

Novel Germline SDHB Mutation in a 35-Year-Old Male with Malignant Bladder Paraganglioma

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ABSTRACT

Objective: Up to 25% of pheochromocytomas and paragangliomas (PGL) are associated with germline mutations in RET, VHL, NF1, and subunits A, B, C, or D of succinate dehydrogenase (SDH). SDHB mutations are associated with malignant extra-adrenal PGL. Codon specific genotype-phenotype relationships have not been identified. Herein is described a case of malignant bladder paraganglioma from a novel W200R SDHB mutation. The literature is reviewed and clinical management is discussed.

Methods: Literature review was performed to analyze the relationship between SDHB and PGL, yielding 45 unique articles, which were reviewed and cross-referenced.

Results: SDHB mutations have a 50% penetrance by age 35, 1/3 of paragangliomas are multifocal, 31 to 48% are malignant, and 50 to 70% of these malignant PGL develop metastases.

Conclusion: Based on the aggressive nature of the SDHB mutation, we recommend preoperative staging, an aggressive treatment regimen, and intensive screening for recurrence.

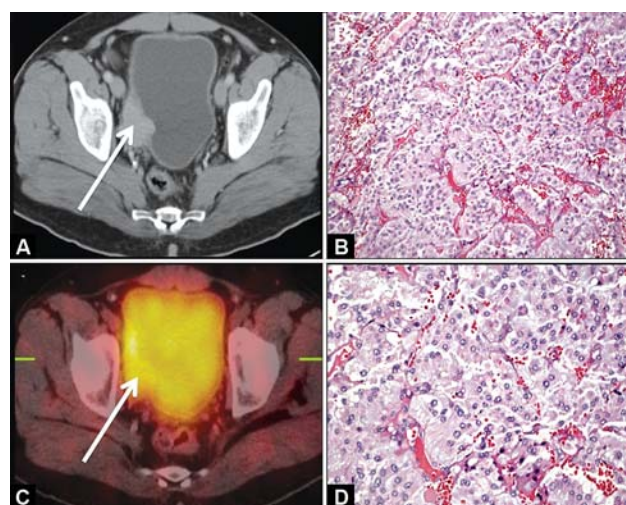
Keywords: Bladder paraganglioma, Succinate dehydrogenase subunit B (SDHB), Extra-adrenal pheochromocytoma.

INTRODUCTION

Bladder paragangliomas (PGLs) make up fewer than 1% of all pheochromocytomas (PCCs) and fewer than 0.06% of all bladder tumors.^{1,2} Due to the rarity of disease, there is a paucity of data on the natural history of bladder PGLs. A high percentage of extra-adrenal PGL is associated with a mutation in subunit B of the succinate dehydrogenase (SDH) complex. In addition, SDHB mutation positive PGL are frequently extra-adrenal and malignant. Codon specific genotype-phenotype relationships have not been clarified for SDHB mutations. The purpose of this paper is to discuss aggressive nature of the SDHB mutation and provide clinicians with a better understanding of clinical implications of this mutation in patients with paraganglioma. Herein is described a case of malignant bladder paraganglioma in a young male with a novel W200R SDHB missense mutation in the 5th exon of the SDHB gene. The pertinent literature is reviewed, and implications for clinical management are discussed.

CASE

A 35-year-old male with a 17-year history of uncontrolled type-1 diabetes and hypertension (HTN) controlled with lisinopril (10 mg) developed proteinuria. A computed tomography (CT) scan identified a 5 cm mass involving the right lateral aspect of



Figs 1A to D: (A) Computed tomography (CT) scan showing enhancing mass involving right side of bladder, (B) 20X H&E, medium power, section of the tumor demonstrating well-defined nests of cuboidal cells in a background stroma that is highly vascularized, (C) 40X H&E, high power, section of the tumor: Individual cells with abundant granular cytoplasm, (D) I-123 meta-iodobenzylguanidine (MIBG) fused with CT scan revealing intense uptake associated with the bladder paraganglioma.

the bladder (Fig. 1A). Urine cytology was benign. Paraganglioma was not suspected clinically. Cystoscopy and transurethral resection of the tumor were attempted, but hypertensive crisis and hemorrhage necessitated truncation of

the procedure after biopsy. Immunohistochemistry and histopathology were consistent with invasive paraganglioma of the muscularis propria of the bladder (Figs 1B and C). Plasma free normetanephrines were 1238 pg/ml (normal < 149 pg/ml) and 24-hour urine normetanephrine levels were 3016 ug (normal < 600 ug), confirming the diagnosis. Cross sectional imaging and I 123 meta-iodobenzylguanidine (MIBG) scan identified locoregional disease but no metastases (Fig. 1D). Alpha and beta blockade were initiated in preparation for a formal resection.

A novel W200R SDHB germline missense mutation in the fifth exon of the SDHB gene was identified. The family history was negative for pheochromocytoma. Partial cystectomy and formal nodal dissection was performed. Final pathology revealed a 4.0 × 2.0 × 1.9 cm paraganglioma extending through the muscularis propria and into the perivesicular fat with lymphovascular invasion but negative margins. A single positive lymph node was found in the right obturator basin. The remaining lymph nodes from the external and common-iliac basins were all negative.

METHODS

The pertinent medical records (history, labs, imaging, and histopathology) were reviewed. A review of the English language literature since 2005 using the PubMed database was performed to analyze the relationship between SDHB and PGL. The search was constrained to articles published within the past 5 years to reduce the chances of over counting. The search terms SDHB, malignant paraganglioma, bladder paraganglioma, and bladder pheochromocytoma resulted in 63 results. The resulting papers were reviewed and cross-referenced for uniqueness and relevance. The final literature review yielded 45 unique articles.

RESULTS

The literature review is summarized in Tables 1 to 3.³⁻¹⁶ The PGL locations and malignancy rates are displayed in Table 1. Roughly one quarter of all extra-adrenal tumors are associated with SDHB mutations. The Burnichon et al (2009)⁴ study includes 80 patients from the previous Amar et al (2005)³ study. However, due to the difficulty in identifying the double-counted population, all data from the Burnichon study are displayed in the table. Reports by Brouwers (2006)⁶ and Amar (2007)⁷ are limited to malignant PGL and pheochromocytomas. These two articles, therefore select for a higher percentage of SDHB positive patients, because SDHB mutations have a greater tendency to be malignant. SDHB mutations are associated with 28 to 76% of malignant pheochromocytomas and PGLs, of which a majority is associated with malignant PGLs.³⁻⁷

Table 2 summarizes the studies that select for SDHB positive pheochromocytoma and PGL populations. The data shows that approximately 3/4 of SDHB positive tumors are extra-adrenal (63-79%), with one study suggesting a 97% extra-adrenal rate.⁸ In addition, the malignancy rate for the SDHB positive populations was 31 to 48%, consistent with commonly cited figures.⁸⁻¹¹

Table 3 documents the SDHB positive bladder paraganglioma cases reported in the literature. To date, there are seven unique SDHB mutations related to bladder PGLs described in the PubMed database.¹⁷ Roughly half of the cases presented with multifocal disease (4/7) and metastases (4/7).^{10,12-15}

DISCUSSION

Up to 25% of pheochromocytomas and PGLs are associated with germline mutations in RET, VHL, NF1, and subunits A, B, C, or D of the SDH complex. This paper is the first report of

Table 1: Location and malignancy rates of pheochromocytomas and paragangliomas. Five large studies were identified in the contemporary English language literature describing the SDHB mutations, location and malignancy rates of pheochromocytomas and paragangliomas. The Burnichon study contains 80 patients already reported in the 2005 Amar article

Article	Location	Patient population	N	Total			SDHB Mutation (+)			Malignant	
				Adrenal	Extra-adrenal	Both sites	Adrenal	Extra-adrenal	Both sites	Total	SDHB
Amar et al (2005) ³	France	Familial and sporadic PCC/PGL	314	256 (82%)	50 (16%)	8 (2%)	4 (2%)	14 (28%)	3 (38%)	54 (17%)	15 (28%)
Burnichon et al (2009) ⁴	France	HNPGL and/or other extra-adrenal PGL	445	0	445 (100%)	0	0	96 (22%)	0	49 (11%)	37 (76%)
Neumann et al (2002) ⁵	Germany/ Poland	Non-familial and non-syndromic PCC/PGL	271	241 (89%)	30 (11%)	0	6 (2%)	6 (20%)	0	N/A	N/A
Brouwers et al (2006) ⁶	United States	Malignant PCC/PGL	39	14 (36%)	25 (64%)	0	1 (7%)	12 (48%)	0	39 (100%)	13 (33%)
Amar et al (2007) ⁷	France	Malignant PCC/PGL	54	29 (54%)	25 (46%)	0	7 (24%)	16 (70%)	0	54 (100%)	23 (43%)

Note: SDHB–Succinate dehydrogenase subunit B, HNPGL–Head and neck paraganglioma, PCC–Pheochromocytoma, PGL–Paraganglioma.

Table 2: Succinate dehydrogenase subunit B mutation positive cases. 4 studies were identified that describe SDHB mutation positive pheochromocytoma and paraganglioma cohorts

Article	Location	Patient population	N	Total			SDHB Mutation (+)			Malignant SDHB
				Adrenal	Extra-adrenal	Both sites	Adrenal	Extra-adrenal	Both sites	
Timmers et al (2007) ⁸	Netherlands	All SDHB (+) PCC/PGL	29	1 (3%)	28 (97%)	0	1 (100%)	28 (100%)	0	14 (48%)
Neumann et al (2004) ⁹	Germany/ Poland	All SDHB (+) PCC/PGL	25	8 (32%)	16 (64%)	1 (4%)	8 (100%)	16 (100%)	1 (100%)	N/A
Srirangalingam et al (2008) ¹⁰	England	All SDHB(+) PCC/PGL	16	4 (25%)	10 (63%)	2 (12%)	4 (100%)	10 (100%)	2 (100%)	5 (31%)
Benn et al (2006) ¹¹	International	All SDHB (+) or SDHD (+) PCC/PGL	43	2 (5%)	34 (79%)	7 (16%)	2 (100%)	34 (100%)	7 (100%)	19 (44%)

Note: SDHB–Succinate dehydrogenase subunit B, HNPGL–Head and neck paraganglioma, PCC–Pheochromocytoma, PGL–Paraganglioma.

Table 3: Unique SDHB mutations associated with bladder paragangliomas. 6 studies were identified that describe 7 unique SDHB mutations associated with bladder paragangliomas. The case from this paper is included in the Table

Authors	Country	DNA	Amino acid	Variation type	Disease site	Malignant
Ghayee et al (2009) ¹²	United States	c. 136C > T	p.Arg46X	Nonsense	Bladder, intra-cardiac, Neck (Mf.)	No
Benn et al (2003) ¹³	Australia	c.194T > A	p.Leu65H	Missense	Bladder, aortic bifurcation (Mf.)	Yes
Benn et al (2003) ¹³	Australia	c. 200 + 3G > C		Splicesite	Bladder, secondary site (Mf.)	N/A
Bauters et al (2003) ¹⁴	France	c.263T > C	p.Leu88S	Missense	Bladder	Yes
Gimenez-Roquepio et al (2003) ¹⁵	France	c.725delC		Frameshift	Bladder	N/A
Lawrence et al (2004) ¹⁶ and Srirangalingam et al (2008) ¹⁰	UK	c.590 > G	p.Prol97R	Missense	Bladder	Yes
Srirangalingam et al (2008) ¹⁰	UK	c.292T > C	p.Cys98R	Missense	Bladder, Pelvic (Mf.)	Yes
Case report	USA	c.598T > C	p.Trp200R	Missense	Bladder	Yes

Note: SDHB–Succinate dehydrogenase subunit B, HNPGL–Head and neck paraganglioma, PCC–Pheochromocytoma, PGL–Paraganglioma, Mf–Multifocal disease, UK–United Kingdom.

a bladder paraganglioma associated with germline missense mutation W200R in the fifth exon of the SDHB gene. Currently, there is no clear genotype-phenotype relationship for the SDHB gene and many of the other genes, making it difficult for clinicians to choose the best treatment regimen. By exploring the documented cases associated with SDHB mutations, we hope to provide clinicians with a guide for clinical management.

SDHB mutations lead to paraganglioma syndrome type 4 and are strongly associated with malignancy. Individuals inherit SDHB mutations in an autosomal dominant manner.¹⁸ Approximately 1/3 of SDHB-associated PGLs are multifocal. Disease is usually diagnosed in the 3rd and 4th decades of life, and accordingly, there is a 50% penetrance by age 35.¹⁹ Up to 75% of SDHB positive tumors are extra-adrenal, and 31 to 48% are malignant.¹⁵ SDHB mutation positive tumors constitute between 28 and 76% of all malignant pheochromocytomas and PGLs.³⁻¹¹ Approximately 20 to 70% of PGLs are SDHB positive. Because of the high prevalence of SDHB mutations in extra-adrenal or malignant PGLs, screening for the SDHB mutations is warranted in these patients.³

Aggressive management appears warranted for pheochromocytomas and PGLs with SDHB mutations based on the relatively high probability of malignancy and the natural history of these tumors. The five-year survival rate at first metastasis is 36%, with a median survival of 42 months.⁷ Given the young age of onset, aggressive nature, and high rate of recurrence of SDHB mutation associated pheochromocytomas and PGLs, it is important to employ genetic testing, preoperative staging, an aggressive treatment regimen, and routine surveillance for recurrence.

CONCLUSION

This is the first report of germline missense mutation W200R in the SDHB gene. This patient presented with an unsuspected aggressive bladder paraganglioma. The high rate of extra-adrenal and malignant tumors caused by SDHB mutations underscores the importance of genetic screening. The aggressive nature of SDHB positive tumors warrants a more aggressive treatment strategy. Further clarification of genotype-phenotype

relationship for specific SDHB mutations might have meaningful clinical implications and should be pursued.

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