

Bilateral Pheochromocytoma in von Hippel-Lindau Syndrome Simultaneously Removed by Lateral Retroperitoneal Endoscopic Approach

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ABSTRACT

Von Hippel-Lindau (VHL) syndrome is an autosomal dominant familial neoplastic syndrome caused by mutation in VHL tumor suppressor gene localized on chromosome 3p25. The disease is characterized by abnormal vascular proliferation and increased risk of developing renal cell carcinoma, pheochromocytoma, hemangioblastoma of the central nervous system, tumors of the endolymphatic bag, cysts of the kidney, liver and pancreas, epididymal cystadenomas, neuroendocrine tumors of the pancreas, angiomas in the retina. We report a case of a bilateral pheochromocytoma, simultaneously removed by unilateral total and contralateral subtotal retroperitoneal endoscopic adrenalectomy.

Keywords: Pheochromocytoma, von Hippel-Lindau syndrome, Adrenalectomy.

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CASE REPORT

We present a 24-year-old woman with upper dyspeptic syndrome. On ultrasound examination, a bilateral adrenal tumor was found. Computed tomographic scan (CT) visualized a soft tissue hyperdense lesion sized 51/42 mm in the right adrenal gland as well as a similar lesion sized 41/24 mm in the left adrenal gland (Fig. 1). The tumor was functionally nonactive with normal catecholamine levels in 24-hour urine. Patient had mother with Von Hippel-Lindau (VHL) syndrome as bilateral blindness for 20 years. The genetic analysis confirmed identical mutation (p.Arg167Gln) of the VHL gene in both our patient and her mother. After appropriate preoperative assessment, total left retroperitoneal endoscopic adrenalectomy and subtotal right retroperitoneal adrenalectomy were performed in one operative time with lateral access. Four ports technique (10 mm optical port and three working—one 10 mm and two 5 mm) was used bilaterally. The first intervention was carried out on the left side in lateral decubitus position. The patient was placed with the umbilicus at the level of the break of the table to optimize trunk extension and reduce

interference with instrument movement by the iliac crest. After repositioning the patient on the operating table the second stage of the operation was done. The specimen was removed with a retrieval bag. Repositioning the patient did not take more than 10 minutes. The total operative time was 180 minutes with blood loss of 100 ml, without significant intra- and postoperative complications. The patient was discharged on the third postoperative day. Histopathologically, bilateral pheochromocytoma was confirmed. There was no relapse of the disease after 5-year follow-up.

DISCUSSION

VHL syndrome is a hereditary autosomal dominant multisystem cancer syndrome. The incidence of the disease is 1:36,000.¹ There is positive family history in 80% of the cases while the other 20% of the cases are due to mutation *de novo*.²

There is a clinical classification that divides VHL syndrome into VHL type 1—without presence of pheochromocytoma, and VHL type 2—with presence of pheochromocytoma. VHL type 2 is subdivided into type 2A (with low risk of renal cell carcinoma or cerebellar hemangioblastoma), type 2B (with high risk for developing renal cell carcinoma or cerebellar hemangioblastoma) and type 2C (familial pheochromocytoma without renal cell carcinoma or hemangioblastoma).³



Fig. 1: Computed tomographic scan of the abdomen indicates bilateral adrenal tumors

In 1988, the VHL gene on the short arm of the third chromosome was found.⁴ Later in 1993, it was cloned with establishment of its tumor suppressor activity by Latiff et al.⁵

The VHL gene encodes a protein (pVHL), consisting of 213 amino acids and containing two functional domains- α and β . The β domain binds directly to the α -subunit of hypoxia-induced factor (HIF) and thus controlling the stability factor and tumor angiogenesis.⁶

VHL type 1 syndrome is due to mutations that distort the spatial configuration of VHL protein. Ninety-six percent of the mutations responsible for VHL type 2 are missense mutations.⁷ Thus, the location, volume and type of the gene modification should predetermine phenotype of the syndrome, despite the wide variety of clinical manifestations.^{8,9} For example, complete deletion of VHL gene reduces the risk of renal cell carcinoma, while missense mutations are associated with a high risk of pheochromocytoma.⁹⁻¹¹

Pheochromocytomas are often sporadic (80-90% of cases) and only 10 to 20% of cases are hereditary. The hereditary group include: Multiple endocrine neoplasia-type 2, VHL syndrome, neurofibromatosis 1, paraganglion syndromes. They are developed in 10% of cases with VHL syndrome type 2.¹²

Pheochromocytoma in VHL syndrome occurs earlier than in sporadic form and is often bilateral or multiple, less frequently malignant.¹³ The classical manifestation of pheochromocytoma in the form of intermittent or permanent hypertension, tachycardia, palpitations, anxiety, headache is not always manifested in patients with VHL syndrome. Not often they can be asymptomatic and are detected during screening examinations in affected families in early childhood.

The diagnosis of pheochromocytoma is based on laboratory and imaging methods. Important for the diagnosis are the catecholamines in a 24-hour urine, serum metanephrines. One of the biochemical characteristics of pheochromocytoma in VHL syndrome is relatively low levels of secretion of epinephrine compared with norepinephrine.¹⁴ Native and contrast CTs or MRI facilitate the image diagnosis of adrenal lesions, while in extra-adrenal location with higher specificity is ¹³¹I-MIBG (metaiodobenzylguanidine)-scintigraphy, which can confirm their catecholamine production.

Detection of pheochromocytoma in patients with VHL syndrome is of great importance in connection with the possible surgical treatment of other tumor sites, such as hemangioblastomas of the central nervous system. Unrecognized pheochromocytoma is a prerequisite for the

development of hemodynamic disturbances during surgery. The screening algorithm should include an annual survey of catecholamines in 24-hour urine, starting at the age of 5, along with the examination from an ophthalmologist. After 16 years of age, abdominal ultrasound is recommended each year, and the establishment of a suspected lesion in the kidney, adrenal gland or pancreas mandates a CT or MRI.¹⁵

The surgical treatment of pheochromocytoma in VHL syndrome is an undeniable therapeutic option with a background of an adequate preoperative α -adrenergic blockade and precise perioperative hemodynamic control. The indications are clinically functional tumors, tumor formations with positive MIBG and tumors over 35 mm.¹³ It is enough to keep one-third of the adrenal gland unilaterally, even after clipping the central vein to ensure preserving sufficient adrenocortical function.¹⁶ A large series from specialized institutions confirmed the effectiveness and safety of the retroperitoneal endoscopic adrenalectomy with both lateral and posterior access. The advantage of the posterior access is performance of bilateral adrenalectomy without repositioning the patient. If necessary, however, a conversion, especially in cases of profuse bleeding, is more effective in lumbar position. In bilateral intervention with lateral access repositioning the patient does not take more than 10 minutes.^{17,18}

CONCLUSION

Early diagnosis, genetic consultation, adequate screening and correct therapeutic management are essential for patients with VHL syndrome. The cortex-sparing minimally invasive intervention is the contemporary therapeutic option for the treatment of pheochromocytoma in this hereditary syndrome. The retroperitoneal endoscopic adrenalectomy with lateral access is an effective and feasible method even in bilateral localization with this pathology, which however, requires extensive experience in both mini-invasive and endocrine surgery.

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