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Sunitinib treatment for multifocal renal cell carcinoma (RCC) and pancreatic neuroendocrine tumor (NET) in patient with Von Hippel-Lindau disease

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Abstract

OBJECTIVE: Von Hippel-Lindau disease (VHL) is an autosomal, dominant, hereditary disease occurring in approximately one in 36,000 births. VHL disease produces a variety of tumors and cysts in the central nervous system and visceral organs. Surgical management, when possible, improves prognosis and extends patient's life. When surgery is impossible, treatment with tyrosine kinase inhibitors demonstrates encouraging response rates.
MATERIAL AND METHOD: We present a 60-year old patient with coexistence of multifocal renal cell carcinomas (RCC) and pancreatic neuroendocrine tumor (NET) in VHL disease, who received Sunitinib as the best option of treatment.
RESULTS: Progression – free survival time is over 4 years. Regarding her acceptable tolerance for tyrosine kinase inhibitors, medical treatment is continued.
CONCLUSION: RCC and pancreatic NET associated with VHL are responsive to Sunitinib for prolonged periods of time. Tyrosine kinase inhibitors treatment for patients with multiple neoplasms associated with VHL disease may too be considered. Sunitinib showed acceptable toxicity.

CASE REPORT

INTRODUCTION

Von Hippel Lindau disease (VHL) is manifested in the variety of benign and malignant neoplasms (Chan-Smutko *et al.* 2010). The VHL includes hemangioblastoma of the brain and the spine, retinal angiomas, clear renal cell carcinoma (RCC), pheochromocytoma (PHEO), endolymphatic sac tumors of the middle ear, pancreatic neuroendocrine tumor (NET), papillary cystadenomas of the epididymis and broad ligament (see Table 1).

Renal cell carcinoma (RCC)

RCC is the most lethal, urologic cancer. Patients with VHL disease are at risk for developing multiple renal cysts and RCCs which occur in approximately two-thirds of patients, aged most commonly from 20 to 50. The type 2B of VHL

disease has high incidence of RCC (Chan-Smutko *et al.* 2010). RCCs are often multicentric and bilateral arising both in conjunction with cysts or de novo from non cystic renal parenchyma. Solid renal tumors less than 3cm in diameter generally have a low metastatic potential and can be safely monitored. They usually grow 0.5 cm of diameter in the year, so radical nephrectomy is not recommended (Kim *et al.* 2009).

Pancreatic neuroendocrine tumor (NET)

Pancreatic abnormalities are common in patients with VHL disease. In a multi-institutional study, 77% of patients had lesions in the pancreas, including cysts, serous cystadenomas and NETs. The most of pancreatic NETs are asymptomatic and grow slowly, without the symptoms of any peptide overproduction (Charlesworth *et al.* 2012).

Pheochromocytoma (PHEO)

PHEO in VHL disease tends to be observed in younger patients. In the Mayo Clinic experience, 18% of the patients with VHL were PHEOs at a median age of 30. They are often multiple or extraadrenal and usually asymptomatic. Surgery is the treatment of choice (Chan-Smutko *et al.* 2010).

Herein we report the patient with RCC and pancreatic NET in VHL disease who has received tyrosine kinase inhibitor (Sunitinib) for 4 years and achieved partial responses .

CASE PRESENTATION

A 60-year-old female was admitted to the hospital with left flank pain for 4 months.

Patient's medical history was paroxysmal hypertension, palpitation and 10 kg weigh loss then she was 30. In 1980, urine analyses of 24 hour vanilinmandelic acid (VMA) was remarkably elevated – 40 mg/24 h (N: 4–8 mg/24 h). As part of diagnostic procedures, clinical examination was followed by adrenal artheriography. Artheriography showed bilateral adrenal tumors. Because of suspicion of PHEOs, she underwent open right and partial left adrenalectomy. Histopathological examination showed PHEOs in both adrenal glands. Surgery was associated with normalization of 24 hour urine VMA and clinical improvement. She had not continued endocrinological follow-up for 30 years.

Abdominal computer tomography scan (CT) performed at our hospital showed masses in both kidneys which were suspected to be RCC (five tumors measuring from 22×25 mm to 47×58 mm in the left kidney and two tumors measuring 50×50 mm and 37×37 mm in the right kidney). The multiple cysts from 10 to 50 mm of diameter in both kidneys were also found. CT scan also showed irregular polycyclic lesion measuring 33×24×42 mm in the pancreatic head, with high enhancement pattern with contrast. The CT scan suggested pancreatic NET or RCC metastases to the pancreas (Figure 1).

She underwent radical right nephrectomy and open pancreatic tumor biopsy. To avoid dialysis, we decided to leave the left kidney, where the suspected RCC tumors were less extensive. Histopatological examination showed multifocal, clear RCC and pancreatic NET tumor (Ki67 2%).

The coexistence of PHEO, RCC and NET brought us to perform a genetic assessment to confirm VHL. Peripheral blood genetic analysis showed a germ line mutation of the exon 3 of the VHL gene (p.R167W,

Tab. 1. Clinical classification in the VHL disease (Shuin *et al.* 2006).

	Clinical manifestation				
	Retinal HB	CNS HB	RCC	PHEO	Pancreatic NET
VHL type 1	+	+	+	–	–
VHL type 2A	+	+	–	+	+
VHL type 2B	+	+	+	+	+
VHL type 2C	–	–	–	+	?

Retinal HB – retinal hemangioblastoma
CNS HB – central nervous system hemangioblastoma
RCC – renal cell carcinoma
PHEO – pheochromocytoma

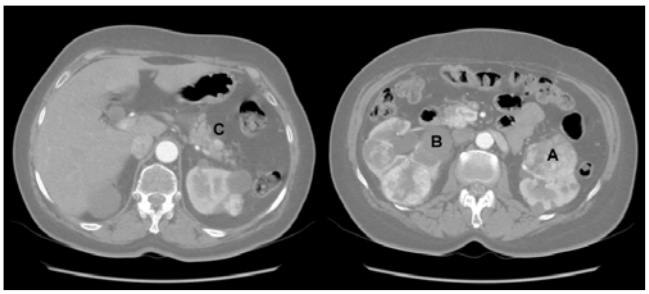

Fig. 1. CT showed masses in both kidneys suspected to be RCC (A), the multiple cysts (B) and irregular polycyclic lesion in the pancreatic head, suspected to be NET or RCC metastases to the pancreas (C).

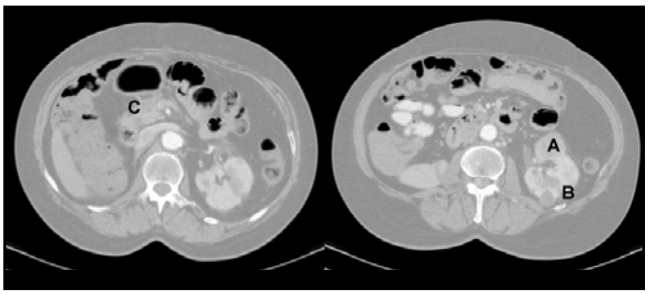

Fig. 2. CT showed partial regression of pancreatic NET tumor (C) and stabilization of RCCs (A) and cysts (B) in left kidney.

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C/T). There was no family history of any endocrine organ diseases.

The patient was started on Sunitinib treatment (50 mg, four week treatment with a two-week withdrawal period). Following treatment with Sunitinib for 4 years, abdominal CT scan showed partial regression of the pancreatic NET tumor (23×20×15 mm) and stabilization of RCCs and cysts in the left kidney (Figure 2). Although the are some side effects like stomatitis, mucositis, skin rash, hypothyroidism, the patient has had good tolerance of treatment. She is currently receiving treatment with Sunitinib as the best option of treatment.

DISCUSSION

VHL is a lifelong disease. Before regular screening of patients with VHL began, their median survival time was about 50 years (Jonasch *et al.* 2011). Mortality and morbidity of the individuals arise primarily from RCC progression and hemangioblastomas of the central nervous system (Jonasch *et al.* 2011). The *VHL gene*, which is known as a tumor suppressor gene, plays a role in angiogenesis. Mutation of the *VHL gene* induces over-expression of proteins, including vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF) and transforming growth factor (TGF). This phenomenon could be the reason for an excessive angiogenesis and cellular proliferation (Kim *et al.* 2013).

RCC occurs in 40–70% of patients with VHL disease. Fewer than 25% of patients have metastatic RCC (Kim *et al.* 2013). RCC are often multicentre and bilateral, arising de novo from noncystic renal parenchyma or coexist with the renal cysts. Solid renal tumors less than 3cm in diameter, generally have low metastatic potential and can by monitored. Partial nephrectomy, particular cryoablation and radiofrequency ablation, may be feasible to preserve renal parenchyma and avoid dialysis. Renal transplantation has been used in VHL patients who required bilateral nephrectomy for multifocal RCC or developed end-stage renal disease. However, the immunosuppressive therapy might enhance the risk of tumor recurrence. New renal tumors are detected in 30% of patients after 5 years and 85% after 10 years (Chan-Smutko *et al.* 2010).

Pancreatic manifestation in VHL patients are NET as a solid tumor (15%), cystic lesions (including simple cysts – 47% or serous cystadenoma – 11%) (Charlesworth *et al.* 2012) or very rare metastases of RCC (Kim *et al.* 2013). Referring to the described patient, pancreatic NETs are generally asymptomatic. Blansfield proposed criteria to predict metastases of pancreatic NETs in VHL disease. Tumor size greater than 3 cm, presence of mutation in exon 3 and tumor dubbing time less than 500 days are the high risk of future malignancy (Blansfield *et al.* 2007). Surgical resection is generally reserved for a lesion greater than 3 cm in diameter in the body or tail of the pancreas or 2 cm in the head of the pancreas.

Pheochromocytomas in VHL tend to be seen in young patients. PHEOs are often extraadrenal or similar to our patient, multiple. Tumors producing catecholamines may be associated with typical clinical signs and symptoms. Bilateral PHEOs in a young patient are usually associated with number of genetic syndromes – VHL, multiple endocrine neoplasia type 2 (MEN 2), neurofibromatosis type 1 (NF1) and mutation of the succinate dehydrogenase (SDH) (Chan-Smutko *et al.* 2010). In our patient, 30 years without regular screening, resulted in late multiple neoplasms in the course of VHL.

Previously, metastatic RCC patients were treated with immunotherapy using interferon alfa (INFα) or interleukin 2 (IL2). More recent treatment includes vascular endothelial growth factor (VEGF) monoclonal antibodies, tyrosine kinase inhibitors (TKI) and mammalian target of rapamycin mTOR inhibitors (Kim *et al.* 2013). Tyrosine kinase inhibitors (TKI) are currently used in the treatment of renal cancer and recently in the pancreatic NETs. These drugs have very promising results in clinical studies, showing more than 40% cases of partial response and up to 90% cases of stable disease in RCC (Jonasch *et al.* 2011). According to reports, using tyrosine kinase inhibitors in patients with malignant PHEO and other VHL disease led to partial response (Jimenez *et al.* 2009).

We supposed that if the major functional consequence of VHL gene mutation is uncontrollable angiogenesis, blocking VEGF signaling with a specific VEGF inhibitor will alter the growth pattern of all VHL related lesions.

Our presented patient, owed two high risk criteria of malignancy – RCCs and NET tumor size over 3cm and mutation in exon 3, which determined our treatment.

Sunitinib is oral, multitargeted receptor tyrosine inhibitor with antiangiogenic and antitumor activity. Our patient has received Sunitinib for over 4 years. Such a response and outcome in the patients with advanced, multifocal RCC conjoined with pancreatic NET has not yet been reported. Antiangiogenic effect of tyrosine kinase inhibitors stabilized lesions in RCC and achieved partial response of pancreatic NET. Although the are some side effects, the patient has good tolerance of treatment.

CONCLUSION

In conclusion, RCC and pancreatic NET associated with VHL are responsive to Sunitinib for prolonged periods of time. Benign cysts or tumors associated with VHL disease could also be controlled with that kind of treatment. Tyrosine kinase inhibitors treatment for patients with multiple neoplasms associated with VHL disease may too be considered. Sunitinib showed acceptable toxicity.

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Consent

Written informed consent was obtained from the patient for publication of this report and any accompanying images.

Competing interests

*The authors declare that they have no compating interests. All authors a*pproved the final manuscript.

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