Spectrum of magnetic resonance imaging findings in pancreatic and other abdominal manifestations of Von Hippel-Lindau disease in a series of 23 patients: A pictorial review

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Authors: G. Lo Bue¹, R. Graziani¹, S. Mautone², M. Falconi², L. Balzarini¹; ¹Rozzano/IT, ²Verona/IT
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Aims and objectives

Von Hippel-Lindau (VHL) disease is a rare, autosomal dominantly inherited multisystem disorder with a 50% chance of inheriting the VHL gene from a carrier (1) and it is associated with inactivation of a tumor suppression gene located on chromosome 3p25.5. The spectrum of most frequent clinical manifestations of the disease includes retinal and central nervous system hemangioblastomas, endolymphatic sac tumors, and multiple abdominal lesions: renal cysts and tumors, pancreatic cystic lesions (simple cysts, serous microcystic or micro/macro-cystic cystadenoma), pancreatic solid lesions, the most common neuroendocrine tumors (NETs), frequently non-functioning, pheochromocytomas, and epididymal cystadenomas.

The diagnostic criteria for VHL disease (2) include the following: a) more than one central nervous system hemangioblastoma; b) one central nervous system hemangioblastoma and visceral manifestations of VHL disease; and c) any manifestation and a known family history of VHL disease.

The abdominal manifestations of VHL tend to be asymptomatic at the onset of the disease and they are frequently diagnosed later than other manifestations. Patients with VHL disease require long-term follow-up of abdominal manifestations with imaging techniques. Magnetic resonance (MR) is imaging method of choice for follow-up, because of the absence of radiation.

The aim of this paper is to focus on principal MR imaging findings of pancreatic and other principal abdominal manifestations of VHL disease patients we have been observed and to review the literature.
Methods and materials

Between January 2007 and January 2011, 72 patients suffering from VHL syndrome were included in this retrospective study in two different institutions (Abano Terme Hospital and University Hospital of Verona).

Inclusion criteria were VHL syndrome confirmed by genetic tests, imaging examination (64-slice multidetector CT (MDCT) scanning and/or 1.5 T magnetic resonance (MR) scanning performed at moment of diagnosis, availability of surgical specimens and histopathological examination of the VHL cases submitted to surgical procedure. Exclusion criteria were imaging (MDCT and/or MR) not performed at the moment of diagnosis (30 patients), patients studied only with MDCT technique (2 patients), unavailability or poor quality of imaging (7 patients), lack of surgical procedure (5 patients) and specimen not available (5 patients) in VHL cases submitted to surgical procedure.

We retrospectively evaluated 23 patients (10 males, 13 females) with mean age of 45 years (range: 24-69 years), who underwent abdominal MR imaging at the clinical onset and diagnosis of the disease.

Seven patients (30.4%) were family members (3 different families).

At diagnosis 10 patients were asymptomatic (43.5%). In the remaining 13 symptomatic patients, referred symptoms were: pancreatic pain (9, 69.2%), acute pancreatitis episodes (4, 30.8%), biliary obstruction (5, 38.5%), exocrine pancreatic insufficiency (6, 46.2%), hypertension (5, 38.5%), palpitations and sweating (4, 30.8%). All patients presented more than one symptom.

Pathological specimen was performed after pancreatic surgical procedures in 13 patients, after renal surgery in 14 (60.9%). In addition, surrenectomy was made in 3 cases (13.0%, 2 were bilateral) and testicular resection in 1 case (4.3%). Multiple different surgical procedures were performed in the same patient in 8 cases (in 2 cases splenopancreatectomy and nephrectomy; in 1 case pancreaticoduodenectomy and partial nephrectomy; in 1 case cystojejunoanastomosis and partial nephrectomy; in 1 case pancreatic enucleation and partial nephrectomy; in 1 case testicular resection and surrenectomy bilateral; in 1 case partial nephrectomy and bilateral surrenectomy; in 1 case tal nephrectomy and surrenectomy).

MR imaging was performed at 1.5 T scanner (Achieva, Philips, Heindoven, Holland; Magnetom Symphony, Siemens, Erlangen, Germany), using 16 and 4 channel phased array coil, respectively.

MR images were retrospectively evaluated by two readers in consensus. The retrospective reviewers were blinded to the presence of abdominal lesions of VHL.
disease, but they were not blinded to the type and abdominal site of lesions. All MR images were assessed at the workstation.

In qualitative analysis about pancreas we evaluated: unilocular fluid lesion or simple cystic lesion; serous micro- or micro/macro-cystic cystadenoma; hypervascular solid lesion or hypervascular non functioning NET; cystic lesion with thickened enhanced walls or cystic non-functioning NET; association of non-functioning NET and cystic lesion (serous cystadenoma, simple cystic lesion); vascular invasion; retroperitoneal lymph nodes; liver metastasis and site of pancreatic lesion. About kidney we evaluated: fluid lesion or cyst; fluid and solid lesion or complex cyst; completely solid lesion or tumor, hypervascular during contrastographic arterial phase with wash-out during portal venous phase; renal vascular invasion; retroperitoneal lymph nodes; liver metastasis.

About adrenal gland we evaluated: solid hypervascular tumor. About scrotum were evaluated: cystic lesion; solid lesion. In quantitative analysis major diameter of single lesion, or major diameter of major lesion in case of multiple lesions, were measured.
**Results**

Thirty-four pancreatic lesions were found in the 23 patients. In qualitative analysis, the MR imaging findings were: 6 (26.1%) unilocular fluid cystic lesions (Figure 1abc); 11 (47.8%) serous micro- or micro/macro-cystic cystadenomas (Figures 1def, 2, and 3); 8 (34.8%) neuroendocrine solid tumors: all of them nonfunctioning NET and hypervascular during arterial pancreatic phase of contrastographic dynamic study (Figures 2 and 3); 1 (4.3%) cystic nonfunctioning NET, diffuse in all pancreatic gland (Figure 2); in 4 (17.4%) cases association of nonfunctioning NET and pancreatic cystic lesions (3 cases of association of non-functioning NET and serous cystadenoma (13.0%); 1 case of association of non-functioning NET and pancreatic simple cystic lesion (4.3%) were present (Figures 2 and 3). Vascular invasion was not detected in any patients.

The 42 renal MR imaging findings present in qualitative analysis were: 18 (78.3%) renal cysts (Figures 2ab, 3 adef, and 5 abcdef); 13 (56.5%) complex renal cysts (Figures 2 ef and 5 bcdef); 11 (47.8%) solid renal carcinomas hypervascular during arterial phase of contrastographic study with wash-out during portal venous phase. Only 1 of these 11 lesions at pathological specimen resulted benign or adenoma.

The adrenal MR imaging findings were: 3 (13.0%) solid hypervascular tumors: 2 of these (66.7%) bilateral and 1 (33.3%) monolateral (Figure 6bcd).

The scrotum MR imaging findings were: 1 (4.3%) fluid cystic lesion or cystadenoma (Figure 7) and none solid lesion. Vascular invasion was not detected in any patients. In 2 cases (8.7%) retroperitoneal lymph nodes, both of them in neuroendocrine tumors, were present. Liver metastasis were detected in none.
Fig. 1: Pancreatic unilocular cysts (a.b.c). Case 1: 35-year-old man with VHL disease. Pancreatic microcystic serous cystadenoma (d.e.f. Case#2: 30-year-old man with VHL disease). Axial (a. d.) and coronal (b. e.) T2-weighted MR images; coronal (c.) and axial (f.) 3D volumetric gradient-echo T1-weighted fat suppressed images after intravenous contrast medium administration during arterial pancreatic phase of contrastographic dynamic study. Case 1. Multiple fluid, cystic lesions of pancreatic parenchyma with different size and site (arrows), hyperintense on T2-weighted MR images, are present (a. b. c). Cystic lesions do not communicate with the main pancreatic duct, which appears not dilated. The cystic walls do not show enhancement after intravenous contrast medium administration (c). In the upper pole of the left kidney (a.) a
complex cystic mass (black arrow) is detected. Case2. A lobulated fluid mass, with thin walls, hyperintense at T2-weighted images (d. e), is present in the body of pancreatic gland (arrowheads). Inside the mass, containing multiple fluid cystic areas, multiple radially aligned thin septa are visible (spongy appearance or honeycomb pattern). The septa and the peripheral walls enhance after intravenous gadolinium administration (f). The septa are well depicted on coronal T2-weighted MR image (e.) but the central scar is not visible. In the remaining portion of pancreatic gland multiple cystic, fluid, round lesions, with different size and site and without enhancement after intravenous contrast medium administration (f), are present.

**Fig. 2:** Pancreatic diffuse microcystic serous cystadenoma and pancreatic non-functioning neuroendocrine tumor in the same patient. A 24-year-old woman with VHL disease and symptoms of pancreatic exocrine insufficiency. Axial (a. b.) and coronal (c.) T2-weighted MR images, MR cholangiopancreatography (d.) and axial 3D volumetric gradient-echo T1-weighted fat suppressed images after intravenous contrast medium administration during arterial pancreatic (e.) and portal venous (f.) phases of contrastographic dynamic study. Pancreatic gland is enlarged and parenchyma is completely replaced by multiple, lobulated fluid cysts, hyperintense on T2-weighted MR images, with a "bunch of grapes" pattern (a. b. c. d.). In the pancreatic head, a round solid mass (arrow), with the signal intensity less high than other pancreatic cysts on T2-weighted MR images and homogeneous enhancement after intravenous contrast medium administration during arterial pancreatic phase (e.), with low wash-out in portal venous (f.) phase, is present. Multiple bilateral renal cystic lesions and large complex mass on the left kidney (short arrow), with fluid signal intensity, multiple solid septa and heterogeneous enhancement after intravenous contrast medium administration during arterial (e.) and portal venous (f.) phases, are detected. Total pancreatectomy and surgical enucleation of the left renal mass were performed. Histological specimen showed the presence of pancreatic diffuse serous cystadenoma, non-functioning neuroendocrine tumors of pancreatic head and cystic renal cell carcinoma of left kidney.

Fig. 3: Pancreatic diffuse microcystic serous cystadenoma and pancreatic non-functioning neuroendocrine tumor in the same patient. Asymptomatic 34-year-old woman, member of family affected to VHL disease. Axial (a) and coronal (b) T2-weighted MR images, MR cholangiopancreatography (c) and axial 3D volumetric gradient-echo T1-weighted fat suppressed images after intravenous contrast medium administration during arterial pancreatic (d), portal venous (e) and delayed (f) phases of contrastographic dynamic study. Pancreatic gland is enlarged and parenchyma is completely replaced by multiple, lobulated fluid cysts, hyperintense on T2-weighted MR images, with a "bunch of grapes" pattern (a, b, c). The wall of cystic lesions and septa inside them shows enhancement after intravenous contrast medium administration during arterial pancreatic (d), portal venous (e) and delayed (f) phases. In pancreatic head and neck, some cysts result so small and so numerous as they show lower signal intensity on T2-weighted MR images.
images compare to fluid lesions and appear at MR imaging like solid mass (short arrow). In the pancreatic body, a round solid mass (arrows), with the signal intensity less high than the other pancreatic cysts on T2-weighted MR images and homogeneous enhancement after intravenous contrast medium administration during arterial pancreatic phase (d) with low wash-out during portal venous phase (e.) but hypointense on delayed (f) phase, is present. Multiple bilateral renal fluid cysts are detected. Splenopancreatectomy was performed. Histological specimen showed the presence of pancreatic diffuse serous cystadenoma and non functioning neuroendocrine tumors of pancreatic body-tail.


Fig. 4: Pancreatic diffuse cystic non functioning neuroendocrine tumor. A 43-year-old woman affected by VHL disease. Axial T2-weighted MR images (a) and 3D volumetric gradient-echo T1-weighted fat suppressed images after intravenous contrast medium administration during arterial pancreatic (b), portal venous (c) and delayed (d) phases of contrastographic dynamic study. Pancreatic gland is enlarged and parenchyma is thickened, completely replaced by multiple, lobulated fluid cysts, the largest in pancreatic head and tail (arrows), hyperintense in T2-weighted MR images, with thickened walls and irregular septa. Multiple small parenchymal nodules (small arrows), hyperintense on T2-weighted MR images but with lower signal intensity compared to fluid lesions, are visible in pancreatic body-tail and head. After intravenous contrast medium administration during arterial pancreatic (b.), portal venous (c) and delayed phases (d) walls and septa
of cystic lesions show enhancement. Also multiple, small, solid parenchymal nodules enhance during pancreatic phase of dynamic MR study (short arrows). A large fluid cystic lesion in pancreatic head causes stenosis of main pancreatic duct and upstream duct dilatation (arrowhead). Total pancreatectomy and retroperitoneal lymphadenectomy was performed. Histological specimen showed the presence of pancreatic diffuse non functioning neuroendocrine carcinoma with malignant cystic and solid lesions. Retroperitoneal adenopathy metastasis were present.


Fig. 5: Renal cysts and cystic renal cell carcinoma. A 43-year-old man with VHL disease. Coronal (a, b) and axial (c) T2-weighted MR images; axial (d) and coronal (e, f) 3D
volumetric gradient-echo T1-weighted fat suppressed images after intravenous contrast medium administration during arterial (d. e) and venous (f) phases of contrastographic dynamic study. Multiple and bilateral simple, fluid renal cysts, with high signal intensity on the T2-weighted images (a. b. c) and hypointense without enhancement after intravenous contrast medium administration during arterial (d. e) and venous (f) phases. In the lower pole of the left kidney a complex cystic mass (arrows) is present, with heterogeneous hyperintensity on the T2-weighted images, septa and solid areas enhanced after intravenous contrast medium administration during arterial (d. e) and venous (f) phases. Surgical enucleation of left renal lesion was performed. Histological specimen showed the presence of a cystic renal cell carcinoma.


Fig. 6: Adrenal pheochromocytomas. A 38-year-old man with VHL disease. Coronal (a) and axial (b) T2-weighted MR images; axial (c. d) 3D volumetric gradient-echo T1-weighted fat suppressed images after intravenous contrast medium administration during portal venous phase of contrastographic dynamic study. In both adrenal glands, small, round solid masses (arrows), with maximum diameter of 20 mm and intermediate signal intensity in T2-weighted MR images (a. b) are present. The nodules show intense and homogeneous enhancement after intravenous contrast medium administration during dynamic study (c. d). Small cyst at lower pole of right kidney (a. short arrow). Bilateral
open adrenalectomy was performed. Histological specimen showed the presence of adrenal bilateral pheochromocytomas.


Fig. 7: Papillary cystadenoma of the epididymis. A 38-year-old man with VHL disease. Coronal 3D volumetric gradient-echo T1-weighted fat suppressed images after intravenous contrast medium administration during portal venous phase of contrastographic dynamic study. Bilateral complex cystic mass of epididymis with extratesticular site, fluid components, irregular septa inside the lesion and solid mural nodules which show enhancement after intravenous contrast medium administration during arterial phase (asterisks). Testicular resection was performed. Histological specimen showed the presence of bilateral papillary cystadenoma of the epididymis.
Conclusion

Pancreatic manifestations of VHL disease have different frequencies depending on the family group (0-77%) and consist of simple unilocular cystic lesions or simple pancreatic cysts, serous microcistic or micro/macro-cystic cystadenomas, neuroendocrine tumors (NET) and rarely adenocarcinoma. Combined lesions occur, but the association of cystic lesions and neuroendocrine tumors is rare (3).

The pancreatic gland in patients with VHL disease may show a single or multiple unilocular cystic lesions, isolated, in groups or cluster. In our series unilocular pancreatic cystic lesions were present in 26.1% of patients with VHL disease (6 out of 23 patients). At MR imaging (3) pancreatic cysts appear hypointense on T1-weighted images and hyperintense on T2-weighted images lesions, with no enhancement after intravenous gadolinium contrast medium administration.

Serous cystadenoma have a lower incidence (approximately 12%) in VHL patients than pancreatic simple cysts (4). As the pancreatic simple cysts, serous cystadenomas are generally asymptomatic. In our series pancreatic serous cystadenomas were present at MR imaging in 47.8% of patients with VHL disease.

The prevalence of NETs in VHL patients is reported to be about 5-17% (5). In VHL patients these tumors are typically not functioning NET, asymptomatic, often slow growing lesions, and fewer than 10-30% of them metastasize. Even when metastases occur, they are associated with relatively long survival times. The NETs occur more frequently in VHL patients with pheochromocytoma and rarely are associated with pancreatic cystic lesions (5). In our series of VHL patients, solid pancreatic NETs.

In our series of VHL patients, solid pancreatic NETs were present in 34.8% of cases, all non functioning and hypervascular during enhanced pancreatic arterial phase of MR dynamic study.

Differently to literature, in our series non functioning NETs had not a preferential site in pancreatic gland, resulting localized in 17.4% of cases in the pancreatic head and 17.4% in pancreatic body-tail. Only in 4.3% of our VHL cases, non-functioning NET was a cystic lesion, diffuse in all pancreatic gland, with fluid signal intensity and thickened walls enhancing during dynamic MR study.

In 17.4% of our series, we reported the association in the same patient of non-functioning NETs and pancreatic cystic lesions, many of them (3/23, 13.0%) were represented by diffuse serous cystadenomas (Figures 2, 3,) and few of them (1/23, 4.3%) were represented by simple cysts.

Renal cysts are present in 59-63% of patients with VHL disease; more frequently they are multiple lesions and are reported bilateral in as many as 75% of patients (5).
According to the literature, in our series simple renal cysts were present in 78.3% of patients. In 69.6% of our cases they were multiple and bilateral.

Renal cell carcinoma occur in 28-45% of patients with VHL disease and it is a frequent cause of morbidity and mortality in these cases (5).

In our series of 23 VHL patients, 14 cases (60.9%) underwent surgical treatment for malignant renal lesions: partial nephrectomy was performed in 8 cases (34.8%) and total nephrectomy in the remaining 6 patients (26.1%).

In the VHL patients pheochromocytomas arise only in presence of specific alleles of the VHL gene. The frequency of this tumor varies therefore from 0% to 60% in different family groups (3).

In our series pheochromocytomas resulted in 13.0% of VHL patients (3 cases), with bilateral lesions in 2 cases (66.7% of pheochromocytomas).

Cystadenoma of the epididymis is a rare epithelial tumor that originates from the Müllerian residual of connective tissue, with prominent papillae lined by glycogen-rich clear cells (6), similar to the appearance of serous cystadenoma of the ovary. In our series we observed only one case of one epididymal papillary cystadenoma (4.3%), confirmed by pathological specimen after testicular resection.

Abdominal manifestations of VHL disease are different and protean. MR imaging plays an essential role in the identification of pancreatic and other abdominal lesions of VHL disease and their follow-up, in the Screening of asymptomatic gene carriers, and in their long-term surveillance, to allow a more conservative therapeutic approach, and helps to improve the survival and quality of life.
References


