RET T244I Germline Variant Mutation in a Patient with Pancreatic Paraganglioma and Primary Hyperparathyroidism

Minha Kim1,2, Krist Aploks1,2, Susana Vargas-Pinto1,2 and Xiang Dong1,2,*

1Division of Surgical Oncology, Nuvance Health, Danbury, CT, USA
2Department of General Surgery, Danbury Hospital, Danbury, CT, USA
*Corresponding author: Division of Surgical Oncology, Nuvance Health, Danbury, CT, USA. Email: eric.dong@nuvancehealth.org

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Abstract

Introduction: Paragangliomas are rare neuroendocrine tumors that arise from chromaffin cells. Often termed extra-adrenal pheochromocytomas, these tumors vary with regards to their functionality, location, and malignant potential. Mutations in the RET proto-oncogene are associated with multiple endocrine neoplasia syndrome type 2 (MEN-2) and paragangliomas. The phenotypes of the individual mutations are documented to help determine prognosis.

Case Presentation: We report a case of a 64-year-old man with a history of parathyroid adenoma who developed a pancreatic retroperitoneal paraganglioma. Despite having laboratory evidence of excess circulating catecholamines, the patient’s only presenting symptom was hip pain. The patient underwent resection, and histologic findings were consistent with paraganglioma with lymph node metastasis. Genetic testing revealed a variant of uncertain significance within the RET gene [c.731C>T (p.T244I)].

Conclusions: Paragangliomas are rare extra-adrenal neuroendocrine tumors that can be associated with germline mutations. Our patient was diagnosed with a pancreatic paraganglioma associated with a RET T244I mutation. Identifying patients with germline mutations is important for documenting phenotypic presentations of RET gene variants of uncertain significance, which will allow physicians to provide proper management and surveillance of paragangliomas and other associated tumors.

Keywords: Pancreatic Paraganglioma, Retroperitoneal Paraganglioma, RET Mutation

1. Introduction

Paragangliomas (PGL) are rare extra-adrenal neuroendocrine tumors that can form within sympathetic and parasympathetic ganglia throughout the body (1). Although PGLs arise from neural crest-derived chromaffin cells, individual tumors differ with regards to location and malignant potential. PGL are genetically heterogeneous tumors that have the highest degree of heritability of any endocrine tumor type (2). Germline mutations in a variety of genes, including succinate dehydrogenase subunit B (SDHB), von Hippel Lindau (VHL), neurofibromatosis type 1 (NF1), and RET have been associated to give rise to the tumors (3).

RET is a 21-exon proto-oncogene located on chromosome 10 that has been associated with the multiple endocrine neoplasia type 2 (MEN-2) syndrome. Individuals with RET mutations leading to MEN-2 are at risk for developing hyperparathyroidism, medullary thyroid cancer, and pheochromocytomas/paragangliomas (4). The University of Utah MEN-2 and RET genetic database has documented approximately 200 different mutations, most of which have not been well characterized (5). Here, we describe a patient with a history of parathyroid adenoma who developed a pancreatic retroperitoneal paraganglioma and was found to have a RET mutation variant of unknown significance. This particular variant has not been previously documented in the University of Utah MEN-2 and RET genetic database, making its clinical significance unknown.

2. Case Presentation

A 64-year-old Caucasian male originally presented to his primary care physician due to gradually increasing right hip pain for more than two months. He denied any significant weight loss, night sweats, heart palpitations, or other systemic symptoms. His past medical history included arterial hypertension. Family history included prostate cancer in his father. On exam, the patient had reproducible right hip pain with passive and active motion. Due to con-
cerns for musculoskeletal pathology, magnetic resonance imaging (MRI) of the spine was obtained and had demonstrated mild degenerative changes in the spine and an 11.2 cm mid-abdominal retroperitoneal mass. Contrast enhanced computed tomography (CT) of the abdomen and pelvis was obtained to characterize the mass; this showed an 11 cm ovoid, solid, enhancing mass in the right mid-abdominal mesentery with no associated lymphadenopathy (Figure 1). Given a low suspicion for a catecholamine-producing tumor (which would have necessitated further workup), the decision was made to proceed directly to an image-guided biopsy to establish a diagnosis and guide treatment. The biopsy demonstrated an atypical epithelioid and spindle cell neoplasm. The patient underwent an elective exploratory laparotomy for removal of the mass. Intraoperatively, the tumor was found to be adherent to the head of the pancreas and to the confluence of the superior mesenteric and portal veins. The tumor was resected en-bloc with a margin of pancreatic tissue and the portal vein defect was repaired primarily.

Histologic evaluation of the tumor showed evidence of neoplastic cells arranged in nests and trabeculae within the tumor's vasculature. Round to oval cells with moderate to abundant eosinophilic granular cytoplasm were found within the tumor bulk. Tumor was metastatic to one of the lymph nodes. The tumor immunohistochemistry demonstrated a Ki-67 index < 1%, positive succinate dehydrogenase subunit A (SDHA), SDHB, chromogranin A, and S-100 stains, (Figure 2) and negative cytokeratin CAM 5.2 and human melanoma black-45 (HMB45) stains. These findings were consistent with a PGL with metastasis to the lymph node.

Once the diagnosis was obtained, urine catecholamines were immediately measured. The patient had elevated urine metanephrines 382 mcg/24 h (normal range 44 - 261 mcg/24 h) and urine normetanephrines 650 mcg/24 h (normal range 138 - 521 mcg/24 h) demonstrating a functional PGL. Gallium-68 DOTATE scan showed no evidence of distant metastatic disease. Genetic analysis was performed on a peripheral blood sample using a hybridization-based protocol to enrich for regions of interest. Amplicons from genomic DNA can be sequenced and compared with diseases associated with the RET gene mutation, ampiclons of genomic DNA can be sequenced and compared to reference data to identify specific mutations. Exons 5, 8, 10, 11, 13, 14, 15, and 16 are specifically screened for the presence of RET mutations (8).

Our case describes a patient with no familial history of genetic syndromes and previous parathyroid adenoma who presented with a pancreatic paraganglioma associated with a RET T244I germline mutation. Since mutations in the RET gene can result in a wide range of presentations, attempts have recently been made to catalog the phenotype of individual mutations for prognostic purposes. This mutation, as of yet, is not listed under the University of Utah MEN-2 and RET genetic database. The mutation has, however, been reported once in ClinVAR database as a RET variant of uncertain significance (9).

Mutations in exons 10, 11, 13, 14, 15, and 16 of the RET gene are clinically relevant as they are associated with MEN syndromes (10, 11). The development of MEN-2A has largely been linked to mutations in exons 10 and 11, coding for the cystine-rich extracellular domain of the tyrosine kinase (codon 634 in exon 11 is the most commonly altered) (12). Conversely, in MEN-2B, a point mutation in exon 16 (Met918Thr, M918T) that results in a conformational change in the intracellular binding pocket is responsible for 95% of hereditary cases (10). In our patient, the point mutation was found in exon 4, which codes for a portion of the extracellular domain of the RET gene. A review of the University of Utah MEN-2 database has not demonstrated any mutations responsible for MEN syndrome occurring in this codon (5). Recently, Zhang et al identified two separate mutations in exon 4 that were thought to be linked to familial medullary thyroid carcinoma in an eastern Chinese population (13).

It is unclear if our patient has MEN-2A syndrome. Given his history of parathyroid adenoma and paraganglioma, our patient may have a pathogenic variant. MEN syndromes are mainly inherited in an autosomal dominant fashion, however the probability of de novo pathogenic
variants to cause MEN-2A is approximately 5% (14). The new finding of the renal mass concerning for renal cell carcinoma may suggest that the patient have some variant of MEN syndrome. RET gene is altered in 1.25% in renal cell carcinoma patients (7). Further urological work-up may assist in determining the genetic syndrome our patient harbor. Given our patient’s unique presentation, his case highlights the importance of documenting phenotypic presentations of newly described mutations as it not only helps in determining prognosis factors, but also guide in clinical surveillance.

The clinical course of a patient with PGL is variable, with survival most notably depending on the malignant potential of tumor. Like other neoplasms, PGLs can be considered malignant if distant metastases are present. One study found that, on average, malignant PGLs reoccurred at a distant site roughly 5.5 years after the time of initial diagnosis. Such patients with distant metastases had a median overall survival of 24.6 years (15). Determining the malignant potential of a solitary tumor, however, remains difficult. The Grading System for Adrenal Pheochromocytoma and Paraganglioma (GAPP) was developed to predict potential aggressive behavior of PGL (16). This grading system showed that a histologic pattern of large, irregular sized nest or pseudo-rosette forming cells, high cellularity, the presence of coagulation necrosis and vascular invasion, Ki-67 immunoreactivity > 3%, and norepinephrine producing PGL were associated with malignant potential. Patients with malignant PGL were also found to have rapid disease progression if associated with male sex, older age at diagnosis, synchronous metastasis, large tumor size, elevated dopamine, and not undergoing resection of the primary tumor (15).

Using the GAPP score, our patient would have a low to intermediate risk with a metastatic rate of 3.6 to 60% and five-year survival of 66.8 to 100%. Considering the likelihood the patient has renal cell carcinoma, we would expect his five-year survival to be less than expected according to
the GAPP score.

Given the morbidities associated with PGL’s and other RET-derived tumors, it is recommended that an affected patient’s family members also obtain genetic testing to determine if they have any somatic RET mutations. Patients and family members with RET mutations will benefit from annual biochemical screening, including serum calcium, carcinoembryonic antigen, calcitonin, 24-hour urine metanephrines, and vanillyl mandelic acid (VMA) levels. Patients should also undergo screening ultrasound for thyroid cancer.6

We recommend that patients be followed every four months in the first year after surgery. Afterwards, patients should be seen semi-annually to annually for the following two years, and then annually thereafter. Our recommendation is similar to that of the National Comprehensive Cancer Network (NCCN), which recommends patients have semi-annual follow up for three years after surgery, and then annual follow up for up to ten years. After ten years, NCCN recommends that physicians consider surveillance as clinically indicated (17). We recommend that patients (regardless of mutational status) should undergo life-long surveillance since recurrence and metastatic disease can present years after from the primary diagnosis (15).

Footnotes

Authors’ Contribution: MK, performed literature review, wrote, and revised the manuscript; KA, performed literature review and revised the manuscript; SVP, reviewed and provided clinical advice for the manuscript; XD, reviewed and provided clinical advice for the manuscript.

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Informed Consent: The patient to which this case pertains was informed of the potential for their medical details to be published in an academic journal. The patient was told that no personal identifying information would be shared. Informed consent was obtained.

References

1. Ginesu GC, Barmina M, PalioGiannis P, Trombetta M, Cossu ML, Feo CF, et al. Nonfunctional paraganglioma of the head of the pancreas: A rare case report. Int J Surg Case Rep. 2016;28:38-4. doi: 10.1016/j.soc.2016.09.012. [PubMed: 27689525]. [PubMed Central: PMC5043404].

2. Crona J, Taieb D, Pacak K. New Perspectives on Pheochromocytoma and Paraganglioma: Toward a Molecular Classification. J Hypertens. 2017;35(6):1489-95. doi: 10.1093/hypertens/hwx075. [PubMed: 28398417]. [PubMed Central: PMC5716829].

3. Lenders JWM, Kerstens MN, Amar L, Prejbisz A, Robledo M, Taieb D, et al. Genetics, diagnosis, management and future directions of research of phaeochromocytoma and paraganglioma: a position statement and consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension. J Hypertens. 2020;38(8):1443-56. doi: 10.1097/HJH.0000000000002418. [PubMed: 32429440]. [PubMed Central: PMC7486815].

4. Norton JA, Krampitz G, Jensen RT. Multiple Endocrine Neoplasia: Genetics and Clinical Management. Surg Oncol Clin N Am. 2015;24(4):795-832. doi: 10.1016/j.soc.2015.06.008. [PubMed: 26363542]. [PubMed Central: PMC4571286].

5. MEN2 Database. ARUP Scientific Resource for Research and Education. Utah, USA: ARUP; 2021. [cited 2 Sep 2021]. Available from: https://arup.utah.edu/database/MEN2/MEN2_display.php.

6. Yi JW, Kang HI, Kim SJ, Seong CY, Choi YJ, Choi HY, et al. A Novel RET D898Y Germline Mutation in a Patient with Pheochromocytoma. Case Rep Endocrinol. 2018;2018:865794. doi: 10.1155/2018/865794. [PubMed: 29850289]. [PubMed Central: PMC5924991].

7. My Cancer Genome. RET. Tennessee, USA: My Cancer Genome; 2021. Available from: https://www.mycancergenome.org/content/genes/ret/.

8. Elisei R, Tacito A, Ramone T, Ciampi R, Bottici V, Cappagli V, et al. Twenty-Five Years Experience on RET Genetic Screening on Hereditary MTC: An Update on The Prevalence of Germline RET Mutations. Genes (Basel). 2019;10(9). doi: 10.3390/genes10090968. [PubMed: 31510043]. [PubMed Central: PMC6771015].

9. MGeND. RET p.D898Y. Kyoto, Japan: MGeND; [cited 2 Sep 2021]. Available from: https://mgend.med.kyoto-u.ac.jp/annotation/info/CLINVAR_RCV000557609.

10. Martucciello G, Lerone M, Bricco L, Tonini GP, Lombardi I, Del Rossi CG, et al. Multiple endocrine neoplasias type 2B and RET proto-oncogene. Ital J Pediatr. 2012;38(9). doi: 10.1186/1824-7288-38-9. [PubMed: 22429913]. [PubMed Central: PMC368781].

11. Martins R, Bugalho MJ. Paragangliomas/Pheochromocytomas: clinically oriented genetic testing. Int J Endocrinol. 2014;2014:794187. doi: 10.1155/2014/794187. [PubMed: 24899893]. [PubMed Central: PMC4037021].

12. Hedayati M, Zarif Yeganeh M, Sheikhol Esfami S, Rezghi Barez S, Hoghgoohi Rad L, Azizi F. Predominant RET Germline Mutations in Exons 10, 11, and 16 in Iranian Patients with Hereditary Medullary Thyroid Carcinoma. J Thyroid Res. 2011;2011:264248. doi: 10.4061/2011/264248. [PubMed: 21765987]. [PubMed Central: PMC342031].

13. Zhang L, Li X, Li Q, Ge S, Chen M, Huang S, et al. Rare RET Variant p.D707E in a Chinese Pedigree with Hereditary Medullary Thyroid Carcinoma. Pathobiology. 2017;84(3):352-60. doi: 10.1159/000448845. [PubMed: 27798940].

14. Eng C. Multiple Endocrine Neoplasia Type 2. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, et al., editors. GeneReviews®. Washington, USA: University of Washington; 2019. p. 1993-2022.

15. Hamidi O, Young WJ, Iniguez-Ariza NM, Kittah NE, Gruber L, Bannayan CG, et al. Multiple endocrine neoplasias type 2B and RET proto-oncogene. Int J Pediatr. 2012;38(9):3929-305. doi: 10.1186/1824-7288-38-9. [PubMed: 22429913]. [PubMed Central: PMC368781].

16. Wachtel H, Hutchens T, Baraban E, Schwartz LE, Montone K, Baloch Z, et al. Predicting Metastatic Potential in Pheochromocytoma and Paraganglioma: A Comparison of PASS and GAPP Scoring Systems. J Clin Endocrinol Metab. 2017;102(9):3295-305. doi: 10.1210/jc.2017-00992. [PubMed: 28605453]. [PubMed Central: PMC558076].

17. Shah MH, Goldner WS, Benson AB, Bergsland E, Blazekowski LS, Brock P, et al. Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(7):839-68. doi: 10.6004/jnccn.2021.0032. [PubMed: 34340212].