Case Report

**A Rare Case of SDHB and A Variant of Unknown Significance in TMEM127 Gene Positive Paraganglioma (PPGL)**

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Received Date: 04-04-2019
Accepted Date: 04-08-2019
Published Date: 04-10-2019
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**Introduction**

PPGL's and pheochromocytomas are neuroendocrine tumors whose pathogenesis and progression are strongly influenced by genetics. Here we present a case of a dopamine secreting PPGL associated with a novel mutation in TMEM127 gene with a unique presentation.

**Case Presentation**

A 60-year-old lady presented with recent onset of headaches, palpitations, sweating and flushing. History was pertinent for anxiety and depression. She was status post chemotherapy for Non-Hodgkin's lymphoma and underwent surgical removal of meningioma and schwannoma. Genetic testing performed due to her personal history as well as history of a benign kidney tumor in her mother, renal oncocytoma in her son, which revealed SDHB specifically p.I27S (c.380T>G) and she was also heterogeneous for p. M85V variant of TMEM127 gene. Her younger son was also found to have same mutation and 2 other children were negative for any mutation. She had a normal blood pressure and heart rate. Physical exam was pertinent for mildly palpable thyroid. She had been on surveillance for pheochromocytoma/PPGL and had had a positive metabolic screen with significantly elevated 24-hour urinary dopamine levels at 3134mcg (0-510) 6 months prior with a corresponding normal MRI of Adrenals. A repeat MRI Adrenal with contrast in 6 months revealed a 1.4 cm hyperintense enhancing nodule adjacent to the right adrenal corresponding to the area of increased uptake on the I-123 MIBG scan. 24 hour urine studies were repeated which confirmed elevation in dopamine levels at 1379 mcg (52-480) and normal fractionated metanephrines. An FDG PET scan ordered to rule out any bilateral or metastatic disease was not done by her. Chromogranin levels were elevated at 27 ng/ml (1.9-15), TSH was normal at 1.6, urinary cortisol levels were normal. After preoperative optimization, she underwent resection of aortic PPGL and pathology confirmed a chromogranin A positive, Synaptophysin Positive PPGL. She clinically improved except for some symptoms of anxiety.
Figure 1: Abdominal MRI showing Paraganglioma.

Figure 2: A) H&E stain showing paraganglioma. B) The para-aortic tissue shows an epithelioid neoplasm with nested and alveolar growth pattern. The cells strongly and diffusely express synaptophysin and chromogranin. No mitotic activity is observed.

Discussion

About one third to a half of paragangliomas is part of an inherited syndrome as seen in our patient above possible etiologies include neurofibromatosis type 1 (NF1), Multiple endocrine neoplasia type 2 (RET), von Hippel-Lindau (VHL), hereditary paragangliomas caused by mutations in the SDHx group of genes, familial pheochromocytomas (TMEM127, MAX) polycythemia paraganglioma syndrome (EPAS1) or Reed syndrome (FH).

1. Our patient was found to have SDHB specifically p.I27S (c.380T>G) and a variant of unknown significance in TMEM127 gene. She was also heterogeneous for p. M85V variant of TMEM127 gene. Her younger son is also found to have same mutation and other 2 children were negative for any mutation.
2. SDHB-related paraganglioma is often diagnosed as a single extra-adrenal tumor in the absence of a significant family history. A mutation in the SDHB gene is a marker for malignancy and a poor prognostic factor. In a series of 195 patients, metastatic bone disease was present in 7 of 13 patients with SDHB mutation and in none of 68 patients with SDHD or SDHC mutations [2]. If a patient with a paraganglioma has an identified SDHB mutation, evaluation for metastatic disease is indicated.
3. SDHB mutation carriers develop disease at a relatively young age. In one report, the mean age at diagnosis was 28 versus 39 years for patients with sporadic paragangliomas [3].
4. SDHB mutations are also associated with renal cell carcinoma (renal oncocytoma mostly), and paraganglioma syndrome [4].
5. In a pooled analysis of 378 affected patients with SDHB mutations, paraganglioma was more common than pheochromocytoma (78 versus 25 percent), and the paragangliomas were usually sympathetic (71 percent) and sometimes multiple (21 percent) [5].
6. SDHB-mutated paragangliomas typically secrete norepinephrine rather than epinephrine, and some can secrete dopamine (which is associated with a poorer prognosis) [6]. Careful analysis of concentrations of plasma free or urinary fractionated metanephros’s can be used to guide genetic testing in patient with pheochromocytomas or paragangliomas. A dopaminergic or noradrenergic phenotype is suggestive of one of the five SDHx mutations or Von-Hippel Lindau. Whereas adrenergic phenotype implies the presence of a RET mutation [7]. Due to downregulation of phenyl ethanolamine N-methyltransferase (which occurs with SDHx mutations), SDHx tumors are not able to complete the production of catecholamines, and cannot produce epinephrine [7, 8].
7. This fits with the presentation of our patient who had elevated urine dopamine levels and urine normetanephrines, and normal levels of urine metanephrines (the metabolite of epinephrine).
8. In 2010, integrative genomics approaches based on linkage or transcriptomic analyses combined with high-throughput sequencing methods in patients with familial pheochromocytomas identified germline mutations in TMEM127, which encodes transmembrane protein 27. This protein partakes
in the mammalian target of rapamycin (mTOR) signaling pathway. Loss of this mechanism activates MTOR phosphorylation by the Rab5-dependant endocytic pathway.[7,9]. Mutations in this gene have been shown to have causative relationship in patients with familial, bilateral, or apparently sporadic paragangliomas [2,7,10].

9. Essentially, the model proposed is TMEM127 is a tumor suppressor gene according to a two-hit model of inactivation (germline mutation associated with loss of wild-type allele). Microarray-based expression profiling analyses sowed that TMEM127- mutated tumors present transcription signature comparable to that of RET- and NF1 mutated pheochromocytomas that characterized by the enrichment for kinase receptor signaling pathways (cluster 2), differentiating them from SDHx and VHL-related tumors, which are characterized by the hypoxic pathway (cluster 1) [7,11].

10. This case is interesting in the sense that genetic testing revealed two mutations which have been related the development of paragangliomas. Her presentation also has features of tumors produced by both mutations. Further transcriptional evaluation was not done in this case to evaluate whether it fit more with cluster 1 (thus SDH mutation), or cluster 2 (thus TMEM127).

Features that support the SDHB mutation being the causative mutation in this patient include extra-adrenal location, dopamine and norepinephrine secretion (sympathetic and secretory), family history of renal oncycctoma, and a hereditary pattern suggestive of an autosomal dominant distribution. Features opposing that include unclear relationship with NHL, meningiomas and schwannomas with which the patient was diagnosed, non-metastatic, and late presentation.

References


