Review Article

Cross-Sectional Imaging Spectrum of von Hippel-Lindau Disease

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Abstract

von Hippel-Lindau (VHL) disease is an autosomal dominant disorder that is associated with germline mutations of VHL tumor suppressor gene, which is located at short arm of chromosome 3. This condition predisposes to the development of various benign and malignant tumors involving multiple organs; the common neoplasms include central nervous system hemangioblastomas (mostly cerebellar and spinal cord), retinal angiomas, endolymphatic sac tumors, renal cysts and tumors, pheochromocytomas, epididymal cystadenomas, and pancreatic cysts and tumors. Among them, hemangioblastomas and renal cell carcinoma are the most common cause of mortality. Cross-sectional imaging techniques such as ultrasound, computed tomography, and magnetic resonance imaging play a pivotal role in the initial diagnosis, assessment of treatment response, follow-up, and long-term surveillance. Additionally, imaging studies are important in screening of asymptomatic at risk individuals. Many of the lesions associated with VHL disease demonstrate characteristic imaging findings that help in timely diagnosis and guide genetic testing. Knowledge regarding cross-sectional imaging features of the wide spectrum of benign and malignant neoplasms in VHL patients should afford appropriate patient management.

INTRODUCTION

von Hippel-Lindau (VHL) disease is a rare, autosomal dominant disorder, characterized by development of both benign and malignant neoplasms affecting multiple organs. VHL disease has an incidence of one in 36,000 live births and demonstrates over 90% penetrance by the age of 65 years [1]. This condition results from the inactivation of VHL gene, which is located at the short arm of chromosome 3. VHL gene is a tumor suppressor gene, so phenotypic manifestations are seen when both copies of genes are lost either by mutations or by loss of heterozygosity [2,3]. The VHL protein normally plays an important role in the oxygen-sensing pathway. During hypoxia, series of events due to the presence of an inactive VHL gene results in upregulation of multiple growth factors including vascular endothelial growth factors, which result in cell proliferation and unregulated cell growth which result in development of tumors in multiple

organs [4]. The commonly involved organs are the pancreas (35-77%), central nervous system (44-72%), kidneys (25-60%), eyes (25-60%), adrenal gland (10-20%), epididymis (25-60%), and inner ear (10-25%) (Table 1) [1]. Among all, the most common tumors include retinal angiomas, cerebellar and spinal cord hemangioblastomas, endolymphatic sac tumors, renal cysts, renal cell carcinomas, pheochromocytomas, epididymal cysts and cystadenomas, simple cysts, serous cystadenomas, and neuroendocrine tumors of the pancreas [5]. Patients with VHL can be divided into two types based on the likelihood of pheochromocytoma within the family: Type 1 disease with low risk of pheochromocytoma and type 2 disease with high risk of pheochromocytoma [6]. Type 1 disease is more common than type 2 and develops due to truncating mutations of VHL gene. Type 2 disease typically develops secondary to VHL missense mutations and can be further subdivided into type 2A and type 2B based on the absence or presence of RCC respectively. VHL type 2C disease is rare and characterized by the development of pheochromocytomas only [6]. The diagnostic criteria for VHL disease include: (a) More than one central nervous system (CNS) hemangioblastomas, (b) One CNS hemangioblastoma and one visceral manifestation, and (c) Any manifestation along with a known family history [6].

In this article, we will present cross-sectional imaging findings of the broad spectrum of benign and malignant neoplasms in VHL patients and emphasize the role of radiologists in the overall patient management.

ROLE OF CROSS-SECTIONAL IMAGING TECHNIQUES

Different imaging modalities such as ultrasonography (US), multidetector - row computed tomography (MDCT), and magnetic resonance imaging (MRI) help to identify and characterize the different manifestations associated with VHL disease. It is very important to screen individuals who carry the VHL gene and are as yet asymptomatic, as the lesions in VHL disease are treatable if identified early. US is being used in the screening and surveillance of renal cysts, renal cell carcinoma, and epididymal lesions. Additionally, pheochromocytomas may be incidentally identified on US while examining the kidneys. MDCT is the modality of

Table 1: Common and uncommon manifestations of von Hippel Lindau Disease.

Body Systems involved	Lesions encountered
Central Nervous System	Cerebellar hemangioblastomas Spinal cord hemangioblastomas Retinal hemangioblastoma Endolymphatic sac tumors
Genitourinary System	Renal simple and complex cysts Renal cell carcinoma Pheochromocytoma Papillary cystadenomas of epididymis Cystadenomas of uterine broad ligament
Gastrointestinal System	Pancreatic cysts Serous cystadenoma of the pancreas Neuroendocrine tumor of the pancreas
Other Organs	Hepatic cysts and hemangiomas Splenic hemangiomas Urinary hemangioblastomas Pulmonary hemangioblastomas

choice in the identification and diagnosis of renal, adrenal, and pancreatic manifestations of VHL disease. Intravenous contrast is routinely used that helps to detect enhancing septations and solid components within the renal cysts, which suggest the possibility of malignancy. In addition, high resolution CT of the temporal bone is extremely helpful in diagnosis of endolymphatic sac tumors. MRI is mainstay of imaging technique for CNS lesions in VHL patients. Both unenhanced and gadolinium-enhanced images of the spine and brain are to be obtained to detect retinal, spinal, cerebral, and cerebellar lesions. MRI is also useful in the evaluation of renal, pancreatic, and adrenal lesions.

CENTRAL NERVOUS SYSTEM LESIONS

Hemangioblastomas of the brain and spine

Hemangioblastomas involving spine and brain are one of the most common manifestations of VHL disease, affecting 60-80 % of all patients; up to 90 % of these go on to develop multiple tumors [7]. VHL patients may develop cerebellar hemangioblastomas in 44-72% and spinal cord hemangioblastomas in 13-50% cases; these tumors usually develop at a younger age and have worse prognosis [1]. Clinical features depend on the location of tumor; while headache and gait ataxia are common presenting symptoms in cerebellar lesions, hypesthesia and weakness are seen in spinal lesions. Tumors develop from multipotent embryonic cell called as 'hemangioblast', which is capable of blood and endothelial cell differentiation [8,9]. At histology, tumors show large polygonal stromal cells enmeshed in a well-developed, fine capillary network.

On CT/MRI, hemangioblastomas can appear as purely solid masses, completely cystic lesions, cystic lesions with mural nodule, and solid mass with internal cysts [10]. On unenhanced CT, cystic hemangioblastomas appear as well defined, thin-walled hypodense lesions with a isodense nodule that enhances intensely following contrast administration [10]. Solid hemangioblastomas appear as either an isodense or hyperdense mass on unenhanced CT and show homogenous contrast enhancement [10]. On MRI, the tumors appear as low to medium signal intense lesions on T1- weighted images and hyperintense lesions on T2- weighted images; on gadolinium administration, marked enhancement of the solid portions is identified due to rich capillary network (Figure 1) [11]. Serpentine signal voids in the periphery of the solid components and 'cyst with mural nodule' may also be detected on MRI. Although spinal cord hemangioblastomas demonstrate similar MRI and CT appearance, smaller lesions may be isointense to spinal cord and require contrast-enhanced T1- weighted images for adequate visualization (Figure 2) [12]. There are no characteristic imaging findings specific to hemangioblastomas in VHL patients and multiple lesions are almost diagnostic of VHL syndrome.

Complete surgical resection is the treatment of choice; preoperative arterial embolization can help to decrease blood loss during surgery [13]. Given the presence of multiple tumors and variable growth pattern, treatment is typically deferred until the development of symptoms. Smaller tumors (less than 3 cm in size) without mass effect may be treated with stereotactic radiotherapy (gamma knife therapy) [7,13]. VHL-associated hemangioblastomas demonstrate saltatory growth pattern with

periods of rapid growth, followed by periods of quiescence. Tumor size, growth, and the presence of peritumoral cysts are associated with high risk of symptom development [14]. In asymptomatic gene carriers, annual screening MRI of the brain and spine is to be performed starting at age 11 years [7].

Retinal angiomas

Also known as hemangioblastomas, retinal angiomas are the first and most frequent manifestations of VHL disease and can develop in up to 60 % patients; they are bilateral and multifocal with a mean age of presentation around 25 years, although 5 % cases may present before the age of 10 years [7,8]. Tumors can develop in both at the macula and in periphery of the retina. Smaller tumors are asymptomatic and visual symptoms including partial or complete vision loss may occur as tumors grow and cause retinal detachment. Retinal angiomas are typically diagnosed by fundoscopic examination and are occult on imaging studies such as MRI unless hemorrhage and sub-retinal exudate is present [15]. Radiological diagnosis is possible only in late stages of the disease, thus ophthalmoscopic diagnosis, which consists of direct and indirect ophthalmoscopy, with fluorescein angiography is a better diagnostic tool [8].

On MRI, retinal angiomas appear hyperintense on non-enhanced T1-weighted sequences and isointense on T2- weighted images and enhance intensely after contrast administration (Figure 3) [5,11]. Cryotherapy and laser photocoagulation are the mainstay of treatment for retinal angiomas; vitrectomy and enucleation in select patients [7]. Early diagnosis and treatment can prevent late, serious sequelae associated with retinal
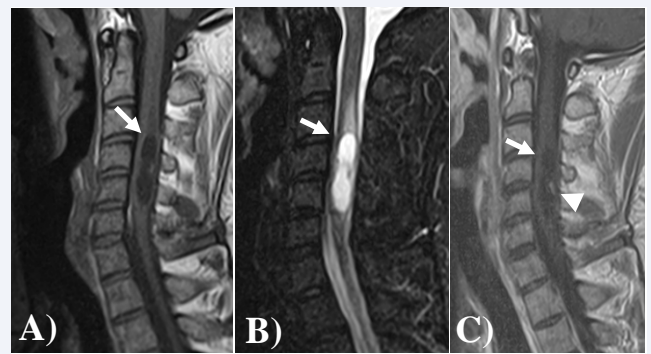

Figure 1 Cerebellar hemangioblastoma in a 42-year-old man with known von Hippel-Lindau disease. Axial T1-weighted (A), T2-weighted (B) and T1-weighted gadolinium-enhanced images (C) depict a well-circumscribed cystic lesion in the right cerebellar hemisphere (arrow) with an intensely enhancing solid component in the periphery (arrowhead) giving a 'cyst with mural nodule' appearance consistent with hemangioblastoma.

Figure 2 Spinal hemangioblastoma in an asymptomatic 33-year-old man with known von Hippel-Lindau disease identified on screening MRI. Sagittal T1-weighted (A), T2-weighted (B) and T1-weighted gadolinium - enhanced MR images demonstrate a focal lesion in the spinal cord which is hypointense on T1- and hyperintense on T2-weighted images (arrows) with an enhancing mural nodule on post contrast images (arrowhead) consistent with hemangioblastoma.

angiomas; yearly screening ophthalmoscopy starting at infancy is recommended in all VHL patients [8].

Endolymphatic sac tumors

Endolymphatic sac tumors (ELSTs) are slow growing, papillary adenomatoid tumors that are found in 10-15 % VHL patients and 30 % of those patients may develop bilateral tumors [16]. Multifocal, VHL-deficient epithelial proliferations throughout the endolymphatic duct and sac could be the potential precursor for the development of ELSTs [7]. Histologically, tumors show papillary architecture of cuboidal cells and cystic spaces filled with proteinaceous material. Although benign, ELSTs can be locally destructive; the clinical presentation is usually late with hearing loss and tinnitus being the most common symptoms.

CT and MRI are the commonly used diagnostic tools to identify ELSTs. High resolution CT of the temporal bone demonstrates locally destructive, soft-tissue density mass involving the posterior petrous bone, centered at endolymphatic sac giving a geographic and moth-eaten appearance, with occasional intra-tumoral calcifications (Figure 4) [17]. In addition, CT may also demonstrate a space-occupying lesion appearing isodense to the brain parenchyma and small bony erosions adjacent to the vestibular aqueduct [7]. On MRI, ELSTs show heterogeneous signal intensity on T1- and T2- weighted images secondary to internal hemorrhage, cysts, calcifications, and incorporated temporal bone; they enhance either homogenously or heterogeneously depending on the intratumoral contents (Figure 4) [5,17]. Intralabyrinthine hemorrhage can also be identified separately from tumor site and appears as high signal intensity focus on T1- weighted images [7]. Despite the benign histological nature of these tumors, surgical excision remains the mainstay of current therapy; postoperative radiotherapy is used as adjuvant therapy in most cases. Preoperative level of hearing is preserved in most patients. In addition, radiotherapy may also be suitable as a salvage treatment in recurrent endolymphatic sac tumors [13]. Early detection based on clinical features, CT/MRI findings, and audiometric characteristics and timely intervention
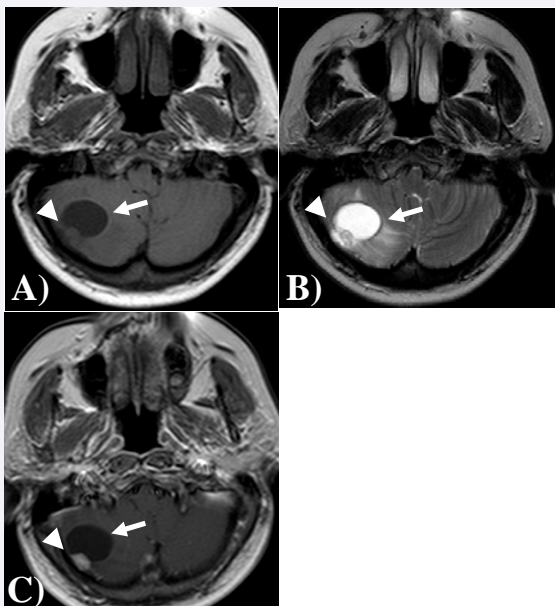
dictates the long-term prognosis. For screening purposes, CT and MRI examinations and audiological functions are indicated at the onset of symptoms [8]. However, some institutions follow an annual audiometry as a first-line endolymphatic sac tumor screening tool.

GENITOURINARY SYSTEM

Renal lesions

Approximately 30%-65% of VHL patients can develop renal manifestations that include simple/complex cysts and clear cell renal cell carcinoma. Multiple renal cysts are the most common renal lesions and may be seen in 60 % of patients and are bilateral in as many as 75% of patients [18]. They may vary from simple cysts to complex cysts, with cystic and solid components. Renal cell carcinoma (RCC) occurs in 30% - 45% of VHL patients with clear cell histologic subtype being most common [19]. Most of the tumors are bilateral and the age of onset of RCC in VHL patients is much earlier (mean age, 30–36 years) than in sporadic cases [20]. RCC is the most dreaded manifestation of VHL disease as it is responsible for about 18-33 % of VHL-associated mortality [21]. Although some patients are asymptomatic, hematuria and flank pain are the most common clinical features. Histologically, the epithelium lining the cyst walls consists of cells with clear cytoplasm [21].

US, CT and MRI play a pivotal role in the diagnosis, characterization, and screening of renal lesions in VHL disease. US helps in differentiating cystic from solid masses and has the advantage of avoiding ionizing radiation, given the fact that these patients require frequent surveillance scans. CT and MRI are very sensitive for cysts or masses smaller than 2 cm. At CT/MRI, bilateral kidneys demonstrate multiple simple and complex cysts, cystic masses with enhancing, solid components, and solid masses of varying sizes with heterogeneous contrast enhancement (Figure 5) [5,22]. MRI eliminates ionizing radiation and is preferred in young patients and on those with renal failure. Complex cysts and solid masses enhance on postcontrast T1-weighted images and sometimes may show a hypointense pseudocapsule on T2-weighted images [23,24]. The preferred treatment in renal cell carcinoma associated with VHL disease is nephron-sparing procedure (either partial nephrectomy or image-guided ablation). Due to the high probability of appearance of new renal neoplastic lesions; lesions greater than 3 cm undergo treatment
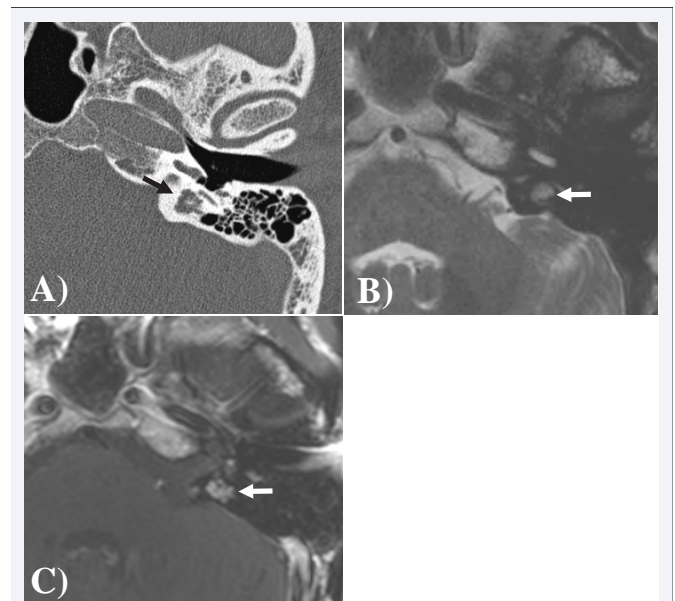

Figure 3 Retinal angioma in a 28-year-old woman with known von Hippel-Lindau-disease. Axial T2-weighted (A) and T1-weighted gadolinium-enhanced MR images (B) demonstrate an intraocular, enhancing, solid mass within the left globe (arrow) consistent with retinal angioma. In addition, associated retinal detachment is also identified (arrowhead).

Figure 4 Endolymphatic sac tumor in a 33-year-old man with known von Hippel-Lindau disease, complaining of hearing loss and tinnitus in the left ear. (A). Axial high resolution CT image of left temporal bone depicts a hypoattenuating mass with geographic bony destruction in the region of petrous temporal bone (arrow). (B and C). Axial T2-weighted (B) and gadolinium-enhanced T1- weighted images (C) show a T2 hyperintense, enhancing lesion (arrows) consistent with endolymphatic sac tumor.

whereas smaller lesions are followed-up at close intervals [8,18]. The natural history of cysts is variable; some may involve leaving small scars while in others the solid component may enlarge. Complex cysts are precursors to renal cell carcinoma and require close follow-up [18]. Screening protocol for renal cysts/masses in VHL includes annual abdominal US examination from the age of 10 years followed-up with CT or MRI studies depending on the US findings or direct annual CT or MRI studies bypassing US [1,5].

Adrenal lesions

The prevalence of pheochromocytomas and extra-adrenal paragangliomas in VHL patients is about 10% - 20% and could be the only manifestation in type 2C patients. Tumors are often bilateral, multiple and may manifest at a younger age with mean age being 30 years, and have a very low risk of malignancy [24,25]. Common presenting symptoms include intermittent hypertension, headaches, sweating, palpitations, and flushing; however, many lesions are asymptomatic with normal laboratory values [1].

Both imaging features and laboratory values play an important role in the diagnosis of pheochromocytomas. While CT and MRI provide anatomic details, iodine - 131 metaiodobenzylguanidine (I131 - MIBG) scan gives functional assessment of pheochromocytomas. Elevation of urine and/ or blood catecholamine levels suggest active tumor. On CT, pheochromocytomas typically appear as solid or complex cystic adrenal masses with scattered areas of necrosis and hemorrhage, with possible calcifications [23]. On MRI, tumors are usually isointense or hypointense on T1-weighted images, and hyperintense on T2- weighted images with marked enhancement
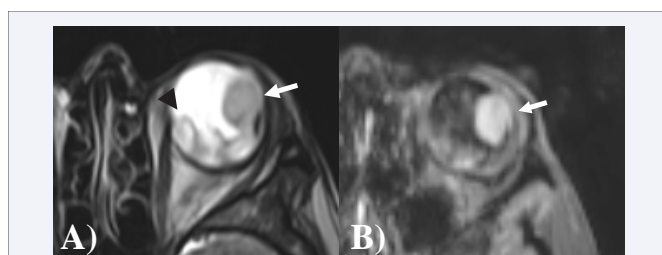
Figure 5 Multiple renal cysts and renal cell carcinoma in a 33-year-old man, who came to emergency room with hematuria. There was no family history of von Hippel-Lindau disease. Coronal T2- weighted (A) and contrast-enhanced T1- weighted MR images show multiple simple and complex cysts involving bilateral kidneys (arrows) and a large heterogenously enhancing renal mass in the right kidney (arrowhead) consistent with renal cell carcinoma. Additionally, multiple simple pancreatic cysts are also identified (not shown here). Based on these findings, the possibility of VHL disease was suspected, which was proved subsequently by genetic testing.

during the arterial phase of dynamic study after contrast administration (Figure 6) [26]. I-131 MIBG scan shows high uptake in 75–95% of cases and is used to localize and identify pheochromocytoma and paraganglioma, especially when the presence of more than one tumor is suspected. The treatment of choice is complete surgical resection with pre-operative pharmacological control of hypertension; tumor size greater than 3.5 cm, increased MIBG uptake, and abnormal function are indications for surgery [1]. The screening protocol includes monitoring of annual plasma or 24-hour urinary catecholamine levels from the age of 2 years along with annual blood pressure measurement [1]. No imaging is deemed necessary until catecholamine levels are increased on follow up.

Epididymal lesions

Simple cysts and cystadenomas of the epididymis are the scrotal pathologies in VHL patients. Cystadenomas are rare, epithelial tumors that originate from the Müllerian residual connective tissue and occur in approximately 10% - 60% of men with VHL disease and very rare in general population; bilateral and multiple tumors are virtually pathognomic of VHL syndrome [8]. These lesions can be both seen in the epididymis and spermatic cord and epididymal head is the most common location. Although most of the lesions are asymptomatic, 'hard' palpable mass in the scrotum, and infertility due to obstructive azoospermia are presenting symptoms if any. At microscopy, cystadenomas show prominent papillae lined by glycogen-rich clear cells, similar to that of serous cystadenoma of the ovary [27].

At US, cystadenomas typically appear as hypoechoic, solid masses with occasional scattered areas of calcifications and small cystic components (Figure 7) [5, 28]. Sonographic criteria include predominantly solid tumor greater than 1.4 cm, occurrence in a man with VHL disease, and slow growth [28]. Other scrotal findings include epididymal cysts, ectasia of the rete testis, and testicular atrophy. Treatment is usually not necessary as these lesions have no malignant potential. Surgical removal is sought if there are uncomfortable local symptoms or infertility.

GASTROINTESTINAL SYSTEM

Pancreatic lesions

The common pancreatic manifestations of VHL disease include simple pancreatic cysts (50-90%), serous cystadenomas (SCAs) (12%), and neuroendocrine tumors (NETs) (5-17%); combined lesions may occur, but the association of cystic lesions and neuroendocrine tumors is rare [23]. The reported prevalence of pancreatic involvement in VHL disease varies from 0% in some family groups to 77% in others [23]. In addition, pancreatic lesions may be the only abdominal manifestation and may precede any other manifestation by several years [29]. Thus, recognition permits earlier diagnosis of VHL disease, which is in turn helpful for treatment and genetic counseling of kindred.

Multiple pancreatic cysts are the most common abdominal manifestation in VHL patients. Given the rarity of unilocular pancreatic cystic lesions in the general population, the presence of a single cyst in a patient undergoing VHL disease screening because of a family history suggests high probability of the disease [29,30]. At CT /MRI, multiple non-communicating cysts replacing the entire pancreatic parenchyma is the typical appearance of VHL; these cysts do not enhance after contrast material administration (Figure 8) [22]. In addition, MRI helps in the assessment of relation to main pancreatic duct and
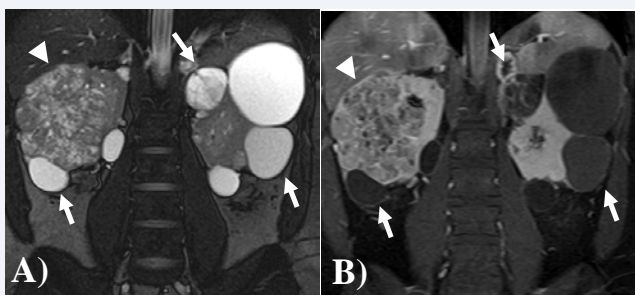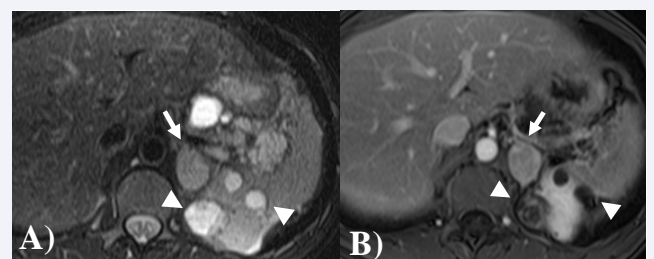

Figure 6 Pheochromocytoma in a 30-year-old woman with known von Hippel Lindau Disease. Axial T2 weighted (A) and contrast enhanced T1 weighted (B) images show a well- circumscribed T2- hyperintense focal lesion in the left adrenal gland, which enhances after contrast adminstration (arrow). In addition, also note mutiple cystic masses in the left kidney (arrowheads).

Figure 7 Epididymal cystadenoma in a 32-year-old man with known von Hippel Lindau Disease. US image of the left scrotum shows a well defined hypoechoic lesion (arrow) in the epididymis consistent with epididymal cystadenoma.

differentiating from other cystic lesions such as side-duct type of intrapancreatic mucinous neoplasm (IPMN).

Serous cystadenomas (SCAs) are well-defined, multiloculated lesions with small individual cysts separated by fibrous septae. In the general population, they are more common in women older than 60 years, but are often found incidentally in VHL patients as young as 25 years [31]. Almost all patients are asymptomatic; however, rare cases with symptoms such as jaundice secondary to mass effect have been reported [31]. On US, SCAs show a variety of findings, such as echogenic masses with or without small cystic portions, multilocular cysts, or mixed hyper- and hypoechoic masses. On CT, SCAs appear as microcystic lesions, with a cluster of numerous small, well-defined cysts with or without central calcifications. Enhancement maybe seen in the periphery of these cysts on contrast administration (Figure 9) [29]. On MRI, fibrous components within the tumor are typically hypointense on T2-weighted MR images which may show enhancement on gadolinium enhanced images. SCAs are difficult to differentiate from simple cysts at times, as they have high signal intensity on T2-weighted images, however, the visualization of enhancing septae and the presence of fibrous central components, which are hypointense on T2-weighted images showing enhancement on gadolinium administration helps in accurate diagnosis [22]. SCAs do not require surgical excision, due to their benign nature, unless they are symptomatic.

In VHL disease patients, most of the neuroendocrine tumors (NETs) are usually multiple, nonfunctional and identified at screening and may be larger at detection [5]. However, functional tumors tend to present earlier, with clinical signs and symptoms related to their cell type – insulinoma, glucagonoma, gastrinoma, and VIPoma. NETs are hypervascular masses on CT, and show homogenous enhancement on the arterial phase; some may show heterogeneous enhancement, when larger in size due to presence of necrosis and calcifications [29]. MRI is more specific and sensitive in identifying NETs; they appear hypointense on T1-weighted and hyperintense on T2-weighted images, but their
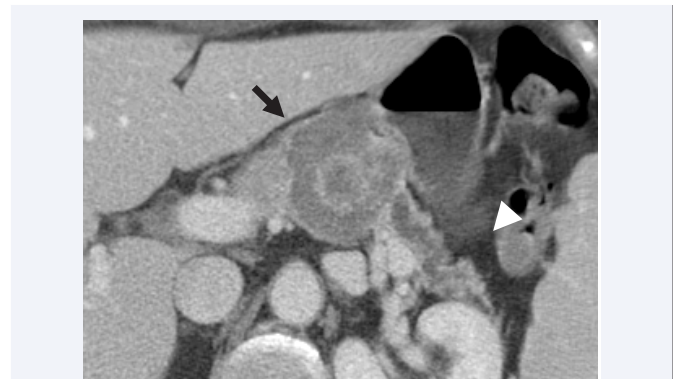

Figure 9 Serous cystadenoma of the pancreas in a 64-year-old woman with known von Hippel-Lindau disease, complaining of recurrent abdominal pain. Axial contrast-enhanced CT image demonstrates a multicystic, peripherally enhancing focal lesion (arrow) in the pancreatic body with associated main pancreatic ductal dilatation (arrowhead). This was proven to be serous cystadenoma on surgical resection.
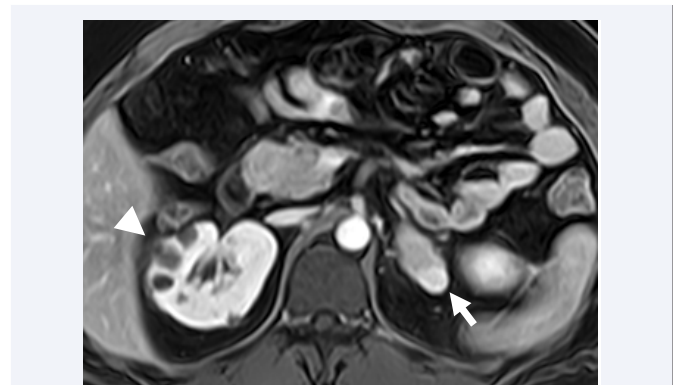

Figure 10 Neuroendocrine tumor of the pancreas in a 32-year-old man with known von Hippel - Lindau disease. Axial contrast-enhanced T1- weighted MR image depicts an intensely enhancing focal lesion in the tail of pancreas consistent with neuroendocrine tumor (arrow). Additionally, multiple cysts are seen in the right kidney (arrowhead).

signal intensity is not as high as that of cysts. Fat- suppressed, contrast-enhanced dynamic MR images are superior to any other available imaging techniques for identification of NETs (Figure 10). Malignant or metastatic potential in these lesions is as low as <10% (24). Blansfield et al proposed three criteria to predict metastatic disease of pancreatic NET in patients with VHL disease: 1) tumor size greater than or equal to 3 cm; 2) presence of a mutation in exon 3; and 3) tumor doubling time less than 500 days [32]. If the patient has none of these criteria, they suggest that the likelihood of the patient's lesion resulting in metastatic disease is very low and the patient can be followed with clinical and radiologic surveillance using CT or MRI examination every 2-3 years. Treatment includes surgical resection with distal pancreatectomy or even Whipple's procedure depending on location and size of tumor [23]. For identification of pancreatic lesions, annual US examination starting at the age of 8 years and yearly CT from the age of 18 years or earlier if clinically indicated are commonly performed. Contrast-enhanced MRI of the pancreas may be considered depending on US/CT findings and clinical manifestations [8].

Figure 8 Pancreatic simple cysts in a 40-year-old woman with von Hippel-Lindau disease. Corornal T2- weighted MR image shows mutiple cysts (arrows) almost replacing the entire pancreatic parenchyma. Also seen is a simple left renal cyst (arrowhead).

⊘SciMedCentral

Miscellaneous and rare lesions

Various other pathologic conditions arising in different organs of patients with VHL disease have been described, including pancreatic hemangiomas and hemangioblastomas, pulmonary hemangioblastomas, hepatic cysts and cavernous hemangiomas, splenic hemangiomas, bladder hemangioblastomas, cystadenomas of uterine broad ligament [33,34]. However, substantial evidence stating their definite association with VHL disease is yet to be confirmed.

CONCLUSION

Improved understanding of the pathophysiology and cross-sectional imaging appearances of the wide spectrum of lesions associated with VHL disease is priceless in reducing the morbidity and mortality and improving quality of life of affected patients. Imaging studies play a critical role in the early identification of lesions associated with VHL disease so that timely genetic testing can be performed. This helps not only the patients but also asymptomatic family members. A multidisciplinary approach including screening, timely medical, surgical, and radiological interventions, and long-term surveillance will help in the optimal management of VHL patients as well as asymptomatic gene carriers.

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Cite this article

Katabathina VS, Vinu-Nair S (2014) Cross-Sectional Imaging Spectrum of von Hippel-Lindau Disease. J Transl Med Epidemiol 2(1): 1021.