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Von Hippel-Lindau Disease with Multi-Organ Involvement: A Case Report and 8-Year Clinical Course with Follow-Up

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 31
Final Diagnosis: Von Hippel-Lindau disease
Symptoms: Abdominal pain
Medication: —
Clinical Procedure: Splenectomy
Specialty: Oncology

Objective: Rare disease

Background: Von Hippel-Lindau (VHL) disease is a rare autosomal dominant syndrome manifested by a spectrum of benign and malignant tumors.

Case Report: The patient presented here was a 31-year-old female with unremarkable family history who presented initially complaining of intermittent abdominal pain. Abdominal CT scan revealed an inhomogeneous solid mass (13×9×7 cm) originating from the tail of the pancreas with splenic and gastric invasion as well as several pancreatic cysts. A nucleotide scan showed left adrenal involvement. The patient underwent tumor resection, splenectomy, partial gastrectomy, and left adrenalectomy. Histopathologic examination reported well-differentiated neuroendocrine carcinoma with low malignant potential of the tumor with splenic and adrenal involvement. Pancreatic cysts had benign component. Three years later, follow-up abdominal CT showed heterogeneously-enhanced solid nodules in both kidneys found to be renal cell carcinoma (RCC) on biopsy. At the same time, brain MRI showed cerebellar hemangioblastomas. Partial nephrectomy was done. Molecular genetic testing for demonstrated NM_000551.3: c.481C > T (p.R161* CGA>TGA), which has been reported previously in VHL disease. The next year, she developed peritonitis, which found to be the result of a perforated gastric ulcer. Histopathologic examination of the ulcer revealed neuroendocrine carcinoma. Then, the next year, a brain MRI revealed 4 solid and enhanced nodules in the cerebellum, suggesting multiple hemangioblastomas. Octreotide (Sandostatin® LAR) and everolimus (Afinitor®) were started for the patient. At the last visit, the patient was asymptomatic with acceptable condition.

Conclusions: Here, we present a young patient with pancreatic neuroendocrine tumor as the first presentation of VHL without a remarkable family history for VHL disease. The patient developed RCC, renal cysts, cardiomegaly, and brain hemangioblastomas during the 8-year follow-up. Regular follow-up with imaging (ultrasound, CT, MRI) are necessary to follow the previous lesions and detect any newly-developed VHL-associate tumors.

MeSH Keywords: Carcinoma, Renal Cell • Hemangioblastoma • Neuroendocrine Tumors • Pancreatic Cyst • von Hippel-Lindau Disease

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/907356

Background

von Hippel-Lindau disease (VHL) is a rare autosomal dominant cancer-predisposition syndrome with an incidence of 1 in 36 000 live births. It is caused by mutation in the VHL tumor-suppression gene located on chromosome 3 [1]. This mutation predisposes patients to the formation of cysts and tumors in various organs [2]. The most commonly reported cysts and tumors include pancreatic neuroendocrine tumors, pancreatic cysts (seen in 35% to 70% of patients with VHL) [2,3], cerebellar and spinal hemangioblastomas (seen in 60–80%) [4], clear cell renal cell carcinoma (RCC) in 24–45% of patients, ovarian cysts, and pheochromocytoma.

Historically, the diagnosis of VHL is made based on the presence of a VHL-associated tumor (retinal or cerebellar hemangioblastoma, pheochromocytoma, or RCC) in a patient with positive family history or 2 tumors in patients without pertinent family history [4]. Most patients have positive family history because the inheritance of VHL disease is autosomal dominant. However, about 20% of patients have a *de novo* mutation [5]. Newer genetic methods such as detection of a germline mutation in VHL gene are available [6].

As VHL is a multi-systemic syndrome, several guidelines have been suggested for management of the tumors in such patients. Because many VHL patients develop manifestations in early adulthood, with a mean age at diagnosis in the 20s, morbidity and mortality can be high [7]. The natural history and clinical course of this syndrome is of outmost importance in developing screening and follow-up protocols. Some limited reports about long-term follow-ups and multi-organ involvement are available in the literature [8–10]. However, description of more patients with multi-organ involvement and follow-ups will further our knowledge of the clinical course of VHL.

Here, we share our experience about the management and follow-up of a VHL patient who was followed up for 8 years, and during this period several VHL-associated tumors developed.

Case Report

The presented patient was a married 31-year-old female who initially presented to our medical center in 2009 complaining of intermittent abdominal pain for the past 3 years. The pain was not localized and had a vague quality. The pain was not associated with nausea, vomiting, or other gastrointestinal symptoms except for occasional diarrhea and constipation. She did not have gynecologic symptoms such as menorrhagia and melena or rectorrhagia. Her history was unremarkable for weight gain or anorexia. However, she reported sweating, palpitation, and dyspepsia. She had undergone myomectomy 3 years earlier. Family history was negative for any condition. Abdominal ultrasound performed 1 year earlier at another center showed 2 cysts measuring 10 mm and 20 mm in the head of the pancreas and 4 cysts measured 14 to 20 mm in the body of the pancreas. In addition, a left ovarian mass with septations with free pelvic fluid had been reported on ultrasound exam. No further work-ups had been done.

At our center, contrast-enhanced abdominal CT revealed an inhomogeneous solid mass (13×9×7 cm) originating from the pancreatic tail. The mass had internal hyperdense foci (calcifications) with resultant mass effect on the stomach fundus and invasion to the spleen. In addition, multiple hypodense lesions were seen in the enlarged pancreas, suggesting pancreatic cysts (Figure 1). A simple ovarian cyst was also seen. The kidneys, adrenals, and liver were normal. The chest CT result was also normal. A nucleotide scan showed round soft tissue uptake in the superior portion of the left kidney due to tumoral involvement.

Due to the large size of the tumor, surgical consultation was made and the patient underwent laparotomy. During the first laparotomy, the tumor was found to be unresectable because of adhesion to the spleen. The histopathology report of the tumor biopsy showed well-differentiated neuroendocrine carcinoma with low malignant potential. IHC (immunohistochemical staining) showed that tumor cells were positively stained for CK, chromogranin A, synaptophysin, vimentin, and S100 protein. No evidence of CD20, CD3, or desmin were detected. Ki67 was positive (5%). The tumoral cells were positive for NSE (neuron specific enolase) and negative for CD45 LCA (leukocyte common antigen). These confirmed the diagnosis of a pancreatic neuroendocrine tumor. The spleen, but not the stomach, was also involved by the tumor. The patient was scheduled for laparotomy for a second time. Complete resection of the tumor, splenectomy, excision of the pancreatic mass, left adrenalectomy, and partial gastrectomy were done. Histopathology examination showed well-differentiated endocrine carcinoma of the pancreas with local extension to the spleen and adrenal gland without extension to the stomach. Post-operatively, SPECT with technetium-99m (Tc-99m)-labeled octreotide (Octreoscan) showed tracer uptake in the right adrenal gland and a large region of faint uptake in the left upper quadrant (LUQ) of the abdomen, with extension to the left lower quadrant (LLQ) area. The patient did not have any symptoms or signs suggestive of excess catecholamines. Routine laboratory tests including fasting blood glucose, CBC, and lipid profile were within normal limits. The patient was advised to present periodically to perform follow-up examinations with imaging of the abdomen.

In 2010, an abdominal CT scan showed an enlarged pancreas with multiple cystic masses (largest dimension was 70 mm) inside it,

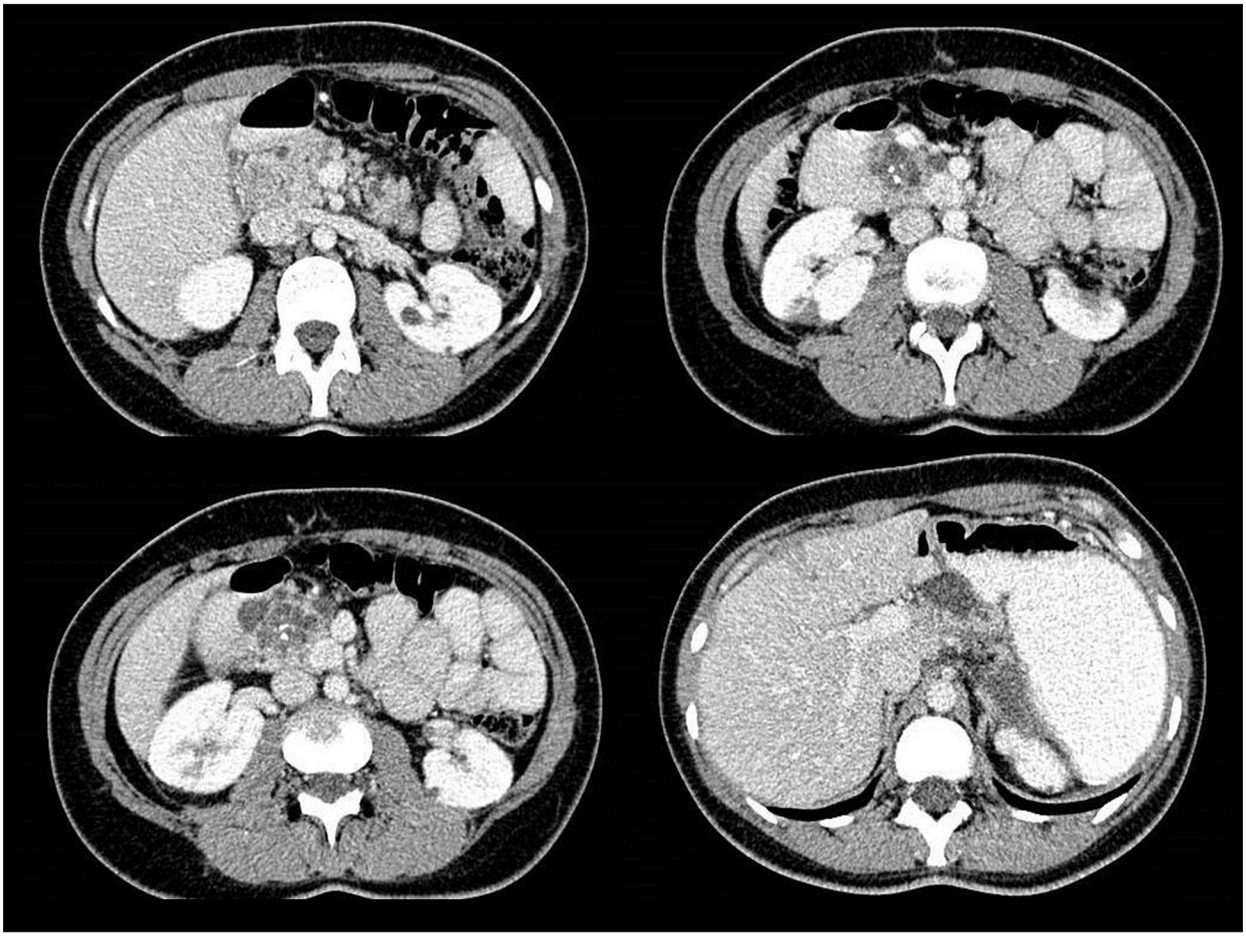

Figure 1. Contrast-enhanced abdominal CT scan showing an inhomogeneous solid mass (13×9×7 cm) originating from the pancreatic tail with mass effect on the stomach fundus and invasion to the spleen.

suggesting a neoplastic process combined with a pseudocyst or cystic neoplasm. The pancreatic cysts showed increased size compared to previous records. Also, a small hypodense area about 10 mm at the right kidney was seen as well as a hypodense lesion about 20 mm at the left kidney. Chest CT was normal. CEA (carcinoembryonic antigen) was 0.98 ng/mL and urine 5-HIAA (5-hydroxyindoleacetic acid) was 9.5 ng/mL. Follow-up with abdominal CT scan every 6 months was scheduled.

In 2012, abdominal CT scan showed several small cysts in both kidneys, with 2 heterogeneously-enhanced solid nodules suggesting renal cell carcinoma (RCC). The CT-guided biopsy of the renal lesions confirmed the RCC diagnosis. Urinary 5-HIAA was 3.5 mg per 24 h, CEA was 0.81 ng/mL, and CA 19-9 was 50 U/mL. At the same time, the patient reported new-onset intermittent headache, nausea, and dizziness. A brain MRI showed 5 round and enhancing lesions with 2 to 10 mm diameters (4 in the cerebellar hemispheres and 1 in the fourth ventricle). These suggested multiple hemangioblastomas. She underwent partial nephrectomy (upper and lower poles of the left kidney as well as ipsilateral adrenal cyst excision). The histopathologic examination confirmed RCC and simple cyst of the adrenal gland. Molecular genetic testing for VHL mutation and DNA analysis (QIAGEN extraction kit amplified by VHL primer pool by Life Technologies, US) demonstrated NM_000551.3: c.481C>T (p.R161* CGA>TGA), which has been reported previously in VHL disease [11].

One year later, in 2013, a follow-up abdominal CT scan showed a newly-developed low-dense lesion in the liver. Biopsy specimen of the hepatic lesion showed cholestasis and was negative for neuroendocrine tumor. The right renal RCC showed enlargement compared with previous images. Therefore, RFA (radiofrequency ablation) of the right RCC and the hepatic masses was performed.

One year later (2014), a follow-up CT scan showed enlargement of a hepatic low-dense ill-defined nodule at the junction of segments V and VIII, which measured 31 mm. There was a new low-dense lesion in the segment IV and multiple hypervascular nodules were seen in both lobes of the liver. Chest CT was normal.

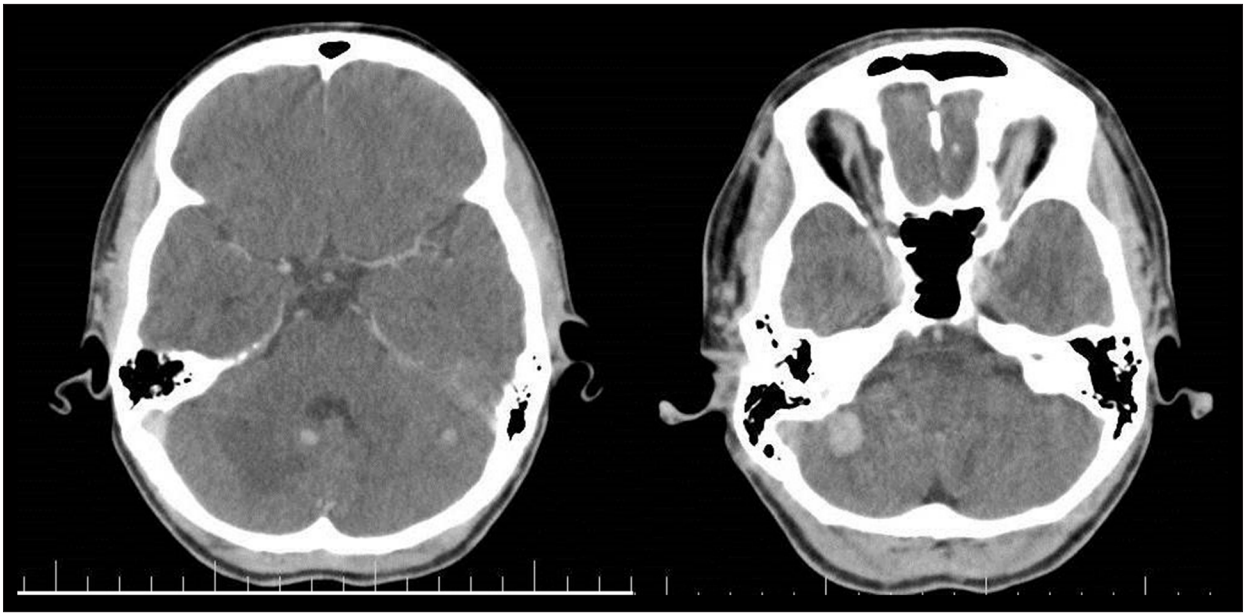

Figure 2. Contrast-enhanced brain CT showing solid and enhanced nodules in the cerebellum with a large lesion (20 mm) in the right jugular fossa with extension to the cerebellopontine angle.

In 2015, the patient presented with abdominal pain. With the diagnosis of peritonitis, she underwent laparotomy, which showed a perforated peptic ulcer of the stomach. Histopathology examination of the ulcer edge showed well-differentiated neuroendocrine carcinoma (Ki67 was 1%). The same year, a follow-up CT showed enlargement of liver nodules and an enlarged (24 mm) hypervascular nodule in the left intercostal muscle. In August 2016, a colonoscopy was performed, which was unremarkable.

In 2016, a brain CT did not show any change in size of the hemangioblastomas (Figure 2). An abdominal CT showed new peritoneal cavity ascites and left adrenal nodule and increased size of metastases and cardiomegaly. Ascites cytology examination showed a chronic inflammatory process without evidence of malignancy.

In 2017, liver mass wedge biopsy showed a well-differentiated neuroendocrine tumor with positive chromogranin, synaptophysin, and Ki67 (1%). Later, the patient presented with dyspnea, which was diagnosed to be the result of pulmonary edema as well as peripheral edema. Trans-thoracic echocardiography showed normal LV systolic function, minimal pericardial effusion, and severe pulmonary artery hypertension, with moderate tricuspid regurgitation. CT pulmonary angiography showed multiple small pulmonary nodules measuring less than 5 mm with enlarged mediastinal lymph nodes. No evidence of acute or chronic pulmonary embolism was detected.

Octreotide 50 mg 4 times daily was initiated and continued for 1 week. Then, intravenous octreotide (Sandostatin® LAR) 20 mg every 3 weeks and everolimus (Afinitor®) 10 mg daily were administered. After 4 courses, pulmonary and peripheral edema resolved. In the last visit, the patient had occasional peripheral edema. She is continuing Sandostatin® LAR and everolimus, furosemide, and spironolactone. Renal function tests were within normal range. Hypoalbuminemia (serum albumin=2 mg/dL) was detected. ALT and AST were normal. Overall, her general condition is acceptable and she is able to perform activities of daily life.

Discussion

The presented case showed several VHL-associated tumors. The primary/metastatic pancreatic involvement is common in VHL and includes pancreatic cysts (70%), serous cystadenoma (9%), and neuroendocrine tumors, which are reported to occur in about 9% of patients [12]. Our patient had a pancreatic neuroendocrine tumor with invasion to the spleen and stomach. Pancreatic endocrine neoplasms can occur in about 17% of patients [13]. Although pancreatic lesions are usually found on routine follow-ups of VHL patients [13], here, the pancreatic tumor was large enough to make the patient symptomatic. These endocrine tumors are usually non-functional and may be located in any part of the pancreas. Tumors larger than 5 cm usually have malignant behavior [14], as was seen in our patient. The tumor invaded both the spleen and stomach, which made splenectomy and partial gastrectomy inevitable during the second laparotomy. Surgical resection of neuroendocrine tumors of the head of the pancreas (>2 cm) and in the body or tail of the pancreas (>3 cm) is recommended, especially when the patient is symptomatic [15]. Involvement of the pancreas

and adrenal gland, as seen in our patient, has been reported to occur in 7% of 40 patients [16]. The solid pancreatic tumors in VHL are usually neuroendocrine tumors. Since these have variable behaviors, life-long imaging follow-ups are necessary [1]. The age of our patient is in agreement with previous reports indicating a median age of 33 to 35 years for diagnosis of pancreatic neuroendocrine tumor in VHL [1].

Pancreatic cysts are usually followed with an expectant approach as was decided in our patient. As histology examinations showed, cystic lesions are usually benign and rarely transform to malignant tumors [13]. The risk of metastasis in pancreatic neuroendocrine tumors is about 17% [14]. In our experience, even after resection of the primary pancreatic endocrine tumor, annual radiologic examinations are necessary, in particular metastases to adrenals. The association of metastasis with size is well documented. In the current case, gastric involvement not only occurred upon presentation, but also during the course the patient developed a perforated gastric ulcer.

Bilateral renal involvement is also a common finding in VHL disease. RCC has been reported to occur in 25% to 50% of VHL patients [8] and almost always are of clear cell type. In contrast to pancreatic cysts and hemangioblastomas, which usually show a benign course, RCC is a major cause of mortality in VHL [5]. Multiple cysts, as observed in our patient, can develop bilaterally but they usually do not compromise renal function. A nephron-sparing approach is the recommended management for multiple renal cysts [5] instead of radical nephrectomy. Here, partial nephrectomy and RFA were the treatments employed, with acceptable outcomes.

Retinal and CNS hemangioblastomas are common in VHL and occur in about half of patients [5,8]. The cerebellum and spinal cord are common sites for hemangioblastoma. These are benign tumors and we decided to implement expectant management. The hemangioblastomas did not enlarge after 4 years. Some hemangioblastomas remain unchanged in size over several years and if they do not cause symptoms, their surgical removal may not be necessary [5].

Somatostatin analog therapy is an option for neuroendocrine tumors in VHL owing to the fact that pancreatic cysts are usually multifocal, which renders surgical treatment difficult. The surgical intervention also makes the patients predisposed to pancreatic insufficiency. At the time of preparing this report, we did not have enough time to follow the patient radiologically and observe the effect of octreotide on pancreatic cysts. In a recent report, the usefulness of octreotide and significant decrease in the size of pancreatic neuroendocrine tumors were documented in a 24-year-old female with VHL disease who received somatostatin analog therapy [17].

Conclusions

Here, we present the case of a young patient with pancreatic neuroendocrine tumor as the first presentation of VHL without family history. The patient developed renal cell carcinoma, renal cysts, cardiomegaly, and hemangioblastomas during the 8-year follow-up. Regular follow-up with imaging (ultrasound, CT, MRI) are necessary to follow the previous lesions and to detect any newly developed VHL-associate tumors.

References:

1. Keutgen XM, Hammel P, Choyke PL et al: Evaluation and management of pancreatic lesions in patients with von Hippel-Lindau disease. Nat Rev Clin Oncol, 2016; 13(9): 537–49
2. Sharma A, Mukewar S, Vege SS: Clinical profile of pancreatic cystic lesions in von Hippel-Lindau disease: A series of 48 patients seen at a tertiary institution. Pancreas, 2017; 46(7): 948–52
3. Ayloo S, Molinari M: Pancreatic manifestations in von Hippel-Lindau disease: A case report. Int J Surg Case Rep, 2016; 21: 70–72
4. Bhuyan M, Dutta D, Baishya BK, Hussain Z: Cerebellospinal hemangioblastoma with bilateral pheochromocytoma and hepatic cyst: A rare entity. Asian J Neurosurg, 2016; 11(3): 311
5. Maher ER, Neumann HP, Richard S: von Hippel-Lindau disease: A clinical and scientific review. Eur J Hum Genet, 2011; 19(6): 617–23
6. Nielsen SM, Rhodes L, Blanco I et al: Von Hippel-Lindau disease: Genetics and role of genetic counseling in a multiple neoplasia syndrome. J Clin Oncol, 2016; 34(18): 2172–81
7. Crespigio J, Berbel LCL, Dias MA et al: Von Hippel-Lindau disease: A single gene, several hereditary tumors. J Endocrinol Invest, 2017 [Epub ahead of print]
8. Junaid M, Ur Rashid M, Afsheen A et al: Von Hippel Lindau syndrome and surveillance: A five year follow up case report. J Ayub Med Coll Abbottabad, 2015; 27(4): 930–32
9. Arao T, Okada Y, Tanikawa T et al: A case of von Hippel-Lindau disease with bilateral pheochromocytoma, renal cell carcinoma, pelvic tumor, spinal hemangioblastoma and primary hyperparathyroidism. Endocr J, 2002; 49(2): 181–88
10. Hwang JJ, Uchio EM, Pavlovich CP et al: Surgical management of multi-organ visceral tumors in patients with von Hippel-Lindau disease: A single stage approach. J Urol, 2003; 169(3): 895–98
11. Nordstrom-O'Brien M, van der Luijt RB, van Rooijen E et al: Genetic analysis of von Hippel-Lindau disease. Hum Mutat, 2010; 31(5): 521–37
12. Hammel PR, Vilgrain V, Terris B et al: Pancreatic involvement in von Hippel-Lindau disease. The Groupe Francophone d'Etude de la Maladie de von Hippel-Lindau. Gastroenterology, 2000; 119(4): 1087–95
13. Safo A-OF, Pambuccian SE: Pancreatic manifestations of von Hippel-Lindau disease. Arch Pathol Lab Med, 2010; 134(7): 1080–83
14. Corcos O, Couvelard A, Giraud S et al: Endocrine pancreatic tumors in von Hippel-Lindau disease: clinical, histological, and genetic features. Pancreas, 2008; 37(1): 85–93
15. Blansfield JA, Choyke L, Morita SY et al: Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (PNETs). Surgery, 2007; 142(6): 814–18; discussion 818.e1-2
16. Delman KA, Shapiro SE, Jonasch EW et al: Abdominal visceral lesions in von Hippel-Lindau disease: Incidence and clinical behavior of pancreatic and adrenal lesions at a single center. World J Surg, 2006; 30(5): 665–69
17. O'Toole SM, Drake WM: Response to somatostatin analog therapy in a patient with von Hippel-Lindau disease and multiple pancreatic neuroendocrine tumors. Pancreas, 2017; 46(7): e57