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Von Hippel-Lindau; A 47-year-old woman with renal cell carcinoma and multiorgan involvement

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Abstract
Von Hippel-Lindau (VHL) is a rare autosomal dominant genetic disease. Affected individuals manifest clinically with tumors involving multiple organs including hemangioblastoma of the central nervous system and retina, cystic kidney disease, renal cell carcinoma (RCC), pheochromocytoma, and pancreatic neuroendocrine tumors. Its diagnosis is based on genetic testing and clinical criteria in suspected patients. Treatment principles are to save organs and periodic surveillance for in-time tumor detection and appropriate follow-ups. This case report presents a 47-year-old woman with five years history of abdominal pain alongside long-standing headaches and progressive hearing loss. On imaging, multiple suspicious tumors throughout her body were detected and she proceeded to surgical resection. She was finally diagnosed with RCC, central nervous system tumor hemangioblastoma, and pancreatic cyst. The patient underwent a right-sided nephrectomy and Sunitinib therapy. She is continuing therapy and currently does not have any sign of metastasis. Due to her constellation of tumors VHL disease was suspected. Although she did not have any positive family history, the VHL diagnosis was conducted based on clinical criteria. The case emphasized the importance of timely recognition and evaluation of suspected cases and evidence base surveillance. Physician familiarity with the underestimated disease is of paramount importance.

Keywords: Von Hippel-Lindau, Renal cell, Carcinoma, Hemangioblastoma
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Introduction

Von Hippel-Lindau (VHL) is a rare autosomal dominant genetic disease. It manifests clinically as tumors involving multiple organs including hemangioblastoma of the central nervous system and retina, Kidney cysts, renal cell carcinoma (RCC), pheochromocytoma, and pancreatic neuroendocrine tumors (1). The prevalence rate is approximately 1 in 36 000 live birth, however, it probably is underestimated (2).

VHL gene encodes for a tumor suppressor protein called protein VHL (pVHL) which inhibits hypoxia-inducible factor-alpha (HIF-α). HIF-α is responsible for the upregulation of many growth factors including vascular endothelial growth factor (VEGF). Lack of pVHL leads to upregulation of HIF-α and its associated genes. This imparts explains the propensity of VHL patients to form vascular tumors such as hemangioblastoma and RCC (3-5).

Clinical diagnosis of the disease requires either one VHL-associated manifestation with a positive familial history or two manifestations in de novo cases. Genetic testing is the diagnostic gold standard, however, it might be unnecessary for individuals who fulfill the clinical criteria with multiple typical tumors (6,7).

Regular follow-ups and evidenced-based surveillance imaging are crucial for the successful treatment of patients. This approach will balance tumor treatment with organ preservation. Unfortunately, the prognosis is unfavorable and the disease is progressive (8,9).

At present besides surgical resections of tumors and symptomatic treatment, there is no available cure. Belzutifan is an emerging novel investigational therapy for the treatment of RCC associated with VHL (10).

Clinical Presentation

A 47-year-old female presented with five years history of intermittent and nonspecific abdominal pain without specific location which radiated to her right flank and sometimes was accompanied by dysuria and frequency without hematuria.

The pain was not associated with GI problem. The patient had regular monthly periods but complained of hypermenorrhea. She complained of chronic generalized headaches occurring two to three times a week. Additionally, palpitation occurred during headache episodes. A complete review of symptoms revealed

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Implication for health policy/practice/research/ medical education

Von Hippel-Lindau (VHL) diagnosed based on genetic testing and clinical criteria. A 47-year-old woman with a history of abdominal pain alongside long-standing headaches and progressive hearing loss has been investigated. On imaging, multiple suspicious tumors throughout her body were detected and she proceeded to surgical resection. She was finally diagnosed with renal cell carcinoma, central nervous system tumor hemangioblastoma, and pancreatic cyst. She underwent a right-sided nephrectomy and sunitinib therapy. Due to her constellation of tumors VHL disease was suspected. This case emphasizes the importance of timely identification of suspicious cases and the doctor's familiarity with the disease.

tinnitus and mild left-sided hearing loss in the last three years. The patient also had a history of long-standing insomnia, anorexia, malaise, weakness, occasional panic attacks, and generalized constant bone pain without mechanical or inflammatory pattern too.

She did not report any excessive perspiration, weight loss, fever, chills, blurred vision, diplopia, decreased visual acuity, vertigo, dyspnea, cough, hematuria, or genital symptoms. She was married and the mother of three children. The patient's only medications were non-steroidal anti-inflammatory drugs as needed for headaches. Past-medical history was remarkable for a craniotomy with ventriculoperitoneal shunt placement many years ago. There were no surgical reports available.

On physical examination the patient was nervous. She was completely alert and cooperative. Heart rate was 98 and regular, respiratory rate was 14 per minute, and systolic and diastolic blood pressures were 170 and 90 mm Hg respectively. Patient's body mass index (BMI) was 25.4 kg/m^2. No focal neurologic deficit, ataxia, nystagmus, dysarthria, or signs of meningism us were present. The cerebellar assessment showed normal finger to nose, heel to shine, and intact tandem gait. Plantar reflex was downward bilaterally. The intact hearing was noted on Rene and weber's test. No retinal lesions including hemangioblastomas, papillary edema, or extraocular muscle dysfunction were present on careful ophthalmic examination. Costovertebral angle tenderness was absent but T9 to L2 vertebras were tender on percussion.

Initial evaluation

To investigate the cause of the symptoms and signs, At first, diagnostic tests were performed, which are listed in Table 1. In the abdomino pelvic ultrasound revealed multiple cyctic in both kidneys with the largest cyst having a diameter of 45 mm and inner stranding. There was also a solid hyperechoic vascular mass measuring 73 by 68 mm with inner hypoechogenicity.

Imaging studies

Out of concern for a systemic illness, she was admitted and further imaging was conducted. An abdominopelvic computerized tomography (CT) scan was significant for a cystic structure in the pancreatic tail (37 by 38 mm) and a solid cystic lesion in its body (28 by 30 mm). Both kidneys were involved with multiple cysts. The left kidney contained a large (53 mm) cyst with enhancing mass-like and linear components. It was classified as Bosniak four. There was a solid cystic mass with enhancing irregular border and necrotic center (78 by 62 mm) in the right kidney upper lobe. Its appearance was suggestive of RCC, metastasis, or pheochromocytoma. Two soft tissue spherical masses, one abutting the cecum and the other one located in the ovaries were visualized (Figure 1).

Abdominopelvic magnetic resonance imaging (MRI) reported a mass measuring 71 by 61 mm with mark contrast enhancement located on the right kidney upper pole. Pancreatic lesions were described as multiple 10 to 25 mm cysts without diffusion restrictions (Figure 1).

According to the long-standing headaches and a history of ventriculoperitoneal shunt placement, a brain MRI was conducted which showed multiple predominantly cystic lesions in the midline of the posterior fossa probably involving vermis with vivid enhancement. At least three enhancing masses measuring 3 to 7 mm were visualized in both cerebellar hemispheres (Figure 2). Internal acoustic meatus had normal width and cranial nerve six to nine were normal on skull base and cerebellopontine angle (CPA) MRI. No evidence of endolymphatic sac tumor was found. Findings were compatible with hemangioblastoma. Spinal MRI was normal as were lungs and mediastinum.

Treatment and follow up

She was admitted to the surgical ward. In the light of

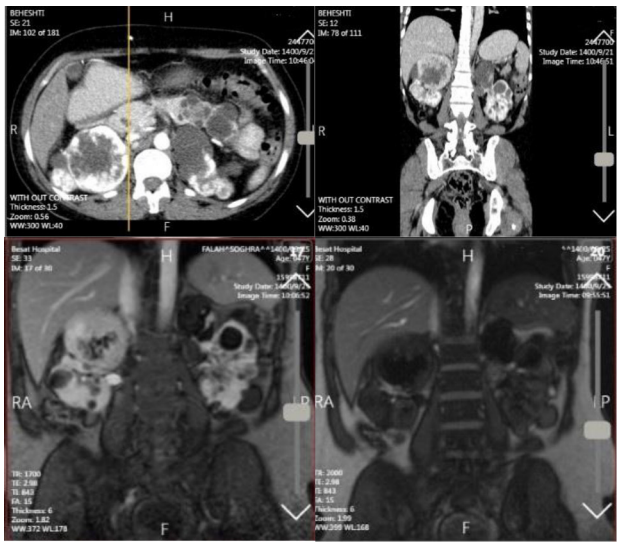

Figure 1. Abdominopelvic CT scan with IV contrast showing multiple cyst in both kidneys. Note right kidney upper lobe necrotic mass and left kidney Bosniak class 4 mass. T1-weighting hypointense and T2-weighting mix signals of right kidney mass. Multiple cysts in both kidneys and pancreas.

Table 1. Primary laboratory data and tumor markers

	Value	Normal Range
CBC		
WBC	7100 per µL	4000–11 000
Hb	12.9 mg/dL	12–15
Plt	245000 µL	150 000–450 000
Iron profile		
SI	139 µg/dL	33–193
Ferritin	28.7 ng/mL	10–291
TIBC	253 µg/dL	250–450
Basic metabolic panel		
Urea	34 mg/dL	15–40
Cr	0.8 mg/dL	0.6–1.3
eGFR	91 mL/min	
Na	139 mmol/L	136–145
K	4.05 mmol/L	3.5–5.1
Ca	10 mmol/L	8.5–10.5
P	3 mmol/L	2.9–5
Mg	1.8 mmol/L	1.9–2.5
FPG	94 mg/dL	65–110
AST	13 U/L	38
ALT	18 U/L	35
ALP	114 U/L	68–306
LDH	255 U/L	230–500
ESR	11 mm/h	30
Coagulation profile		
PTT	27s	23–40
PT	13s	11–13
INR	1	1
Tumor markers		
CEA	1.16 ng/mL	Nonsmoker <5; Smoker <6.5
AFP	3.2 IU/mL	≤5.8
CA19.9	20.64 U/mL	Up to 34
CA125	16.7 U/mL	0–35
Endocrinology		
TSH	1.6 µIU/ML	0.35–5.5
T4	9.7 µg/dL	4.1–15.1
FSH	7.4 mIU/mL	Follicular phase: 3.5–12.5; Pre-ovulatory phase: 4.7–21.5; Luteal phase: 1.7–7.7; Post-menopause: 25.4–134.8
LH	16.4 mIU/mL	Follicular phase: 2.4–12.6; Ovulatory phase: 14–96; Luteal phase: 1–11.4; Post-menopause: 7.7–59
Estradiol	5 pg/mL	Follicular phase: 30.9–90.4; Ovulatory phase: 60.4–533
Testosterone	0.8 ng/mL	0.08–0.48
17-OH-progesterone	0.71 ng/mL	Follicular phase: 0.4–1.51; Luteal phase: 1–4.51
DHEA	31.82 µg/dL	According to age 18–243
Hydroxy vitamin D3	18.06 ng/mL	Sever deficiency < 10; Mild to moderate deficiency 10–25; Optimal 25–80
Androstenedione	1.5 ng/dL	Folicular phase: 0.85–3.1; Luteal phase: 0.94–3.2
Metanephrine	58.6 pg/dL	<90
Urine Chemistry		
Creatinine (24 h urine)	880 mg/24 h	600–1800
Urinary Pro (24 h)	27 mg/24 h	<150
Urine volume (24 h)	1500 mL/24 h	600–2500
Urinary normetanephrine	671 µg/24 h	<600
Urine free cortisol	122 µg/24 h	1.5-63
Urine metanephrine	511 µg/24 h	<350

CBC: Complete blood count, WBC: White blood count, Hb: Hemoglobin, Plt: Platelets, SI: Serum iron, TIBC: Total iron-binding capacity, Cr: Creatinine, eGFR: Estimated glomerular filtration rate, Na: Sodium, K: Potassium, Ca: Calcium, P: Phosphorus, Mg: Magnesium, FPG: Fasting plasma glucose, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALK-p: Alkaline phosphatase, LDH: Lactate dehydrogenase, ESR: Erythrocyte sedimentation rate, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International normalized ratio, CEA: Carcinoembryonic antigen, AFP: Alpha-fetoprotein CA: Carcino-antigen, TSH: Thyroid-stimulating hormone, T4: Thyroxine, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, DHEA: Dehydroepiandrostenedione sulfate.

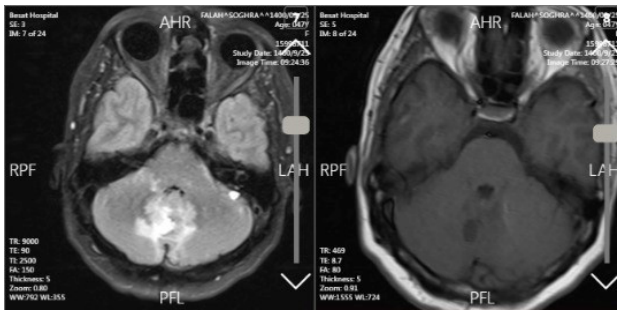

Figure 2. Brain MRI revealed a ventriculoperitoneal shunt, evidence of previous surgery, and multiple lesions in the posterior fossa.

imaging findings, the utmost concern was an RCC. She proceeded to open laparotomy with distal pancreatectomy, right-sided nephrectomy, and suprarenal and para ovarian mass resection. The surgery went uneventful and she quickly recovered. Microscopic evaluation of right kidney and suprarenal mass revealed a clear cell RCC measuring 7 by 6 by 5 cm (Figure 3). This finding was further confirming with an immunohistochemistry panel of mass which was positive for CK, PAX8 and CD10 markers.

Pancreatic mass was identified as begin serous cystadenoma (size: 6.5 by 3 by 2.7 cm). The para-ovarian mass was a para tubular cyst. Based on clinicopathologic findings she was diagnosed with VHL disease. The genetic study was deemed unnecessary.

Six months later, the patient was reevaluated and was still complaining of headaches, fatigue, and malaise. Her systolic and diastolic blood pressure on losartan were 115 mm Hg and 80 mm Hg respectively. A whole-body bone scan and abdominopelvic MRI did not show any sign of metastatic lesions. Laboratory data were insignificant. Due to the lack of any evidence of distant metastasis, posterior fossa lesions were considered to be hemangioblastoma in nature and periodic follow-up was recommended by neurosurgeons.

Discussion

Von Hippel-Lindau is a rare inherited autosomal dominant disease. Affected individuals harbor a mutated germline VHL gene. The gene encodes for a tumor suppressor protein called pVHL. Clinical presentations encompass a wide range of manifestations including different benign and malignant tumors, such as RCC, retinal and CNS hemangioblastoma, pheochromocytoma, benign pancreatic cysts, and middle ear endolymphatic sac (11,12).

Deactivation of the tumor suppressor protein, pVHL, leads to dysregulation of key cellular processes and angiogenesis. In summary, VHL protein is responsible for the suppression of oxygen-sensitive subunits of the HIF-alpha. Muted allele code for a defective VHL protein which can no longer promote proteasome degradation of HIF-1α. This is as if the cells are under constant hypoxic

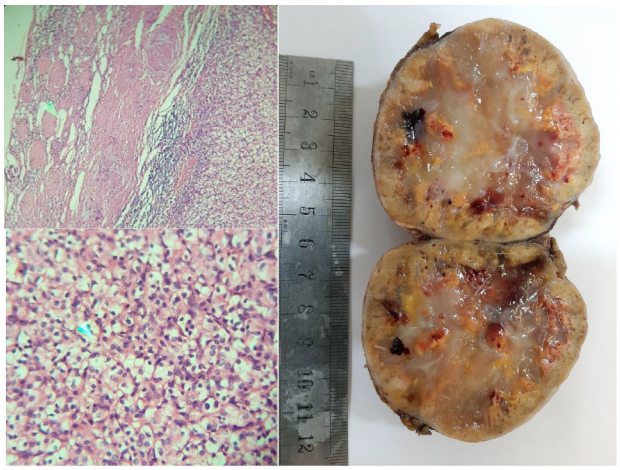

Figure 3. Macroscopy: well-defined tumor with pushing borders and variegated cut surface with creamy golden-yellow color. Microscopy: encapsulated renal cell carcinoma with glomerulosclerosis in remnant glomerulus and sheets of clear cells with distinct cell membrane and clear cytoplasm (Scale; ×40 H&E, ×100 H&E).

conditions. This in turn leads to increased production of VEGF, Platelet-derived growth factor–beta, transforming growth factor-alpha, and other growth factors resulting in tumor formation and unleashed angiogenesis (13,14).

Diagnosis is based on genetic studies and documentation of the defective alleles. Rarely, a diagnosis can be made solely based on clinical findings as is the case with our patient. Our patient presented with RCC, pancreatic cystadenoma, CNS hemangioblastoma, and para-ovarian mass. She fulfilled both Danish and international diagnostic criteria, however, no reliable family history was documented (6).

Except for individuals with a positive family history, diagnoses are often delayed. This imparts due to myriad clinical manifestations, the rarity of the disease, and the ensuing unfamiliarity of practitioners. Five years of abdominal pain and a remote CNS surgery probably due to a neoplasm in our patient is compatible with these facts. As an example, diagnosis of CNS hemangioblastoma on average is delayed for 4 to 5 years.

Successful treatment of patients requires careful follow-ups therefore, new lesions can be diagnosed as soon as possible. Previously established tumors must be kept under close surveillance. Based on evidence-based guidelines our patient needs annual comprehensive indirect ophthalmoscopy, serum metanephrines, and 24-hour urine metanephrine measurements. In addition, she must have a brain, spine, and abdominal MRI and audiogram every two years (11).

In recent years, organ sparing therapies have gained popularity and lowered patients' need for transplantation. This is especially the case with RCC. Currently, tumors less than 3 cm can forgo surgery and be followed with periodic imaging. A larger tumor size might be eligible for partial nephrectomy, cryotherapy, or radiofrequency ablation (10,15). Unfortunately, this was not the case with

our patient. Due to the heavy Right kidney tumor burden, she required a total nephrectomy.

Belzutifan is a novel HIF-1 alpha inhibitor that can be used in patients who have RCC. More than 80 percent of patients with RCC treated with the drug showed stable disease or no progression. CNS hemangioblastoma and primitive neuroectodermal tumors are showing promising results (10,16).

Metastatic RCC is treated no differently than RCC in non-VHL individuals. Tyrosine kinase inhibitors and immune checkpoint inhibitors are the mainstay therapy (17-19).

Conclusion

Although rare, the case presented here emphasized that VHL disease is an important multiorgan syndrome with myriad clinical manifestations. Diagnosis is often delayed as many physicians are unaware. Affected individuals need careful periodic follow-ups and therapeutic intervention as indicated. When needed, organ sparing procedures have paramount importance. Novel therapies are emerging.

Data Availability Statement

All readers can access the case data including full images, pathologic reports and images, etc except where it violates patient privacy and data confidentiality.

Authors' contribution

Conceptualization, investigation, original draft preparation and review and editing: AT
Methodology, formal analysis, investigation: AD.
Visualization: SK.
Validation, resources, original draft preparation and review and editing, supervision and project administration: SB.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This case report was conducted in accord with the World Medical Association Declaration of Helsinki. A written informed consent was obtained from the patient for publication as a case report. Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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