Case Report

Role of cortical sparing adrenalectomy and novel variant of mutation in patient with von Hippel–Lindau disease

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ABSTRACT

Neurofibromatosis type 1 is the most common phakomatoses and is inherited in autosomal dominant fashion with complete penetrance. Secondary hypertension is common in these patients due to various causes including adrenal tumors. Pheochromocytoma is a rare catecholamine producing tumor seen in 0.5% to 5% of patients with neurofibromatosis. The combination of pheochromocytoma with neurofibromatosis is rarely reported in the literature. We recently encountered an elderly lady with this combination who successfully underwent adrenalectomy. We report the case for the uncommon occurrence and to highlight the relevant literature review about pheochromocytoma in neurofibromatosis.

Key words: Multiple endocrine neoplasia, neurofibromatosis 1, pheochromocytoma

Introduction

Von Hippel–Lindau (VHL) disease is an autosomal dominant disorder which includes a spectrum of highly vascular tumors (hemangioblastomas) in different organs like the retina, cerebellum, medulla and spine. This disorder is also associated with pheochromocytoma, renal cell carcinoma, cysts and adenomas of the pancreas and kidney, and endolymphatic sac and renal cell carcinoma. The morbidity of VHL depends on the organ system involved. The *VHL* gene is mapped to 3p25-26 and it consists of three exons. Mutations in this gene have been identified in ~75% of VHL families, emphasizing the need for screening through surveillance programs, both for early detection and treatment of these tumors. Further, the presence of mutations in the index case will help in screening siblings and early diagnosis of these tumors. We discuss an interesting case with VHL disease with strong familial predisposition.

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Case Report

A young lady (18 years of age) presented with recurrent episodes of headache for 3 years, associated with episodic sweating and palpitations. She was recently documented to have blood pressure (200/160 mmHg) and was referred to us for further management.

A detailed family history revealed the occurrence of central nervous system (CNS) tumors in her father and two of his siblings [Figure 1]. Her father had undergone C7–D3 decompression laminectomy for D2, D3 hemangioblastomas. He recovered, but subsequently developed recurrence of the spinal tumor. At this stage, he was also detected to have a right adrenal mass, and both tumors were left untreated. He developed paraplegia and eventually died following a cerebrovascular accident.

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His two brothers underwent surgery for cerebellar hemangioblastomas at age 46 and 50 years, and they were reportedly well following surgery. Our subject has two siblings aged 17 and 20 years, both of whom had no symptoms suggestive of VHL.

Clinical examination revealed no neurocutaneous markers. Her blood pressure was 170/140 mmHg (supine) and 150/120 mmHg (standing). Fundus examination revealed bilateral papilledema. Her neurological examination was normal.

Her 24-hour urine metanephrine level was 100 mcg and normetanephrine level was >5700 µg [normal range up to 600 mcg (metanephrine) and 900 mcg (normetanephrine)]. She also had impaired glucose tolerance. Computed tomography (CT) scan revealed a large heterogeneous right adrenal mass with patchy peripheral enhancement, a smaller left adrenal mass and an enhancing lesion in the distal body of the pancreas [Figure 2]. Metaiodobenzylguanidine (MIBG) scan showed significantly increased uptake over both adrenal glands [Figure 3]. At surgery, she was found to have an 8-cm tumor in the right adrenal, a 2-cm tumor in the left adrenal and a 2-cm hard pancreatic neoplasm in the distal pancreas [Figure 4]. She underwent bilateral adrenalectomy (right total adrenalectomy, left cortical sparing adrenalectomy) and distal pancreatectomy with splenectomy. Histology of the tumor showed bilateral pheochromocytoma and well-differentiated neuroendocrine tumor of the pancreas. The postoperative period was uneventful, and she was advised regular follow-up. We also advised genetic screening to all her first-degree relatives. After surgery, she was asked to continue Tab. Prednislone 5 mg once daily (in the morning). This patient is on telephonic follow-up and came last month back for follow-up. We planned to taper off steroids and assess response but she herself stopped the medicines and her serum cortisols were checked which were in normal range off all medicines. She is not on any antihypertensive medication. Following surgery, she had no visual complaints and her papilledema had resolved.

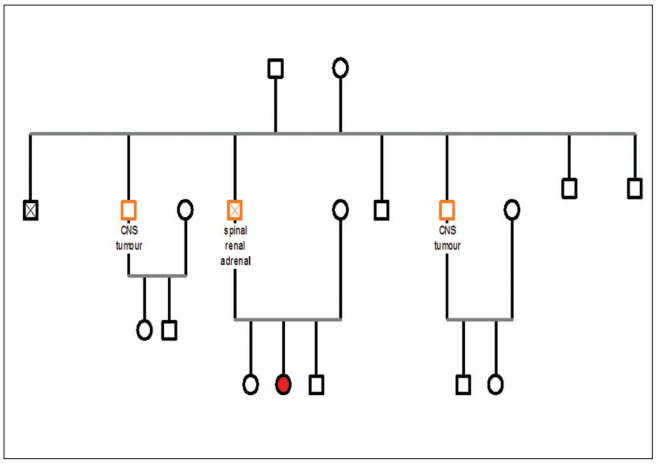

Figure 1: Pedigree analysis of patient

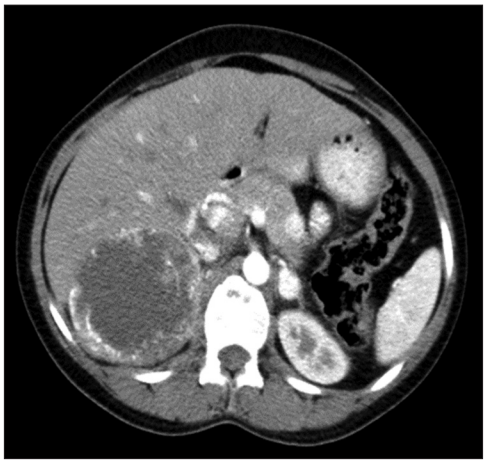

Figure 2: CT scan of patient

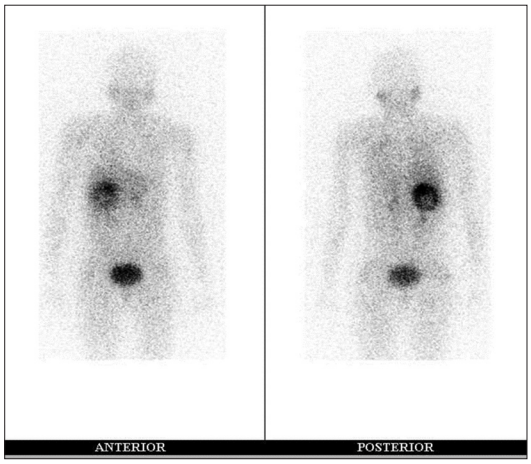

Figure 3: Metaiodobenzylguanidine scan of patient

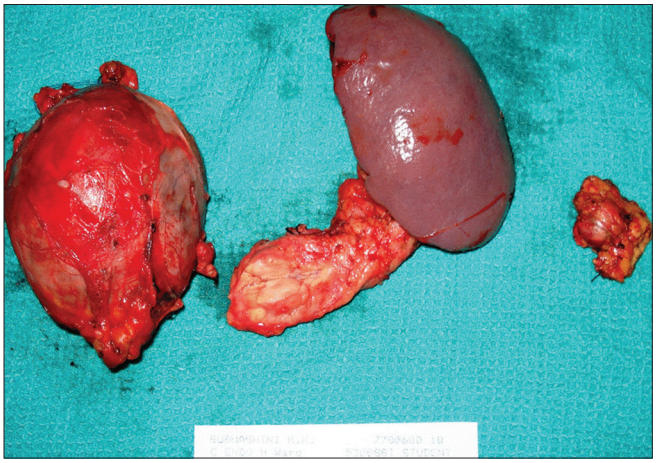

Figure 4: Operative specimen of patient

Two hundred microliters of blood was used for extraction of genomic DNA using the QIAamp DNA blood minikit (QIAGEN, Hilden, Germany). Twenty picomoles of primers was used for amplification of exons 1, 2, and 3 in a 25-μl volume containing 1 unit of amplitaq gold (Applied Biosystems, Foster City, California, USA) and was amplified in a Veriti thermal cycler (Applied Biosystems, USA). The polymerase chain reaction (PCR) products were detected using 1.5% agarose gel and both the sense and antisense strands for all three exons were sequenced using the ABI PRISM 310 genetic analyzer with the ABI PRISM BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems, USA). A variation, c.IVS 2 + 3 A > G, was found in the intronic region following exon 2 of the *VHL* gene [Figure 5]. This variant appears novel as it has not been reported before and is not among the 823 mutations described at http://www.umd.be/vhl/gene.shtml.

Discussion

VHL is a rare autosomal dominant disorder with an estimated prevalence of 2–3 per 100,000 with similar prevalence in both genders across different ethnic groups.[1,2] The *VHL* gene is involved in the regulation of blood vessel formation and it gives rise to highly vascular tumors in various organs. Retinal angiomas are the most common presenting feature in VHL; they are multiple and bilateral in more than 50% of patients.[3] CNS hemangioblastomas are commonly found in the cerebellum, spinal cord or brain stem and they occur in 60–80% of patients with VHL.[3] Lifetime risk of developing renal cell carcinoma is up to 70%, with mean age of presentation at 40 years. These tumors are the most lethal.[3]

Pheochromocytomas are associated with multiple endocrine neoplasia type 2 (MEN 2), VHL, neurofibromatosis type 2 and familial paraganglioma syndromes. Ten to twenty percent of pheochromocytomas are hereditary.[4] The association of VHL with pheochromocytoma is seen in younger patients; these lesions are mostly multiple and bilateral (in up to 50% cases). Pheochromocytoma developed in 7–20% of patients with VHL in a reported series.[5] The average age at diagnosis in VHL patients is around 20 years as compared to 44 years in sporadic cases. This early presentation could also be the result of high-risk families. Pancreatic cysts and serous cyst neoplasm occur in 17–56% patients with VHL.[6] Neuroendocrine pancreatic tumors are rare and are reported in 8–17% of patients with VHL.[6] These lesions may be malignant and metastasize to regional lymph nodes.[7,8] Based on pre-operative imaging alone, it is very difficult to differentiate pancreatic neuroendocrine tumors from serous cyst neoplasm.

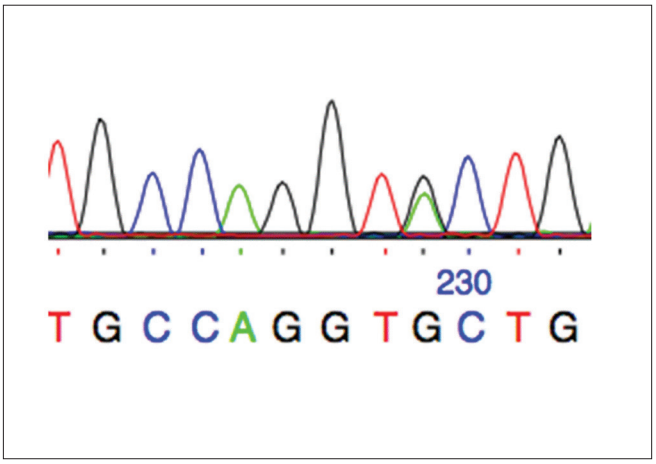

Figure 5: Variant of genetic mutation in patient with Von Hippel–Lindau

Bilateral open adrenalectomy for bilateral pheochromocytoma results in lifelong corticosteroid replacement dependence and the risk of life-threatening Addisonian crisis in up to 23% patients.[9] Cortical sparing adrenalectomy on the side with the smaller tumor has been advocated as a method of steroid independence and with reduced risk of hypoadrenal crisis. Segmental arterial anatomy and dual venous drainage of the adrenal gland support the concept of cortical sparing adrenalectomy and it has been shown to be effective by open or laparoscopic technique; the use of intraoperative ultrasound may be useful in achieving clear tumor margin and optimizing the quantum of residual cortex. A third of one gland with or without the main adrenal vein may be the minimum amount necessary for homeostasis.[10] The outcome of cortical sparing adrenalectomy in patients with VHL with bilateral adrenal disease is encouraging and is recommended as the surgical procedure of choice whenever feasible.[9] It obviates the need for lifelong corticosteroid replacement. It is especially important in patients whose compliance with long-term medication is doubtful and who may not understand the risks of Addisonian crisis. The germline mutation puts all adrenal medullary tissue at risk for tumorigenesis; however, follow-up studies show that the risk of local recurrence is low (3.4–11%).[9]

A c.IVS 2 + 3 A > G variation noted in this patient in the intronic region following exon 2 has not been reported earlier.[11] The presence of such variations at or around splice sites could lead to altered splicing, ultimately leading to the production of an altered protein. While this needs to be corroborated by mRNA and protein workup, the presence of such a variation highlights the need to track similar variations among siblings and other family members of this patient.

In conclusion, we recommend the screening of patients with pheochromocytoma for familial syndromes and a multidisciplinary team approach for the screening, diagnosis, treatment and follow-up of patients and their family with VHL.

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