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Von Hippel Lindau Syndrome: A Case Report

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Abstract: *Von Hippel-Lindau syndrome (VHL) is an autosomal dominant multisystem neoplasticdisease (8). It is caused by germline mutations of the tumor suppressor gene VHL, on the short arm of chromosome 3(2). Diagnosis of VHL is incited by clinical suspicion and confirmed by radiological and molecular testing (2). The spectrum of clinical manifestations of this disease is broad and includes hemangioblastomas (retinal and central nervous system), endolymphatic sac tumors, renal cysts and tumors, pancreatic cysts and tumors, pheochromocytomas, and epididymal cystadenomas (1). The aforementionedfindings can be demonstrated with imaging modalities such as ultrasonography, computed tomography, magnetic resonance imaging, and nuclear medicine (1). Genetic testing is important for screening of asymptomatic gene carriers but imaging plays a key role in early detectionof abnormalities, consequent follow-up and long-term surveillance of lesions as the lesions in VHL disease are treatable hence may enhance the patient's length and quality of life (1). Here a case of Von hippel lindau is discussed with imaging findings.*

Key words:*von Hippel-Lindau; hemangioblastoma; pheochromocytoma, endolymphatic sac tumor; renal cyst and tumors.*

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I. Introduction

Von Hippel–Lindau (VHL) disease is a rare, familial disorder involving multiple organs, and characterized by development of numerous benign and malignant tumors. This syndrome is an autosomal dominant disorder with high penetrance and variable expressions, andoccurs due to germline mutations of the VHL tumor suppressor gene located on the distal part of the short arm of the third chromosome (3p25-26) (7).

VHL syndrome shows broad spectrum of lesions covering more than 10 organs (5) including retina, CNS, adrenal glands, liver, kidneys, pancreas etc. Symptoms caused by VHL disease depend on the organ, which was involved (8). Lesions include retinal and central nervous system (CNS) hemangioblastomas, endolymphatic sac tumors, renal cysts and tumors, pancreatic cysts and tumors, pheochromocytomas, and epididymal cystadenomas (1) but the most common causes of death in patients with VHL disease are renal cell carcinomas and neurologic complications from cerebellar hemangioblastomas (1).

The diagnostic criteria for VHL disease (6) rests on the following: *(a)* more than one CNS hemangioblastoma, *(b)* one CNS hemangioblastoma and visceral manifestations of VHL disease, and *(c)* any manifestation and a known family history of VHL disease (1).

The aforementionedfindings can be demonstrated with imaging modalities such as ultrasonography, computed tomography, magnetic resonance imaging, ophthalmoscopy and nuclear medicine (1). Genetic testing is important for screening of asymptomatic gene carriers but imaging plays a key role in early detection ofabnormalities, consequent follow-up and long-term surveillance of lesions as the lesions in VHL disease are treatable hence may enhance the patient's length and quality of life (1). It is also important in screening of individuals who carry the VHL gene and are as yet asymptomatic (1).

II. Case Report

A 36-year-old male patient presented with periodical complaints of cervical and lower back pain. Patient had similar complaints in the past (7 to 8 years back) for which he was diagnosed with spinal hemangioblastoma and was operated. Few years after the operation i.e. 3 to 4 years back he had complaints of excessive sweating, headache and backache for which he was evaluated and diagnosed with bilateral pheochromocytoma with liver metastases and recurrence of spinal hemangioblastoma. Lab finding also revealed raised 24 hour urine catecholamines. MIBG scan revealed concentrating primary tumor (pheochromocytoma) in bilateral suprarenal regions and metastasis to liver. He was then operated forbilateralpheochromocytoma and liver segmentectomy for metastasis. After the operation patient showed improvement but backache persisted.

In November 2017 patient came to our hospital in view of past history clinical impression of compressive myelopathy was made. MRI brain and spine was done which revealed heterogeneous lesions with solid cystic components and showing heterogeneous intra lesions and peripheral enhancements at L1 and L2. The size of the lesions was approximately 39*15 mm with multiple vascular flow voids seen adjacent to lesions.

Another heterogenous enhancing lesions of size 9.5*4.3 mm seen in extra medullary location at C2 level. Multiple vascular flow voids were seen adjacent to lesions. In brain small nodular enhancing lesions adjacent to left cerebellar peduncle measuring 3*1 mm and in left cerebellar hemisphere measuring 4*2 mm were s*een.*Ultrasound abdomen revealed right renal cyst and postoperative changes in liver. USG scrotum revealed small epididymal cyst.

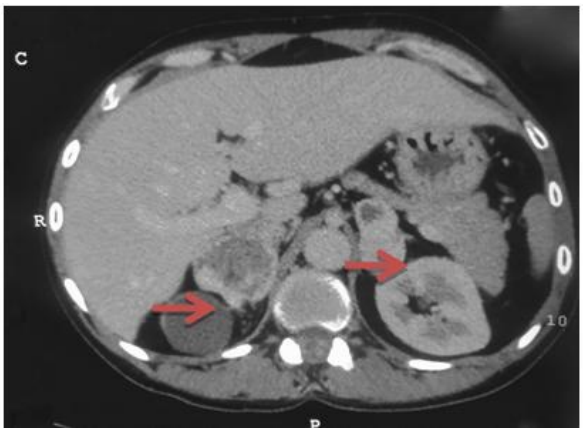
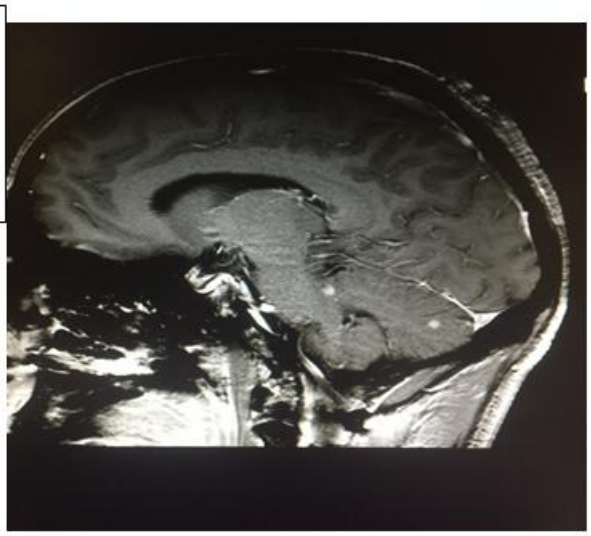


Fig. 1 Axial CECT: Pheochromocytoma - heterogeneously enhancing bilateral suprarenal mass(→).

Fig. 2 Sagittal gadolinium enhanced T1 weighted: Hemangioblastoma – multiple nodular enhancing lesions in cerebellar peduncle and in left cerebellar hemisphere.



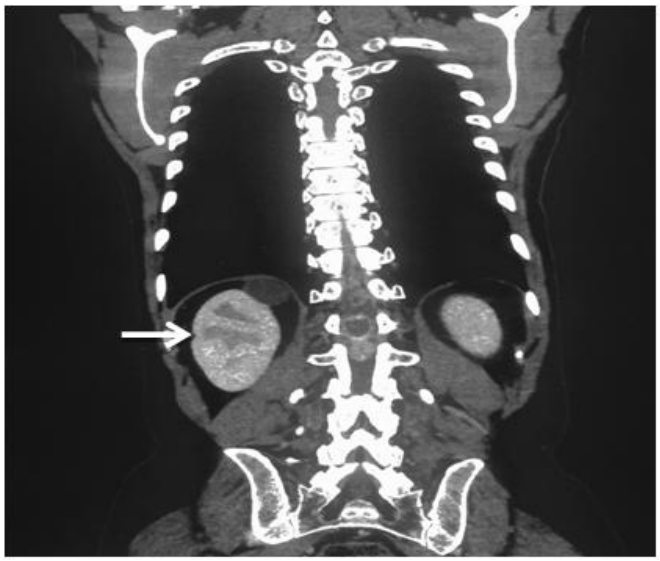


Fig 3 Coronal CECT : (a)Hemagioblastoma- Heterogeneously enhancing lesion in spinal canal. (b) Right renal exophytic cortical cyst.

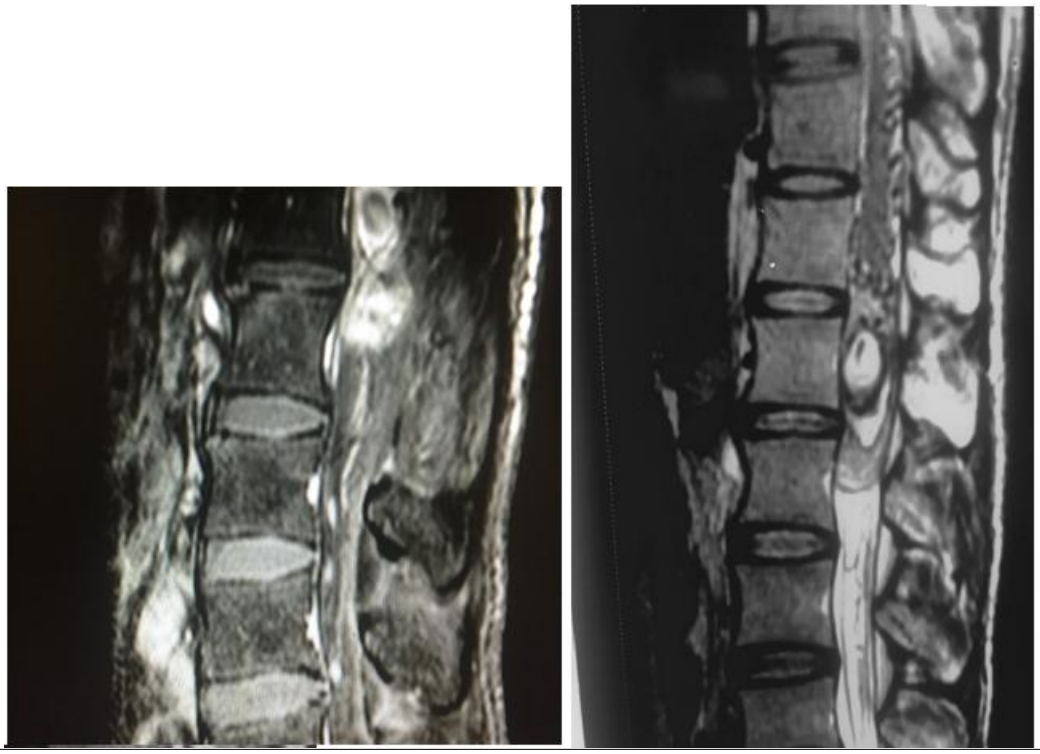


Fig 4 (a) sagittal T1Gd showing heterogeneously enhancing lesion at L1-2. (b) sagittal T2 weighted heterogeneous lesion at L1-2.

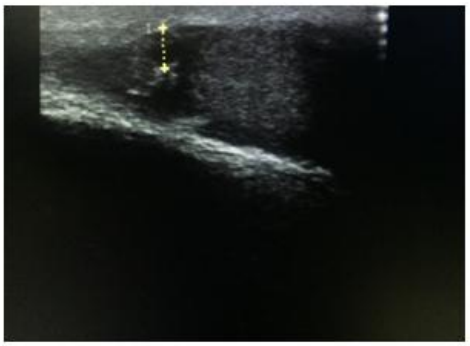


Fig.5 (a)Opthalmoscopy exam showing retinal hemangioblastoma with feeding artery. (b) USG Scrotum showing epididymal cyst

CECT abdomen revealed exophytic cortical cyst in right kidney, evidence of adrenaletomy and liver lobectomy (segment 6), heterogeneously enhancing lesion in spinal canal with cystic component likely hemangioblastoma.

In view of clinical findings and previous operative history of intra medullary spinal lesion and adrenalectomy for bilateral pheochromocytoma, diagnosis of Von Hippel Lindau was established.

Diagnosis was further substantiated by fundoscopic examination, which revealed multiple retinal angiomas in both eyes.

Genetic testing was done and was found to be positive for VHL.

III. Discussion

VHL disease is an autosomal dominant progressive disorder associated with many different tumours and cysts involving the CNS and other visceras (8).These include

S.NO	VISCERAL MANIFESTATIONS
1	CNS hemangioblastoma
2	Retinal hemangioblastoma
3	Spinal hemangioblastoma
4	Endolymphatic sac tumors
5	Renal cell carcinoma
6	Renal cell cyst
7	Pancreatic cyst
8	Pancreatic tumors
9	Pheochromocytoma
10	Hepatic hemangioma
11	Ovarian cyst
12	Paraganglioma
13	Broad ligament cystadenomas
14	Epididymal cystadenomas

The diagnostic criteria for VHL disease are:
• More than 1 haemangioblastoma in the CNS,
• 1 CNS haemangioblastoma and visceral manifestations of VHL, or
• 1 manifestation and a known family history of VHL.
Imaging is of vital importance in the identification of lesions and in their follow-up. It is also important in screening of asymptomatic individuals(8).

There have been important improvements in the management of VHL in the last decade. The Daily adjusted life years of patients with VHL disease has shown reduction (8).The removal of the tumors, cyst aspiration, stereotactic radiosurgical ablation, photocoagulation, and cryotherapy of any retinal lesions are the choices of the treatment. The conservative approach to the treatment of VHL lesions is now more widely accepted, a radio- logic follow-up with non-invasive imaging especially with MRI is important.

Lesions Associated With VHL

1. Central nervous system hemangioblastomas

General features

CNS hemangioblastomas are the most common tumors in VHL syndrome affecting 60–80% of all patients (2). The tumors are benign but are a major cause of morbidity and mortality due to mass effect on nearby CNS structures. These hemangioblastomas can be found in the cerebellum (16–69%), brainstem (5–22%), spinal cord (13–53%), cauda equina (11%), or supratentorial region (1–7%) (2).

Radiological findings

The modality of choice for detecting CNS hemangioblastomas is contrast-enhanced magnetic resonance (MR) imaging (8). Routine screening of the CNS in VHL should include, pre and post contrast T1 weighted images of the brain and spinal cord, with thin sections through the posterior fossa and spinal cord and surface coil images of the entire spinal cord. CHb (cerebellar hemangioblastoma) commonly contain cystic areas with a solid mural nodule. Small (10 mm or less) hemangioblastomas are mostly isointense on T1-weighted images and hyperintense on T2-weighted images showing homogeneous post contrast enhancement. Small hemangioblastomas are located at the surface of the spinal cord while larger ones tend to be hypointense or show mixed signal intensity on T1-weighted images and appear heterogeneous on T2- weighted images. These lesions show heterogeneous post contrast enhancement. The solid and contrast-enhancing portions give low signal on diffusion-weighted imaging (DWI) with resultant increase in the apparent diffusion coefficient (ADC). These findings indicate rich vascular spaces of the hemangioblastomas, which is not seen in the other tumours. DWI may be useful for distinguishing hemangioblastomas from other enhancing cerebellar tumours. . SHb (spinal hemangioblastomas) can be intramedullary, partially intra and extramedullary or exclusively extramedullary (6). In our patient few enhancing nodules were seen in cerebellar peduncles and heterogeneously

enhancing lesion at L1-2 of spinal cord with adjacent flow voids.

2. Retinal hemangioblastomas

General features

Retinal hemangioblastomas arise frequently in VHL patients. Complications of retinal hemangioblastomas include blindness or severe visual deficits in 5–8% of VHL patients. In our patient ophthalmoscopic exam revealed well- defined, orange-red mass associated with a prominent feeding artery and a draining vein.

3. Endolymphatic sac tumors

General features

ELSTs develop from endolymphatic epithelium within the vestibular aqueduct. They are benign tumors that do not metastasize but may be locally aggressive. Patients may present with ear fullness, disequilibrium, and hearing loss. Larger lesions (>3 cm) can result in facial paresis (6).

Radiological findings

Radiologic examination should include the use of precontrast and postcontrast computed tomography (CT) and magnetic resonance imaging (MRI) (6). The internal auditory canal is the target location. On CT, these tumors exhibit similar density as the brain parenchyma; however, there may be focal areas of low and high attenuation. Centered within the endolymphatic duct, large tumors are visualized as expanding into the temporal bones on CT (6). On precontrast T1-weighted MRI, they appear hyperintense.OnPostcontrast T1-weightednon cystic component show enhancement.

4. *Renal cell carcinoma and renal cysts*

General features

Renal manifestations of VHL include benign renal cysts and clear cell carcinoma. Renal cysts are asymptomatic; RCC is the leading cause of mortality in this group of patients (1).

Radiological findings

Serial imaging of the kidneys is useful in detecting RCC because it often remains asymptomatic for long periods of time. Abdominal CT with contrast is the gold standard for diagnosis of renal lesions of VHL (6). CT can differentiate simple cysts from complex cysts (2). In our patient CT abdomen revealed right renal cortical cyst.

5. *Pheochromocytomas*

General features

Pheochromocytomas occur in up to 20% of VHL patients. These tumors produce catecholamines, such as excessive norepinephrine, causing hypertension, tachycardia, palpitations, headaches, sweating, pallor, and nausea (6).

Radiological findings

Postcontrast abdominal CT imaging is sensitive in detecting adrenal and extra-adrenal pheochromocytomas. Contrast-enhanced MRI of the abdomen is between 90% and 100% sensitive in the detection of these tumors and is the preferred modality compared to CT. The diagnosis of pheochromocytoma is based on Plasma free metanephrines is the most sensitive method (97% sensitivity) for detecting pheochromocytoma Identification of extra- adrenal tumors may benefit from meta-iodobenzylguanidine (MIBG) scintigraphy (6).

6. *Pancreatic neuroendocrine tumors and cysts*

General features

About 35–70% of patients with VHL present with pancreatic findings. There are usually multiple cysts that present without symptoms. Serous cystadenomas and neuroendocrine tumors are other manifestations of pancreatic lesions in VHL syndrome (5).

Radiological findings

Pancreatic cysts are often clinically silent; therefore, routine imaging is important for diagnosis in VHL patients (6). On postcontrast CT imaging, a PNET can be seen as an enhancing mass (5, 6). Once the presence of the tumor is established, MRI can help confirm the diagnosis. Endoscopic ultrasound and somatostatin receptor scintigraphy are additional options for detecting these lesions (6)

7. *Epididymal cystadenomas*

General features

Males with VHL can develop cystadenomas in the epididymis. They may arise unilaterally or bilaterally in 25–60% of VHL males. They are benign in nature.

Radiological findings

These lesions can be difficult to palpate due to small size; therefore, ultrasonography is the modality of choice (1). In our patient ultrasound scrotum revealed right epididymal cyst.

IV. Conclusion

Genetic testing is important for screening of asymptomatic gene carriers butradio imaging plays a key role in early detection of abnormalities, long term follow-up and surveillance of lesions as the lesions in VHL disease are treatable hence; may enhance the patient's length and quality of life.