau disease. This relatively rare autosomal dominant disorder occurs with a frequency of 1 per 36000 of the population. Major manifestations include the development of RCC, pheochromocytoma, retinal angiomas, and hemangioblastomas of the brain stem, cerebellum, or spinal cord (Table 1) [1]. RCC develops in about 50% of patients with von Hippel-Lindau disease and is distinctive for its early age at onset, often in the third, fourth, or fifth decade of life, and for its bilateral and multifocal involvement [1]. Sophisticated molecular genetic linkage studies in patients with von Hippel-Lindau disease eventually led to the identification of the VHL tumor suppressor gene [2]. This gene, which is located at chromosome 3p25-26, has now been completely sequenced, and its role as a tumor suppressor gene for both the sporadic and the familial forms of clear cell RCC has been confirmed [3].

The VHL gene consists of 3 exons, and it encodes a protein of 213 amino acids. Both alleles of the VHL gene must be mutated or inactivated for development of the disease. Almost all patients with von Hippel-Lindau disease were found to have germ line mutations of 1 allele of the VHL tumor suppressor gene, and autosomal dominant inheritance from the affected parent was confirmed [3, 4]. The second allele is commonly lost by gene or chromosome deletion. A critically important function of the VHL protein complex is to target the hypoxia-inducible factor 1 (HIF-1) for ubiquitin-mediated degradation, keeping the levels of HIF-1 low under normal conditions. HIF-1 is an intracellular protein that plays an important role in regulating cellular responses to hypoxia, starvation, and other stresses. Inactivation or mutation of the VHL gene leads to dysregulated expression of HIF-1, and this protein begins to accumulate in the cell [5, 6]. This, in turn, leads to a several-fold upregulation of the expression of vascular endothelial growth factor (VEGF), the primary pro-angiogenic growth factor in RCC, contributing to the pronounced neovascularity associated with clear cell RCC [4]. HIF-1 also upregulates the expression of tumor growth factor-α, platelet-derived growth factor (PDGF), glucose transporter (Glut 1), erythropoietin, and carbonic anhydrase 9

Figure 3. Biologic functions of the VHL protein. The wild-type VHL protein targets HIF-α for degradation. Mutation of the VHL gene allows HIF-α to accumulate, leading to increased expression of VEGF, Glut 1, and PDGF. This, in turn, has important implications with respect to tumor angiogenesis, metabolic activity, and autocrine stimulation.
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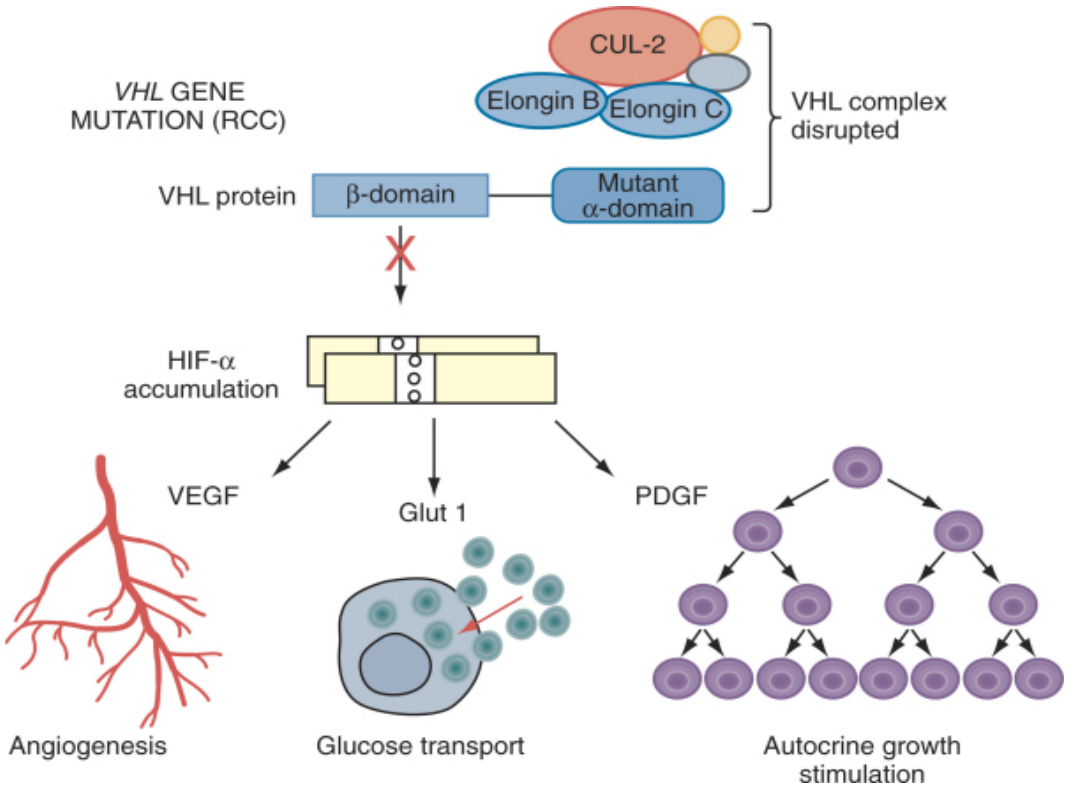

Table 1. Manifestations of von Hippel-Lindau syndrome.
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Organ System	Lesion	Incidence (%)
Eye	Benign retinal angiomas	49–59
Central nervous system	Benign hemangioblastomas	42–72
Kidney	Clear cell RCC	24–70
	Renal cysts	22–59
Adrenal gland	Pheochromocytoma	18
Pancreas	Islet cell tumors	12
	Malignant islet cell tumor	2
	Pancreatic cysts	21–72
Epididymis	Cystadenoma	10–26
Ear	Endolymphatic sac tumor	10

(CA-9), a tumor-associated antigen with specificity for clear cell RCC (Figure 3) [4, 7, 8].

This syndrome should be considered in any patient with early-onset or multifocal RCC or RCC in combination with any of the following: a history of visual or neurologic symptoms; a family history of blindness, central nervous system tumors, or renal cancer; or coexistent pancreatic cysts, epididymal lesions, or inner-ear tumors [1, 4, 9]. Patients suspected of having von Hippel-Lindau disease, or the appropriate relatives of those with documented disease, should strongly consider genetic evaluation. Patients with germ line mutations can be identified and offered clinical and radiographic screening that can identify the major manifestations of von Hippel-Lindau disease at a presymptomatic phase, allowing potential amelioration of the considerable morbidity associated with this syndrome [10]. Investigators at the National Institutes of Health have recommended that such patients be evaluated with (1) an annual physical examination and ophthalmologic evaluation beginning in infancy; (2) estimation of urinary catecholamines at the age of 2 years and every 1 to 2 years thereafter; (3) an MRI of the central nervous system biannually beginning at the age of 11 years; (4) an ultrasound examination of the abdomen and pelvis annually beginning at the age of 11 years, followed by CT scanning every 6 months if cysts or tumors develop; and (5) periodic auditory examinations [10].

References

1. Neumann HPH, Zbar B. Renal cysts, renal cancer and von Hippel-Lindau disease. *Kidney Int*. 1997;51(1):16–26. PubMed ; CrossRef

2. Latif F, Tory K, Gnarra J, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science*. 1993;260(5112):1317–1320. PubMed ; CrossRef

3. Gnarra JR, Tory K, Weng Y, et al. Mutations of the VHL tumour suppressor gene in renal carcinoma. *Nat Genet*. 1994;7(1):85–90. PubMed ; CrossRef

4. Linehan WM. Molecular Targeting of VHL Gene Pathway in Clear Cell Kidney Cancer. *J Urol*. 2003;170(2):593–594. PubMed ; CrossRef

5. Ratcliffe PJ, Maxwell PH, Wiesener MS, et al. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature*. 1999;399(6733):271–275. PubMed ; CrossRef

6. Yu F, White SB, Zhao Q, Lee FS. Dynamic, site-specific interaction of hypoxia-inducible factor-1α with the von Hippel-Lindau tumor suppressor protein. *Cancer Res*. 2001;61(10):4136–4142. PubMed

7. Zbar B, Kaelin W, Maher E, Richard S. Third International Meeting on von Hippel-Lindau disease. *Cancer Res*. 1999;59(9):2251–2253. PubMed

8. Grabmaier K, de Weijert MCA, Verhaegh GW, Schalken JA, Oosterwijk E. Strict regulation of CAIX (G250/MN) by HIF-1α in clear cell renal cell carcinoma. *Oncogene*. 2004;23(33):5624–5631. PubMed ; CrossRef

9. Choyke PL, Glenn GM, Walther MM, Zbar B, Linehan WM. Hereditary renal cancers. *Radiology*. 2003;226(1):33–46. PubMed ; CrossRef

10. Maranchie JK, Linehan WM. Genetic disorders and renal cell carcinoma. *Urol Clin North Am*. 2003;30(1):133–141. PubMed ; CrossRef