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Clinical Behavior of a V84L Mutation Pheochromocytoma

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Abstract

A 38 year old male with a history of anxiety, headaches, and diarrhea was referred to the hypertension clinic for evaluation. Clinical work-up revealed a right adrenal mass that was subsequently shown to be a pheochromocytoma and he underwent a total right adrenalectomy, with symptom resolution. The patient was referred to Medical Genetics for an evaluation and genotyping indicated von-Hippel Lindau ('vHL') V84L mutation. Four years later, the patient presented with a recurrent complaint of diarrhea. Diagnostic imaging showed a left ureteral tumor, though this was inconsistent with the gene mutation previously identified. A careful examination of the pathologic specimen disclosed the histologic presence of adrenal cortex at the tumor edge during evaluation. The patient had an adrenal "rest" on the left ureter, thus, he remained true to the clinical behavior of the V84L mutation in that pheochromocytoma was limited to the adrenal gland. Genetic testing is strongly recommended for those patients with cancer genetic risk factors.

Keywords: Pheochromocytoma; Genetic testing; V84L mutation

Introduction

Pheochromocytomas are a rare type of neuroendocrine tumor that arise in the adrenal medulla and are derived from chromaffin cells [1-3]. Research shows that there is a hereditary component in pheochromocytomas in up to 30% of cases. At least ten pheochromyoctoma susceptibility genes have been identified [4]. These gene mutations, while they appear to have different functions, produce clinically and histologically indistinguishable tumors. Clinical features may vary however. In this case report we describe an interesting case of pheochromocytoma in a 38 year old male with a von-Hippel Lindau gene mutation.

Case Report

A 38 year old male with a two month history of anxiety, headaches, and diarrhea was referred to the hypertension clinic for evaluation by his local practitioner. He complained of a two month history of anxiety, headaches, and diarrhea. His past medical history was significant for a diarrheal illness at the age of 12 years that was associated with an increase in blood pressure. Further investigation revealed a right adrenal mass that was subsequently shown to be a pheochromocytoma and he underwent a total right adrenalectomy. After surgery both his diarrhea and hypertension resolved and he was well in the intervening years. Review of systems at the time of this presentation (age 38 years) was positive for sleep disturbances which consisted of awakening secondary to anxiety, and several loose stools per day. His weight was stable, with a body mass index (BMI) of approximately 25. The patient was hypertensive with blood pressures >140 mmHg systolic and >90 mmHg diastolic on several occasions. Upon examination, there was an S4 gallop present, but no other abnormal physical examination findings. His laboratory testing demonstrated normal basic metabolic and lipid panels, as well as a normal urinalysis. His diagnostic workup included a negative electrocardiogram. Given the past history a computerized tomography (CT) scan was performed which showed a left adrenal mass. Urine cortisol, aldosterone, and catecholamine metabolite studies were performed. The urine cortisol and aldosterone concentrations were normal. The urine normetanephrine excretion was severely elevated at 2286 ucg/day (normal <500 mcg/24 hr), as was the urinary metanephrine at 296 ucg/d (normal <96 mcg/24hr). Pre-operatively he was treated with phenoxybenzamine 10 mg twice daily, titrated to 20 mg twice daily. Five mg of amlodipine was added for additional blood pressure control and 10 days prior to surgery, alpha-methyl-tyrosine was administered (titrating up over three days to 500 milligrams four times daily for 7 days before surgery).

In the summer of 1999, he underwent a laproscopic total left adrenalectomy. This surgical intervention rendered him Addisonian and hydrocortisone therapy was initiated. Postoperatively, urinary normetanephrine excretion decreased to <500 ucg/24hr and urinary metanephrine was below assay detection limits. The phenoxybenzamine and the alpha-methyl-tyrosine were discontinued. He continued to receive amlodipine and oral cortisol replacement. The patient was referred to Medical Genetics for an evaluation because of the bilateral pheochromocytomas, suspecting a syndromic form. Genotyping indicated von-Hippel Lindau ('vHL') V84L mutation, an autosomal dominant transmission in which guanine is substituted for tyrosine at nucleotide 463 of the vHL gene resulting in a valine to leucine switch in the vHL protein. In this variant the neuroendocrine tumor tissue is typically limited only to the adrenal gland and while often bilateral, it does not metastasize [1,2]. Four years later, in the summer of 2003, the patient presented with a recurrent complaint of diarrhea. Repeat catecholamine studies demonstrated normetanephrine level elevation to >1500 ucg/24hr, while metanephrine levels remained below assay detection limits. Diagnostic imaging showed a left ureteral tumor, though this was inconsistent with the gene mutation previously identified. Following the presurgical protocol outlined above he underwent a third surgery which confirmed the presence of pheochromocytoma. A careful examination of the pathologic specimen disclosed the histologic presence of adrenal cortex at the tumor edge during evaluation.

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Take Away Messages

This patient had an adrenal "rest" on the left ureter, a known site where adrenal rests occur. Thus, he remained true to the clinical behavior of the V84L mutation in that pheochromocytoma was limited to the adrenal gland. In his case it resided in the third adrenal gland. Genetic testing is strongly recommended for those patients with cancer genetic risk factors. The American Society of Clinical Oncology [6] guidelines suggest genetic testing for all patients with a 10% genetic cancer risk, though the literature suggests rates to be much higher and implying that all patients with pheochromcytoma be referred for genetic testing [4]. A thorough evaluation of the patient's risk for genetic syndrome associated with pheochromocytomas; family and past medical history; and genetic testing should be completed. If positive, treatment modalities which take the germline mutation into consideration, should be initiated [3-8]. The benefit of germline mutation determination include identification of genetic syndromes what may have subsequent cancer risk, increased screening vigilance for additional and/or new pheochromocytomas, and identification of family members at risk [3]. Long term follow-up can also be tailored to the mutations specifications [7].

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