Case Report

SUCCINATE DEHYDROGENASE SUBUNIT B MUTATION PRESENTING WITH SPERMATIC CORD AND NECK PARAGANGLIOMA

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ABSTRACT

Objective: Paragangliomas (PGLs) are rare neuroendocrine tumors often associated with hypersecretion of catecholamines, and are found along the sympathetic chains or parasympathetic paraganglia. PGLs can occur in the context of hereditary syndromes and commonly with succinate dehydrogenase (*SDH*) complex gene mutations. PGLs of the spermatic cord or testes are extremely rare and reports of synchronous spermatic cord and neck PGLs have not been reported before. In previous cases of spermatic cord PGLs, screening for an underlying genetic cause was not performed apart from 1 case where the patient was positive for a *SDH* subunit D mutation.

Methods: We present a case report and a review of the literature using the PubMed, Medline, and Google Scholar databases.

Results: We report the case of a 55-year-old man with a 1-year history of dysphonia resulting in radiological diagnosis of a right vagal PGL treated with radiation. Laboratory investigations excluded a secretory PGL. Simultaneously he was diagnosed with a positron emission tomography-avid testicular mass. An orchidectomy histologically confirmed a spermatic cord PGL. Genetic testing was positive for a heterozygous germline variant c.380T>G, p.(IIe127Ser) within exon 4 of the *SDH* subunit B gene which has not been reported with spermatic cord PGL before.

Conclusion: This case reports the synchronous occurrence of spermatic cord and neck PGLs with *SDH* subunit B mutation. It highlights the necessity for clinicians to screen patients with PGLs for an underlying genetic etiology, even if found in unusual locations, as this has significant implications for future treatment, screening, and family planning. **(AACE Clinical Case Rep. 2018;4:e324-e328)**

Abbreviations:
18F-FDG PET = 2-deoxy-2-[fluorine-18]fluoro-D-glucose positron emission tomography; **PCC** = pheochromocytoma; **PGL** = paraganglioma; **SDH** = succinate dehydrogenase; **SDHB** = succinate dehydrogenase subunit B

INTRODUCTION

Paragangliomas (PGLs) are vascular neuroendocrine tumors, which derive from either sympathetic chromaffin tissue of the adrenal medulla and are termed pheochromocytomas (PCCs), or from extra-adrenal chromaffin cells of the paraganglia along the sympathetic chains and are termed sympathetic PGLs. The latter are usually located in the chest, abdomen or pelvis. Parasympathetic PGLs, on the other hand, arise from the non-chromaffin paraganglia that are distributed along the parasympathetic nerves in the head, neck, and upper mediastinum (1,2). PCCs and sympathetic PGLs are very similar histologically as well as functionally and generally produce large amounts of catecholamines and usually cause symptoms. Parasympathetic

Submitted for publication January 21, 2018
Accepted for publication February 5, 2018
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DOI:10.4158/ACCR-2018-0037

PGL are histologically similar but are usually not functional. PGLs and PCCs are usually benign tumors and malignancy is defined as the presence of distant metastases (1,2). The origin of PGLs of the spermatic cord is not fully clear, however, it has been postulated that paraganglionic nests in the spermatic cord may occur in the setting of dysgenesis during embryogenesis (3).

Most PCCs and PGLs occur as sporadic tumors but a significant proportion are associated with hereditary syndromes such as multiple endocrine neoplasia type 2, von Hippel-Lindau disease, Carney triad, neurofibromatosis type 1, or mutations in the genes encoding different subunits of the succinate dehydrogenase (*SDH*) complex. Several other genes have also been identified (4). Patients with hereditary tumors that have underlying *SDH* subunit B (*SDHB*) gene mutations are at a high risk of developing malignant PCCs, PGLs, or multiple lesions (5).

We report the case of a 55-year-old man who presented with dysphonia, was radiologically diagnosed with a right neck PGL, and was subsequently treated with radiotherapy. A scan using 2-deoxy-2-[fluorine-18]fluoro-D-glucose positron emission tomography (18F-FDG PET) also revealed a left testicular lesion, which following orchidectomy was confirmed as a PGL. There were no additional 18F-FDG PET-avid lesions. Genetic testing detected a *SDHB* mutation.

CASE REPORT

In 2016 a 55-year-old man presented with a 1-year history of dysphonia. He was diagnosed with palsy of the right vocal cord and a lesion in the right carotid sheath. The patient underwent magnetic resonance imaging of the brain and neck which showed a well-defined T1 and T2 hypointense, heterogeneous lesion in the carotid space measuring 27 × 15 mm and extending along a length of 45 mm craniocaudally with post-contrast images demonstrating mild enhancement. There was anteromedial displacement of the internal and external carotid arteries. A computed tomogram of the neck showed dense enhancement of the focal lesion in the carotid space. Ultrasound of this lesion showed a solid, hypoechoic structure deep to the right internal jugular vein. A fine-needle aspiration was deemed unsafe on ultrasound examination.

Multidisciplinary meetings at 2 tertiary hospitals agreed that the findings were typical of a right vagal PGL and the patient was recommended to proceed with radiotherapy. A scan using 18F-FDG PET was performed prior to radiation and demonstrated an avid tumor in the right nasopharyngeal region with inferior extension or possible nodal involvement in 2 level IIb nodes. Further investigations excluded a secretory PGL and in detail showed: normetadrenaline at 436 pmol/L (reference range is <900 pmol/L), metadrenaline at 244 pmol/L (reference range is <500 pmol/L), 3-methoxytyramine at 30 pmol/L (reference range is <110 pmol/L). His 24-hour urinary catecholamines were within normal range with hydroxymethylmandelic acid at 22 μmol/24h (reference range is <25 μmol/24h), noradrenaline at 483 nmol/24h (reference range is <750 nmol/24h), adrenaline at 41 nmol/24h (reference range is <80 nmol/24h), dopamine at 1,180 nmol/24h (reference range is 200 to 3,500 nmol/24h), normetadrenaline at 1.6 μmol/24h (reference range is <2.3 μmol/24h), metadrenaline at 0.81 μmol/24h (reference range is <1.7 μmol/24h), 3-methoxytyramine at 0.7 μmol/24h (reference range is <1.3 μmol/24h), 5-hydroxyindoleacetic acid at 20 μmol/24h (reference range is <40 μmol/24h).

The patient received a total dose of 50.00 Gy in 25 fractions over 32 days to the primary lesion and lymph node areas II to VII on the right side. Serial follow up 18F-FDG PET scans are shown in Figure 1.

The patient's initial 18F-FDG PET scan also revealed abnormal uptake in the left testis and discrete uptake in the left lobe of the prostate (Fig. 2 *A*). Scrotal ultrasound

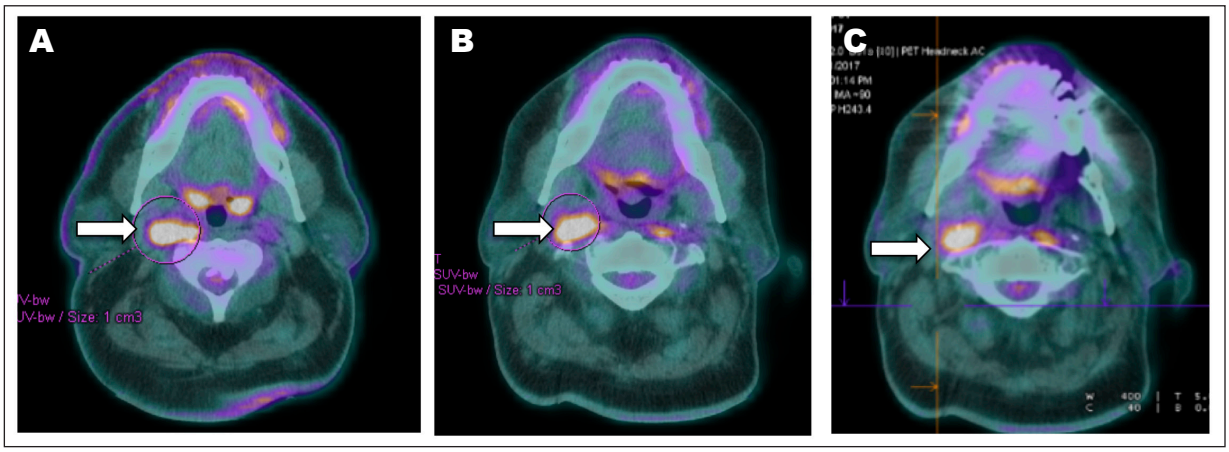

Fig. 1. Images showing the progression of the neck paraganglioma (arrows) using 2-deoxy-2-[fluorine-18]fluoro-D-glucose positron emission tomography. (*A*) Initial tomogram showing an avid tumor in the right nasopharyngeal region with inferior extension. (*B*) Subsequent tomogram 11 months later showing an unchanged, avid lesion in the right carotid space. (*C*) tomogram at 14 months showing the lesion in the right carotid space with reduced tracer avidity.

showed a solid lesion in relation to the left spermatic cord measuring 21 × 21 × 15 mm. Prostate-specific antigen was 0.61 μg/L (reference range is <3.5 μg/L), alpha fetoprotein was 2.2 μg/L (reference range is <10 μg/L), human chorionic gonadotrophin was 0.2 IU/L (reference range is <5 IU/L). The patient underwent a left orchidectomy and macroscopically this demonstrated a firm nodule immediately superior to the testis measuring 20 × 20 × 15 mm (Fig. 2 *B*). It was associated with the epididymis and well demarcated from the testis.

Microscopically the tumor exhibited a nested pattern of variably sized polygonal cells with associated spindled cells and arborizing vessels in keeping with a PGL (Fig. 2 *C*). The tumor cells were immunoreactive for chromogranin, neuron-specific enolase, synaptophysin and CD56. S-100 staining highlighted sustentacular cells (Fig. 2 *D* and *E*). The Ki-67 immunolabeling index was <1%. Immunohistochemistry for tyrosine hydroxylase was not performed. There was no immunoreactivity for melanoma antigen recognized by T cells 1 (Melan-A) or human melanoma black 45 (HMB-45). Follow up 18F-FDG PET scans and magnetic resonance imaging of the scrotum showed complete removal of the lesion. Additional lesions have to date not been identified with serial follow up 18F-FDG PET scans or computed tomography scans.

Polymerase chain reaction and sequence analysis of the *SDHB* gene (NCBI: NM_00300.2 and NG_012340.1) for detection of point mutations and small intragenic deletions or insertions were carried out on DNA from a sample of blood and were positive for the heterozygous germline variant c.380T>G, p.(IIe127Ser) within exon 4 of the *SDHB* gene.

The patient's past medical history was significant for ischemic heart disease, hypertension, schizophrenia, type 2 diabetes mellitus and gastroesophageal reflux. His family history was positive for multiple PCCs on the paternal side.

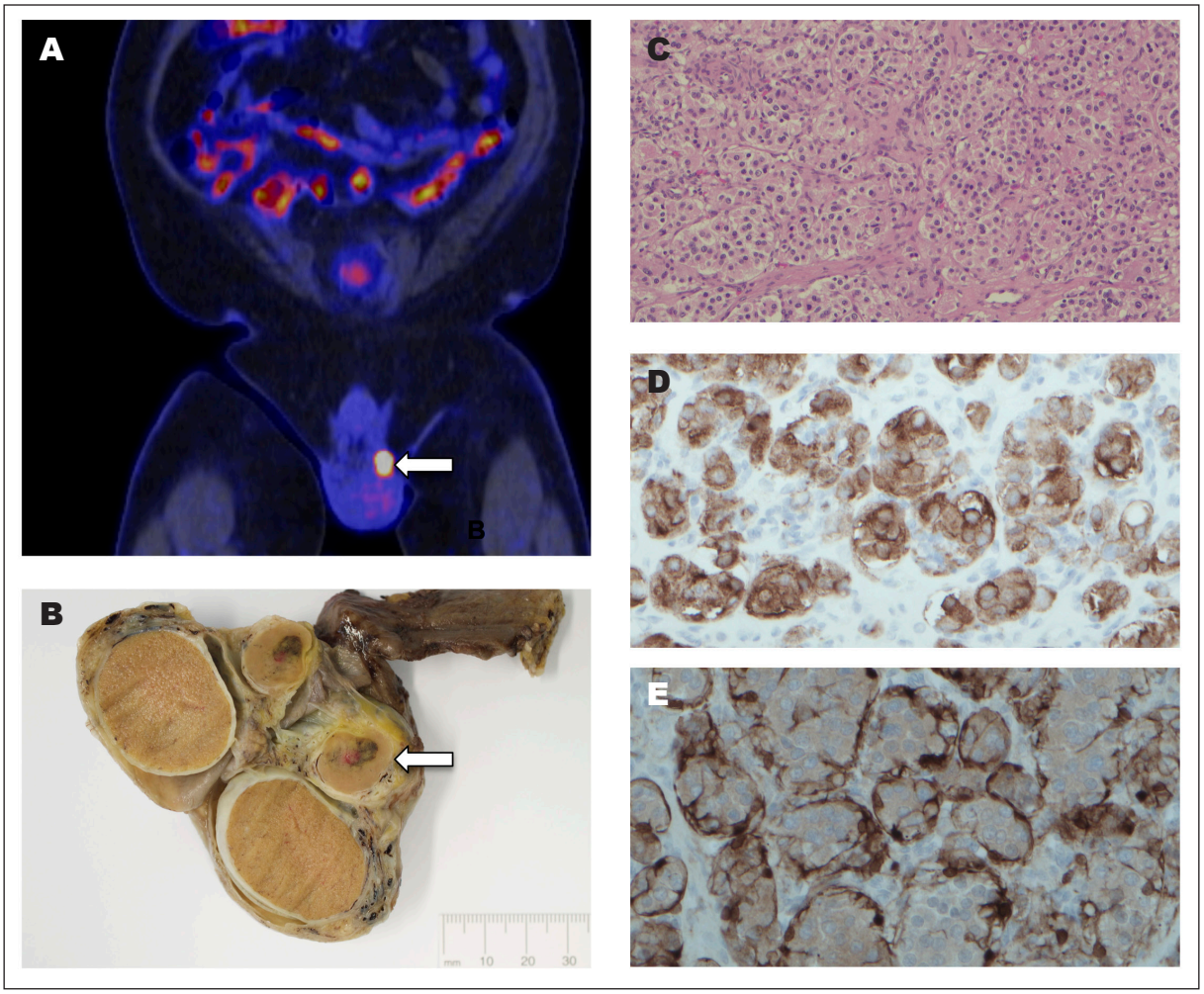

Fig. 2. Radiologic, macroscopic, and microscopic appearance of scrotal paraganglioma. (*A*) 2-deoxy-2-[fluorine-18]fluoro-D-glucose positron emission tomography showing intense uptake in the left testis (arrow). (*B*) Macroscopic appearance of left orchidectomy with paraganglioma (arrows). (*C*) Typical histology showing nests of polyclonal and uniform cells, characteristic Zellballen pattern (hematoxylin and eosin stain; ×100). (*D*) Chromogranin A immunohistochemistry showing positive staining (×200). (*E*) S100 immunohistochemistry with positive staining (×400).

DISCUSSION

PGLs of the spermatic cord or testes are extremely rare tumors. A literature review of several databases including PubMed, Medline, and Google Scholar regarding testicular and paratesticular PGLs was performed. Based on this literature review, only 14 case reports have been published to date (Table 1). Multiple or synchronous lesions are even rarer. There was 1 case published by Abe et al (6) that reported a left spermatic cord PGL 5 years after bilateral carotid body PGL and bilateral PCC. Makris et al (7) published the first case of a primary testicular (not spermatic cord) PGL invading the testis with possible lymph node metastasis. In 2017 Peng et al (8) published a case of an invasive testicular and spermatic cord PGL with lymph node metastases to the retroperitoneal area. To the best of our knowledge, this is the first report of synchronous spermatic cord and carotid body PGLs. Interestingly, none of the previously reported spermatic cord PGLs were associated with *SDHB* mutations (Table 1).

Our patient was radiologically diagnosed with a neck PGL but his 18F-FDG PET-avid testicular lesion was only later found to be a PGL after orchidectomy. While a metastatic lesion may have occurred, it seems more likely that the findings represent synchronous lesions given the absence of other 18F-FDG PET-avid areas on repeated imaging. This postulation is supported by the patient's positive *SDHB* mutation, which predisposes patients to multiple lesions (4). Furthermore, in a recent study investigating malignant PGLs, metastases in *SDHB* mutations were most often found in bones, lungs, mediastinum, lymph nodes, and liver (5). The finding of a *SDHB* mutation in our patient has important implications for future management and screening for both the patient and his extended family, as *SDHB* germline mutations are known to have a higher risk of malignancy and predispose patients

Table 1
Spermatic Cord and Testicular Paraganglioma Reports

Age	Symptoms	Tumor site	Succinate dehydrogenase gene mutation	Additional tumors	Reference
37	10-year history of painless scrotal mass	Right spermatic cord	N/A	No	Eusebi et al (11)
52	10-year history of painless scrotal mass	Left spermatic cord	N/A	No	Soejima et al (12)
18	2-year history of painless scrotal mass	Right spermatic cord	N/A	No	Bacchi et al (13)
37	9-month history of painless scrotal mass	Right spermatic cord	N/A	No	Mashat et al (14)
40	Painless scrotal mass	Left spermatic cord	N/A	No	Attaran et al (15)
52	1-month history of tender scrotal mass	Right spermatic cord	N/A	No	Young et al (16)
55	1-month history of painless scrotal mass	Left spermatic cord	N/A	Bilateral carotid body paragangliomas and phaeochromocytomas 5 years prior	Abe et al (6)
69	Weight loss, malaise and painless scrotal mass	Right spermatic cord	N/A	Prior non-small cell carcinoma of the lung 5 years prior	Garaffa et al (17)
33	Longstanding scrotal pain, and scrotal mass	Right spermatic cord	N/A	No	Gupta et al (3)
45	Painless scrotal lump for months	Left spermatic cord	Yes, subunit D	No	Alataki et al (18)
50	3-month history of painless scrotal mass	Left spermatic cord	N/A	No	Majdoub et al (19)
66	4-month history of painless scrotal mass	Right testis	N/A	Nodular lesion of the left subdiaphragm	Makris et al (7)
40	Painless scrotal mass	Left spermatic cord	N/A	No	Kwon et al (20)
28	17-year history of headaches, palpitations and sweating, 2 painless scrotal masses	Right spermatic cord and testis	N/A	Multiple regional lymph node metastases	Peng et al (8)

Abbreviation: N/A = not available.

to further tumors including renal cell carcinomas, papillary thyroid carcinomas, gastrointestinal stromal tumors, and pituitary lesions (9).

Interestingly, despite the size of the tumor, our patient's urinary catecholamines and plasma metanephrines suggested the tumor was non-secretory. Immunostaining for tyrosine hydroxylase and measurement of its activity would have provided additional information regarding the biosynthetic function of catecholamines in the tumor cell.

CONCLUSION

This case highlights the necessity for clinicians to screen every patient with a PGL for an underlying genetic etiology even if found in an unusual location such as the spermatic cord. Failure to do so may result in delayed detection of further tumors and result in poor patient outcomes. If genetic testing is positive, it is of utmost importance to implement regular surveillance for early detection and removal of associated tumors. It is highly advisable to use established society guidelines in the care of patients with PGLs or PCCs (10).

ACKNOWLEDGMENT

We would like to thank our patient for providing consent to participate in this case report.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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