von Hippel-Lindau disease: much more than cysts

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Learning objectives

- To review the most common abdominal manifestations/lesions of von-Hippel-Lindau (VHL) disease;
- To recognize the imaging specificities of the lesions when they occur in patients suffering from this disease;
- To increase awareness for the need to conduct screening programs in these patients because the lesions are treatable.
Background

Grouped as a hereditary phakomatosis, von Hippel-Lindau (VHL) disease is a rare inherited, autosomal dominant syndrome with high penetrance (80-100%) but variable expression that manifests as a multisystem disorder. The prevalence of the VHL gene abnormality (inactivation of a tumor suppression gene located in chromosome 3p25.5) stands between 1 in 31,000 and 1 in 53,000 individuals. Sex distributions are equal. The mean age at initial presentation is 26 years and the median life expectancy is 49 years.

Genetic abnormalities are believed to induce the development of a wide range of benign and malignant tumors affecting different organs. Abdominal manifestations of this disease are protean and tend to be asymptomatic at the onset, being frequently diagnosed later than other manifestations. The most common abdominal lesions in decreasing order of frequency are: pancreatic cysts, renal cysts, renal cell carcinomas (RCC), pheochromocytomas and neuroendocrine tumors (NET) of the pancreas.

Pancreatic cysts are extremely rare in the general population but constitute the most common lesion in VHL patients (50-91%). These lesions are benign and generally asymptomatic or associated with mild symptoms (related to mass effect). They may precede other manifestations by some years facilitating earlier diagnosis of VHL disease, when detected in screening.

Serous cystadenomas are other cystic pancreatic lesions that occur associated with VHL disease (12% of patients).

Renal cysts tend to be bilateral and multiple. They occur in 50-75% of patients with VHL disease. Cysts can be simple or complex (with malignant potential), the latter being a precursor of RCC and requiring follow-up or surgery.

Renal cell carcinoma is the abdominal lesion responsible for the highest mortality rate and occurs in 24-45% of patients with VHL disease. Tumors usually appear at a younger age (mean, 30-36 years) than the sporadic forms of RCC.

Pheochromocytomas develop in less than 30% of patients with VHL disease. These lesions develop at a younger age, are often bilateral (50-80%) and usually benign. 15-18% are extraadrenal (paragangliomas).

Neuroendocrine tumors of the pancreas occur in 5-17% of patients with VHL disease. Most tumors are slow growing, nonfunctional and asymptomatic. NETs are often multiple and have no particular pancreatic location. The frequency of malignancy and metastases
in these tumors is lower than in the general population (only 10%), thus they may be observed rather than immediately removed.

Molecular genetic testing allows confirmation of the diagnosis in most patients with VHL disease. These tests permit identification of mutation carriers among asymptomatic family members. The high-risk gene carriers must undergo regular surveillance both clinically and radiologically. Screening is important because the lesions in VHL disease are treatable. Early detection enables more conservative therapy to be performed and may enhance the patient's length and quality of life. Those family members who did not inherit the mutation do not require regular monitoring. Genetic counseling is essential both before and after molecular testing.
Findings and procedure details

Although genetic testing is available, imaging plays a key role in the identification of the most common abdominal manifestations of VHL disease and their subsequent follow-up, in the screening of asymptomatic gene carriers, and in their long-term surveillance.

The various lesions can be demonstrated with different imaging techniques such as ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI).

Pancreatic cysts are commonly detected with US or CT (the latter improving the detection of small lesions). The walls of simple cysts enhance poorly or not at all. Serous cystadenomas are usually well-circumscribed clusters of small cysts (<2 cm), which are radially aligned and sometimes show central calcification. Enhancement occurs at the periphery of these microcysts. US can show a variety of findings, such as echogenic masses with or without cystic portions or multilocular cysts. On MRI, serous cystadenomas have high signal intensity on T2-weighted images. It may be impossible to distinguish a cluster of benign cysts from serous cystadenomas. Enhancing septa favor the diagnosis of serous cystadenoma. The differential diagnosis is not important because these lesions require no treatment.

Renal cysts are usually detected with US, given the purpose to reduce the amount of radiation exposure. CT is more sensitive than US for detection of small (<2 cm) lesions; cysts demonstrate little or no wall enhancement, and solid components enhance briskly (50-200 HU) after contrast administration. MRI is useful in young patients and those with renal failure who still require screening. Simple cysts are hypointense on T1-weighted images and hyperintense on T2-weighted images, with no enhancement after administration of gadolinium. Complex or solid lesions enhance on post-contrast T1-weighted images.

Renal cell carcinomas associated with VHL disease often are multicentric and bilateral solid hypervascular masses or complex cystic masses with mural nodules and thick septa. CT is more reliable than US for the detection of renal cancer. MRI is an alternative to CT for patients with impaired renal function and to reduce radiation exposure.

Pheochromocytomas typical appear at CT as solid or complex cystic highly enhancing masses that may have areas of necrosis, hemorrhage, and sometimes calcifications. MRI is superior to CT in evaluating ectopic sites. At MRI, the majority of lesions has low or intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images and show marked gadolinium enhancement.
Neuroendocrine tumors of the pancreas appear at US as round or oval nodules, hypoechoic relative to pancreatic parenchyma. At unenhanced CT, they are hypo or isoattenuating relative to the normal pancreatic parenchyma. At MRI, they are hypointense on T1-weighted images and hyperintense on T2-weighted images, but not as bright as cysts. Intense enhancement in the arterial phase is characteristic. As the tumor enlarges, calcification, necrosis, and cystic degeneration may be seen.
**Fig. 1:** 21 year-old woman with VHL disease. (A) Coronal and (B) axial T2-weighted image show multiple pancreatic cysts virtually replacing the pancreatic parenchyma (white arrows). (C) Axial contrast-enhanced CT image in the late arterial phase shows the same lesions as multiple hypodense non-enhancing nodules (white arrows). Poor wall enhancement is visible.

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Fig. 2: 33 year-old man with VHL disease. Axial contrast-enhanced CT images in the portal phase. (A) A serous cystadenoma is visible in the pancreatic body (white arrow). Various microcysts are barely discernible. (B) The same lesion is shown (white arrow) along with other smaller pancreatic cysts (blue arrow).

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Fig. 3: 31 year-old man with VHL disease. Coronal contrast-enhanced CT image in the late arterial phase shows a large renal cell carcinoma in the upper pole of the right kidney (white arrows) as a hyperenhancing mass with central necrosis. A simple cyst is identifiable in the lower pole of the left kidney (blue arrow).

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**Fig. 4:** 42 year-old man with VHL disease. Axial T2-weighted image shows a left adrenal pheochromocytoma (white arrow) as a complex cystic mass, with a small hemorrhagic component (blue arrow).

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Fig. 5: 29 year-old man with VHL disease. (A) Axial T2-weighted image shows bilateral pheochromocytomas (white arrows) as predominantly solid masses with small cystic (high-signal) components (B) Axial T1-weighted image in the portal phase after gadolinium administration shows the same lesions demonstrating homogeneous enhancement except for the central necrosis (low-signal) in the right lesion (blue arrow).

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**Fig. 6:** (A) Axial T1-weighted image in the arterial phase after gadolinium administration and (B) subtraction of the same image show a neuroendocrine tumor (NET) in the pancreatic head (white arrows), in a 27 year-old man with VHL disease. There is intense enhancement. (C) Axial T1-weighted image in the portal phase in a 34 year-old woman with VHL disease showing another NET in the pancreatic head (white arrow) as a hypervascular nodule with a central area of necrosis or cystic degeneration.

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Fig. 7: 36 year-old woman with VHL disease. (A) Axial T2-weighted image and (B) axial T1-weighted image in the portal phase after gadolinium administration show a large neuroendocrine tumor (NET) in the pancreatic tail (white arrows) as a hypervascular mass with central necrosis. Multiple pancreatic cysts are also visible (blue arrows).

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Fig. 8: 43 year-old woman with VHL disease. Axial contrast-enhanced CT image in the arterial phase shows a bulky pancreatic tail neuroendocrine tumor (white arrows) with central hypodense necrosis and coarse calcification (black arrow). Pancreatic cysts are also visible (blue arrows). Ascites is present (*).

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Conclusion

Radiology plays a central role in the management of VHL disease. Imaging detection of the various abdominal lesions requires implementation of screening protocols for high-risk gene carriers. Screening protocols for detection of the most common abdominal lesions commonly include the following:

- Annual physical examination and urine test;
- Annual abdominal US examination, beginning at 11 years old;
- Abdominal CT scanning every 2/3 years, beginning at 20 years old (more often if multiple renal cysts are present);
- Annual 24-hour urine collection for vanillylmandelic acid levels, beginning at 2 years old.

These screening protocols are the key for early detection of treatable lesions, improving the probability of a successful conservative treatment.
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