A Novel MAX Gene MutationVariant in a Patient With Multipleand “Composite”Neuroendocrine–NeuroblasticTumors

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Introduction: Pheochromocytomas (PCCs), paragangliomas (PGLs), ganglioneuroblastomas (GNBs), and ganglioneuromas (GNs) are neuroendocrine neoplasms (NENs) that were thought to share a common embryologic origin from neural crest cells. However, they rarely occur concurrently and recurrently. We describe the case of a 40-years-old woman with “composite PCC-GN” and multiple NENs and neuroblastic tumors.

Case presentation: The patient was first referred to our department at the age of 15 years for paroxysmal hypertension, headache, sweating, and watery diarrhea. Her personal history included the diagnosis of a pelvic GNB with lumbar–aortic lymph node metastases at 11 months. Her family history was positive for cerebral glioblastoma multiforme (father). An abdominal ultrasound showed a right adrenal mass that histologically was a “composite adrenal PCC-GN.” The symptoms disappeared after surgery. At the age of 20 years, the symptoms returned: computed tomography (CT) and 131I-metaiodobenzylguanidine (MIBG) scintigraphy showed an inter-aortocaval mass, found histologically to be an inter-aortocaval PGL. Her symptoms reappeared again at 28 years: CT and magnetic resonance imaging revealed four left adrenal gland nodules, found histologically to be multifocal PCCs with some atypia. Genetic screening for VHL, RET, NF1, Tp53, SDHD, SDHB, SDHC, SDHAF2, SDHAF3, SDHA, and TMEM127 was negative. Mutational analysis of the MAX gene revealed the presence of a novel heterozygous variant, c299G>C (p.Arg100Pro, NM_002382.5) that the bioinformatics prediction programs defined as noxious and causative of pathology.

Conclusion: This report represents the first description of a co-occurrence of multiple composite PCC-GN and neuroblastic tumors. The long timeline of the presentation of the NENs/neuroblastic tumors from infancy to adulthood requires a lifelong follow-up for this patient. Moreover, the importance of this case lies in the presence of a novel MAX gene variant deleterious, harmful, and causative of pathology, confirmed by Sanger
INTRODUCTION

Pheochromocytomas (PCCs) are chromaffin tumors arising from the adrenal medulla, while extra-adrenal chromaffin and non-chromaffin paragangial tumors are classified as paragangliomas (PGLs) (1). PCCs, PGLs, ganglioneuroblastomas (GNBs), and ganglioneuromas (GNs) are neuroendocrine neoplasms (NENs) (1). The International Neuroblastoma Pathology Classification divides neuroblastic tumors into four categories on the basis of their morphology, clinical features, and behavior: neuroblastoma, nodular GNB, intermixed GNB, and GN (2). Neuroblastoma is a malignant tumor comprising neuroblasts with a poor Schwannian stroma, and has the lowest degree of cell maturation and differentiation. It typically undergoes spontaneous regression or differentiation into GNB and GN (3). GNB consists of ganglion cells and neuroblasts with a varying proportion of Schwannian stroma and has an intermediate malignant potential; the nodular subtype is more aggressive, has a worst prognosis and a poorer response to therapy than the intermixed subtype. GN is a benign tumor characterized by the dominance of Schwannian stroma over neuronal elements (4, 5). PCCs are rarely associated with other types of neuroblastic non-PCC tumors with the same embryologic origin, the so-called “composite pheochromocytoma” (6, 7).

From the perspective of precision medicine (8), the recommended workup for NENs includes plasma or 24-h urine fractioned metanephrine, chest/abdominal multiphasic computed tomography (CT), and magnetic resonance imaging (MRI) or fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) in association with functional diagnostic tests. MIBG scintigraphy and somatostatin receptor scintigraphy as well as Gallium-68 [68Ga] SSA radiotracer PET/TC are valuable techniques especially in cases of multiple tumors and disseminated disease (9, 10). Genetic counseling and genetic testing for a number of genes involved in the pathogenesis of PCCs (NF1, RET, von Hippel-Lindau gene [VHL], SDHD, SDHC, SDHB, EGLN1/PHD2, KIF1, SDHA, IDH1, FH, HIF2, SDHAF2, and SDHAF3) are recommended when appropriate (11–15). If multiple or CT-negative tumors are suspected, a 131I-metaiodobenzylguanidine (MIBG) scintigraphy scan should be performed (16–19).

Alpha blockade (phenoxybenzamine or doxazosin) with aggressive volume repletion associated with preoperative rapid-acting intravenous alpha-adrenergic antagonists and beta-blockers are the mainstay of treatment (20). Tumor excision represents the therapy of choice of non-metastatic PCC/PGL. Whenever possible with metastatic disease, primary tumor resection should be recommended in order to alleviate cardiovascular and other symptoms from catecholamine excess or from tumor invasion. For metastatic PCCs/PGLs, there are few established molecular targeted therapies, which have or may have a positive impact. [68Ga] PET/TC gives the predictive power for the efficacy of peptide receptor radionuclide therapy (PRRT) which, together with 131I-MIBG, may have a beneficial efficacy in unresectable disease (10, 21). Radiofrequency ablation, cryoablation, and ethanol injection may be considered in the treatment of metastatic (oligo-metastatic) PCC/PGL (22, 23). Conventional chemotherapy (Averbuch scheme and temozolomide) have been widely used (24, 25).

Conventional external beam radiation therapy (cEBRT) or radiotherapy/radiosurgery (gamma-knife/cyberknife) is recommended for locally unresectable disease (18, 19), in the case of bone metastases and may play a significant palliative role in oligo-metastatic disease.

In recent years, growing interest in precision medicine and molecular diagnosis concerning the expanding etiology for hereditary PCCs and PGL has led to the inclusion of SDHA, TMEM127, MAX, and SDHAF2 as susceptibility genes (26–28). Genetic testing is recommended in patients at clinically high risk who are negative for the classic gene mutations (10, 28).

We describe herein the case of a 40-years-old woman with multiple NENs, comprising a pelvic GNB, right adrenal composite PCC-GN, inter-aortocaval PGL, and multiple left adrenal PCCs, associated with a novel variant of MAX gene mutation.

CASE REPORT

Informed consent was obtained from the patient for the collection, analysis, and publication of personal, familial, clinical, and genetic data and the conduct of genetic blood tests. This manuscript was written in accordance with CARE guidelines.

Pedigree and Family History

The patient’s pedigree is shown in Figure 1. The proband is a 40-years-old Italian woman of Caucasian ancestry. Her father died from glioblastoma multiforme aged 55 years. She has no siblings. The medical history of her children was negative for any reported disease or apparent NEN-associated clinical signs.

Abbreviations: alfaFP, alfa fetoprotein; CgA, chromogranin A; CT, computed tomography; FDG, fluorine-18-fluorodeoxyglucose; GN, ganglioneuroma; GNB, ganglioneuroblastoma; MIBG, 131I-metaiodobenzylguanidine; MRI, magnetic resonance imaging; NEN, neuroendocrine neoplasm; PET, positron emission tomography; PCC, pheochromocytoma, PGL, paragangliomas, VMA, 24-h urine vanillylmandelic acid.

Keywords: composite NEN, pheochromocytoma, ganglioneuroblastoma, MAX gene, paraganglioma

sequencing and never been associated before with multiple composite PCC-GN. The present case underlines the importance of precision medicine and molecular diagnoses for hereditary pheochromocytomas and paragangliomas, suggesting that when they occur in early childhood, it is necessary to perform an extensive genetic investigation and a lifelong follow-up.
Her son (age 14 years) is negative for clinical manifestations and genetic analyses were not performed.

Case Presentation
The timing of the multiple and composite NEN-neuroblastic tumor presentation of the present case is shown in Figure 2.

A 15-years-old Caucasian girl with a history of blood and mucus-free watery diarrhea (up to four times in 24 h), headache, and sweating was referred in 1994 for paroxysmal hypertension. Her personal history included, at the age of 11 months, a GNB with lumbo-aortic lymph node metastases, which was surgically excised and then treated with chemotherapy, radiotherapy, and immunotherapy. Given the symptomatology, an endocrinological workup was performed showing normal 24-h urine vanillylmandelic acid (VMA) and total metanephrines. An abdominal ultrasound and adrenal washout CT scan demonstrated a 5.0-cm right adrenal lesion. The patient underwent abdominal surgery. The histological diagnosis was right composite adrenal PCC-GN. This diagnosis derives from the histological description of an alveolar pattern of round polygonal cells with an eosinophilic granular cytoplasm and spindle cells with a fascication pattern that were outlined by collagen fiber septa. The tumor cells showed round, pleomorphic nuclei with prominent nucleoli. The lymph nodes contained ganglioneuromatous tissue. After surgery, the symptomatology soon improved.

Five years later, the patient presented with a recurrence of paroxysmal hypertension. Neuroendocrine tumor marker tests were positive for 24-h urinary total metanephrines (2,168 µg/24 h; reference range <354 µg/24 h), 24-h urinary catecholamines (239 µg/24 h; reference range <100 µg/24 h), and VMA (VMA urinary spot test: positive). Serum chromogranin A was also positive (CgA 248 ng/ml; reference range <90 ng/ml), while CEA (1.20 ng/ml; reference range <5 ng/ml), NSE (4.00 ng/ml; reference range <10 ng/ml), and alfa fetoprotein (alfaFP 4.90 ng/ml; reference range <5 ng/ml) were normal. An abdominal CT scan showed a 2.2-cm inter-aortacaval right mass. MIBG scintigraphy showed a distinct hot spot in that region (Figure 3). The patient was therefore referred for surgical treatment. The histological diagnosis was inter-aortacaval PGL (see Figure 3). Histological description showed that the tumor consisted of a trabecular-nesting cell pattern with abundant basophilic granular cytoplasm. The tumor cells had oval nuclei with prominent nucleoli and were strongly positive for CgA and NSE on immunohistochemistry. A positivity to S100 antibodies was found at immunohistochemistry.

Eight years later, the patient presented with a recurrence of paroxysmal hypertension. The endocrinological workup was positive for 24-h urinary total metanephrines (1,989 µg/24 h), serum noradrenaline (2,100 pg/ml; reference range 300–900 pg/ml), and serum adrenaline (156 pg/ml; reference range 0–100). Serum CgA (260 ng/ml) and alfaFP (5.31 ng/ml) were also positive. CEA (3.00 ng/ml) and NSE (7.70 ng/ml) were normal. Adrenal washout CT scans showed four non-adenomatous left adrenal masses between 10 and 18 mm (Figure 4). Abdominal MRI confirmed these lesions.
with significantly high signal T2-hyperintensity, suggesting a neuroendocrine (NE) origin. Surgical excision was performed. The diagnosis was *multifocal left PCCs with some atypia*. The macroscopic observation showed four adrenal nodules measured 18, 20, 25, and 27 mm that were enclosed in a thin capsule with a reddish-tan surface and having multiple hemorrhagic areas. Histologically, spindle cells were found in 30% of the neoplasm, with prominent nucleoli. The nodules were strongly
positive for CgA and synaptophysin on immunohistochemistry. Large polygonal cells with eosinophilic granular cytoplasm and strong atypia were found in 40% of the nodule tissue. The Ki-67 proliferation index was >5%. There were no sustentacular cells. The symptoms disappeared and plasma and urinary catecholamines and 24-h urinary metanephrines returned to normal levels.

The patient is currently in good health. She is in follow-up with no evidence of metastases and recurrence. The trend of NE markers over the course of the clinical history is shown in Figure S1. A review of the pathology slides of all the resected tumors confirmed the four diagnoses, which can be summarized as metastatic GNB, bilateral metastatic PCCs, and inter-aortocaval PGL.

METHODS

Genetic Analyses

Next-Generation Sequencing was performed for VHL, RET, NF1, Tp53, SDHD, SDHB, SDHC, SDHAF2, SDHAF3, SDHA, TMEM127, and MAX genes in the Molecular Diagnostic Laboratory for Hereditary Tumors, Veneto Institute of Oncology, Padova and Genetic Ames Group Laboratory, Naples, Italy. Mutation of the MAX gene was confirmed by Integrative Genomics Viewer (IGV), a high-performance visualization tool. Consequently, the MAX gene was also analyzed for intragenic mutations by Sanger sequencing.

RESULTS

No mutations were found in VHL, RET, NF1, Tp53, SDHD, SDHB, SDHC, SDHAF2, SDHAF3, SDHA, or TMEM127. In the MAX gene, a novel heterozygous variant, c299G>C (p.Arg100Pro, NM_002332.5), was found. This variant of germline mutation (from peripheral blood) was analyzed with the bioinformatics prediction programs “Sift,” “PolyPhen,” and “Mutation Taster” at Genetic Ames Group Laboratory, Naples, Italy. See Table 1. The programs have defined that this variant is deleterious, harmful, and causative of pathology. For diagnostic completeness, this variant has been confirmed by Sanger sequencing. The variant is not currently reported in the ClinVar and dbSNP databases and in GnomAD database. See Figure S2.

DISCUSSION

The lesson from this case report highlights several important messages.

First, the metachronic occurrence of PCCs/PGL and neuroblastic tumors. Although previously PCCs, PGLs, and neuroblastic tumors were thought to share the same embryonic origin from neural crest cells, several recent studies showed that the progenitor cells have partly overlapping origin and that chromafin cells of adrenal medulla arise from peripheral glial stem cells or Schwann cell precursors. The simultaneous presence of PCCs and PGLs is rarely found and it is reported in RET-positive patients with MEN2B and also in SDH mutated patients.

To our knowledge, 34 composite PCC-GN cases are reported in literature (6, 31–45). Most of these did not involve any genetic factors, while four cases involved an association with MEN2 (31, 42), VHL (40), or NF1 (43) syndrome.

In this view, the second message of scientific interest is represented by the association of the new described MAX gene heterozygous variant, c299G>C (p.Arg100Pro, NM_002332.5), with the tumors. An association between a MAX gene mutation and composite PCC with a ganglioneuromatous component has never been described in the literature, while just one composite case has been described involving PGL, in an adolescent who had been successfully treated for a stage IV-S neuroblastoma 15 years earlier (46).

MAX is a crucial component of the MYC-MAX-MXD1 transcription factor network, which regulates cell proliferation and differentiation and apoptosis (47). The formation of MAX-MXD1 heterodimers counteracts the dimerization of MYC with MAX, which would act as a transcriptional activator (47). MAX is thus a tumor suppressor gene and its mutation favors the development of hereditary PCCs and PGLs (28, 46–48).

Germline mutations affecting the MYC-associated protein X (MAX) gene are considered a major genetic predisposition factor for the development of hereditary PCC and/or PGL (49). The only tumor suppressor genes known to show a “parent-of-origin” phenotype are the recently described genes SDHAF2 and MAX, located on chromosome 11q12.2 and 14q23, respectively (50). MAX mutations cause hereditary and sporadic PCC/PGL. Genotype-phenotype associations suggested that MAX mutations were associated with bilateral PCC and with an apparent paternal transmission of the disease (47).

Little is known about genetic alterations in sporadic tumors. Mutations in PCC/PGL susceptibility genes are detrimental for neuronal precursor cells. This could explain the apparent rarity of somatic mutations in these genes in apparently sporadic PCC/PGL (51).

Third, the genetic pattern is confirmed by the intermediate biochemical phenotype that in NENs’ patients seems to be associated with a germline MAX gene mutation (52). Given that the patient showed a noradrenalin secretion as biochemical phenotype, “cluster 2” of PCC/PGL would appear to be

| TABLE 1 | In silico prediction table. |
| Genetic variant in Max gene | Predictor tool | In silico predictions information | Score | Range |
| --- | --- | --- | --- | --- |
| c.299G>C p.Arg100Pro NM_002332.5 | Sift | Deleterious | 0.01 | Values <0.05 usually considered intolerant |
| | Polyphen | Probably damaging | 0.93 | Values more than 0.5 usually considered damaging |
| Genetic variant in Max gene | Predictor tool | In silico predictions information | Accuracy | Range |
| c.299G>C p.Arg100Pro NM_002332.5 | Mutation taster | Disease causing | 1 | Values close to 1 corresponding to the most “secure” prediction |
delineated (10). Indeed, before MAX gene identification, our patient had undergone various genetic tests over the years (RET for associations with MEN2; VHL for associations with Von Hippel Lindau Syndrome; NF1 for associations with Neurofibromatosis type 1; and Tp53 for associations with Li Fraumeni Syndrome), all proved negative. Furthermore, SDH gene mutation analyses performed to explore PGL context (53) were also negative.

Literature analysis showed that the case of a young woman with adrenergic phenotype and bilateral PCC with PGL associated to a germline mutation in MAX gene (c.70_73delAAC/p.Lys24fs*40) was reported by Shibata et al. (54). Recently, a case of a 49-years-old woman with bilateral PCC and adrenergic phenotype plus pituitary prolactinoma was also associated to a pathogenic MAX mutation c.296-1G>T (NM_002382), which has not been previously described (55).

Moreover, a 25-years-old patient with multiple PCCs associated with adrenal medullary hyperplasia and with a nonsense germline MAX mutation was described (56).

Other data from literature reported a complex MAX rearrangement with the loss of the wild-type MAX and FUT8 in a family with malignant PCCs, renal oncocytoma, and erythrocytosis (57).

Given the role of MAX as a tumor suppressor gene, the novel heterozygous variant identified and the relative youth of the patient, her follow-up will require considerable attention, given the risk of other endocrine and non-endocrine neoplasms and because loss of MAX function is correlated with greater aggressiveness and metastatic potential (47) than the other mutated pathways involved in these types of tumor. The significance of the MAX variant (c.299G>C; p.Arg100Pro) is currently unknown (49).

In addition to the multiplicity of tumor lesions, the earliness of onset also represents a peculiar characteristic (46, 58).

The mean onset age among the known described patients was 33 years (range 13–58 years), while in our case, the first presentation was in infancy. This is a crucial point in relation to MAX gene penetrance. Indeed, nowadays no reliable penetrance estimations are available for MAX mutation carriers.

Our patient had no family history for PCC/PGL. Given that her father died of glioblastoma multiforme, the present study may suggest an evidence of paternal mode of transmission in MAX mutation carriers. If this mode of inheritance was confirmed, disease is only passed on to children by their father, resulting in the phenomenon of generation-skipping. In this view, it would be even more important to analyze whether the mutation was transmitted to the patient’s son, who would be able to transmit the disease to the offspring as well as the MAX genetic mutation (28).

The limitations of this case include the fact that the assessments performed on the patient over the last 25 years are obviously not all in line with the current guidelines. The 24-h urinary VMA measurement is no longer recommended for the diagnosis of PCC (9). For this reason, no clinical significance can be attributed to the normal concentration of 24-h urinary VMA at the time of the second and the third tumor. In fact, a false-negative rate of 41% has been described in PEHO (progressive encephalopathy with edema, arrhythmia and optic atrophy) and neuroblastoma patients (59). In addition, MIBG scintigraphy is less efficacious than FDG- or F-DOPA-PET for the diagnosis of PGLs; however, the latter techniques were not available at the time of the patient's earlier workups.

In conclusion, we describe, for the first time, a novel heterozygous MAX gene variant: c299G>C (p.Arg100Pro, NM_00.42382), associated with the occurrence of multiple and composite PCC/neuroblastic tumors, occurred yet from infancy in a young women. The molecular mechanism of the MAX gene and the impact of MAX mutations require thorough investigation, to enable the prognosis of affected patients to be promptly established and targeted treatments to be developed.

ETHICS STATEMENT

The patient gave her written consent to sample collection, genetic testing, and the use of genetic test data for the purposes of research. The sample collection and preparation protocols were approved by the Department of Experimental Medicine Sapienza University of Rome, Italy. Institutional review board review and approval was not required for this case report. Consent for publication has been obtained from the patient, including permission for the details/images to be available on the Internet and viewable by the general public.
AUTHOR CONTRIBUTIONS

EG, CP, and FSe conceived and designed the study. FSe, CD, ES, and RP collected the clinical samples and analyzed and interpreted the patient’s data. FSc carried out the genetic analyses that first demonstrated the presence of the MAX gene mutation in this patient in 2011. CP, FSe, AF, and EG co-wrote the manuscript. VB, AI, and AL contributed to the revision of the manuscript. All authors have read and approved the final manuscript.

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The reviewer MP declared a past co-authorship with one of the authors FS to the handling editor.

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