A Case of a "Voiding" Hypertension

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INTRODUCTION

Paragangliomas are rare neuroendocrine tumors arising from extra-adrenal autonomic paraganglia. At the cellular level, they are indistinguishable from pheochromocytomas, which are intra-adrenal. Localization to the bladder wall is infrequent (<5%) and they constitute less than 0.05% of all bladder neoplasms.[1] These tumors may be functional, secreting catecholamines, or nonfunctional. Biochemical testing generally has a high sensitivity for detecting pheochromocytomas and paragangliomas (PPGLs), and effectively excludes a diagnosis when negative.[2] We present a rare case of a hormonally active bladder paraganglioma for which both biochemical and functional imaging tests were normal, highlighting the challenges in the diagnosis and management of bladder PPGLs.

CASE PRESENTATION

A 53-year-old Korean woman, previously well, presented with a 1-year history of isolated episodes of palpitations, light-headedness, and flushing, which occurred after voiding. Her blood pressure on self-monitoring was markedly elevated (up to 170/100 mm Hg) during these episodes, whereas it was normotensive on all other occasions. She was on no regular medications, and denied any use of illicit drugs, herbal supplements, nasal decongestants, nonsteroidal anti-inflammatory drugs, or licorice. She had had 2 previous unremarkable pregnancies, and her family history was negative for hypertension or neurocutaneous disorders.

On physical examination, she had a normal body mass index and a small neck circumference. Cardiac and respiratory examinations were unremarkable. There were no renal bruits. An integumentary examination did not reveal any neurocutaneous findings. There were no features suggestive of Cushing disease. Blood pressure was initially normal (121/62 mm Hg) but, immediately after voiding, rose to 174/106 mm Hg at 1 minute, 161/104 mm Hg at 2 minutes, and normalized to 111/80 mm Hg at 5 minutes. Serum biochemistry revealed a creatinine of 51 μmol/l, serum potassium of 4.1 mEq/l, and no alkalosis (bicarbonate 25 mmol/l). Urine microscopy was bland. An ambulatory blood pressure monitor confirmed the pattern of paroxysmal hypertension following micturition (Figure 1).

The patient was started on labetalol without improvement. Given episodic hypertension with palpitations, there was a high index of suspicion for PPGL. Urine metanephrines and catecholamines were collected during symptomatic episodes, and were normal on both occasions (Table 1). A meta-iodobenzylguanidine (MIBG) scan radiolabeled with I-131 was also negative. The temporal association of symptoms with voiding raised the suspicion of bladder pathology. Although pelvic ultrasound failed to detect any bladder abnormality, magnetic resonance imaging revealed an enhancing bladder wall lesion (Figure 2). Cystoscopic examination confirmed an extramucosal bladder mass. The patient was started on phenoxybenzamine in advance of laparoscopic surgical excision, which was uneventful.

Histopathology revealed a 2-cm tumor composed of neuroendocrine-type cells with abundant eosinophilic granular cytoplasm, arranged in cords and nodules surrounded by delicate fibrous stroma. The appearance was suspicious for the ''zellbollen'' architectural pattern characteristic of PPGLs. This was confirmed by positive chromogranin staining, although on S100 staining, the sustentacular cells were only focally
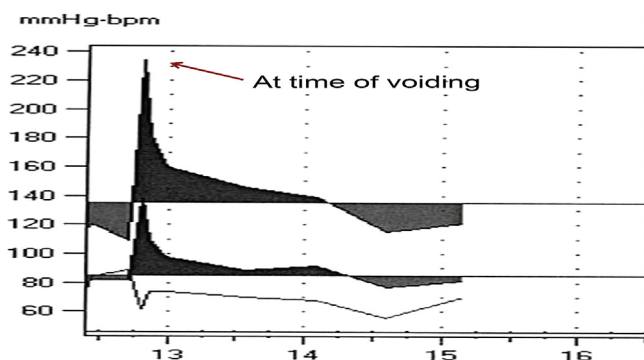
Figure 1. A snapshot of 24-hour ambulatory blood pressure monitoring revealing paroxysmal hypertension following voiding.

identified (Figure 3). There was no evidence of significant atypia, necrosis, high mitotic activity, or vascular invasion to suggest malignancy. Immunohistochemistry for succinate dehydrogenase subunit B (SDHB) was normal, showing expression of the SDHB protein, thus making a *SDHx* gene mutation (*SDHA, SDHB, SDHC, SDHD,* and *SDHAF2)* unlikely. Genetic testing was performed for 12 genes associated with hereditary PPGL (*FH, MAX, MEN1, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL*) and did not detect any mutations.

Surgical excision resulted in complete resolution of paroxysmal symptoms. However, the postoperative course was complicated by prolonged postural hypotension, which was managed by high sodium intake. The patients remains well to date, with no further lesions identified in 3 years of follow-up thus far, although monitoring is challenging, given the initially negative screening tests.

DISCUSSION

Bladder PPGLs are rare, with only a few hundred cases reported in the literature.[3] A tetrad of micturition syncope, sweating, palpitations, and hematuria is highly suggestive of the diagnosis.[4] The typical diagnostic pathway includes urinary and plasma metanephrine quantification followed by localization with imaging. Our patient presented with typical symptoms of micturition before syncope and palpitations.

Table 1. Urinary biochemistry results from collections obtained immediately after symptomatic episodes

Hormones	Collection 1[a] (μmol/mmol creatinine)	Collection 2[a] (μmol/mmol creatinine)	Reference range (μmol/mmol creatinine)
Vanillylmandelic acid	1.3	2.4	< 4
Epinephrine	4.1	6.5	< 7
Norepinephrine	33.1	63.4	< 70
Metanephrines	0.18	0.28	< 0.6

[a]Values from 6-h urine collections, expressed as a ratio of urine hormone level : urine creatinine.
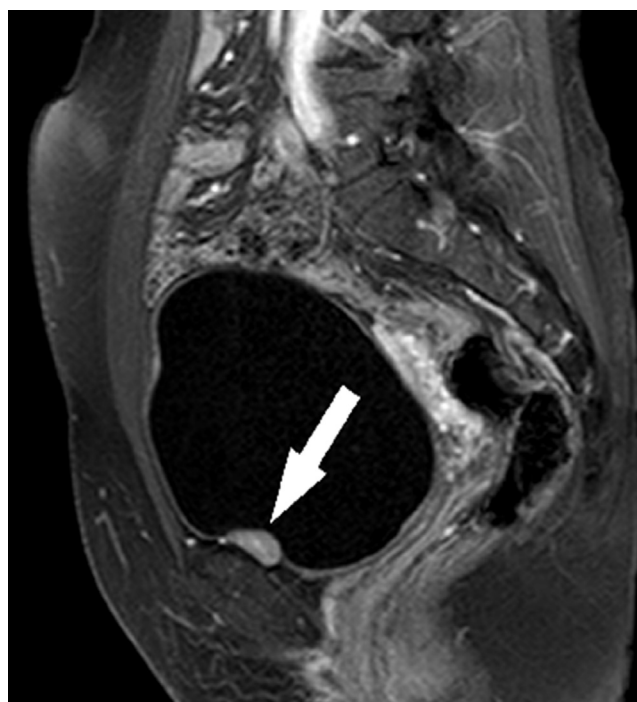

Figure 2. Sagittal magnetic resonance image demonstrating a 2.1 × 1.8 × 0.8-cm enhancing lesion (white arrow) on gadolinium-enhanced, fat-saturated, T1-weighted imaging.

However, negative biochemical and functional screening test results confounded the diagnosis. Testing-related factors may have accounted for these negative findings.

Current guidelines for evaluation of suspected PPGLs recommend biochemical testing as the initial investigation.[5] This includes measurement of plasma or urinary catecholamines (epinephrine, norepinephrine, dopamine) or their breakdown products (metanephrine, normetanephrine, vanillylmandelic acid, and 3-methoxytyramine). However, catecholamine breakdown occurs continuously within the tumor, independent of catecholamine release. Thus, measuring urinary or plasma fractionated metanephrines carries higher sensitivity (97% and 99%, respectively) when compared with parent catecholamines (up to 85%), particularly if acquired during symptomatic episodes.[6] It is therefore the diagnostic test of choice for PPGLs.[5] Sensitivity is highest with the use of liquid chromatography with mass spectrometric or electrochemical detection methods as compared to immunoassays.[7] Sensitivity of plasma free metanephrines is further increased when serum samples are drawn in the supine position in the fasting state.[8]

In our patient, urine collections for metanephrines were performed during symptomatic episodes on 2 distinct occasions, the results of which were both negative. The urinary total metanephrines level refers to both normetanephrine and metanephrine measured
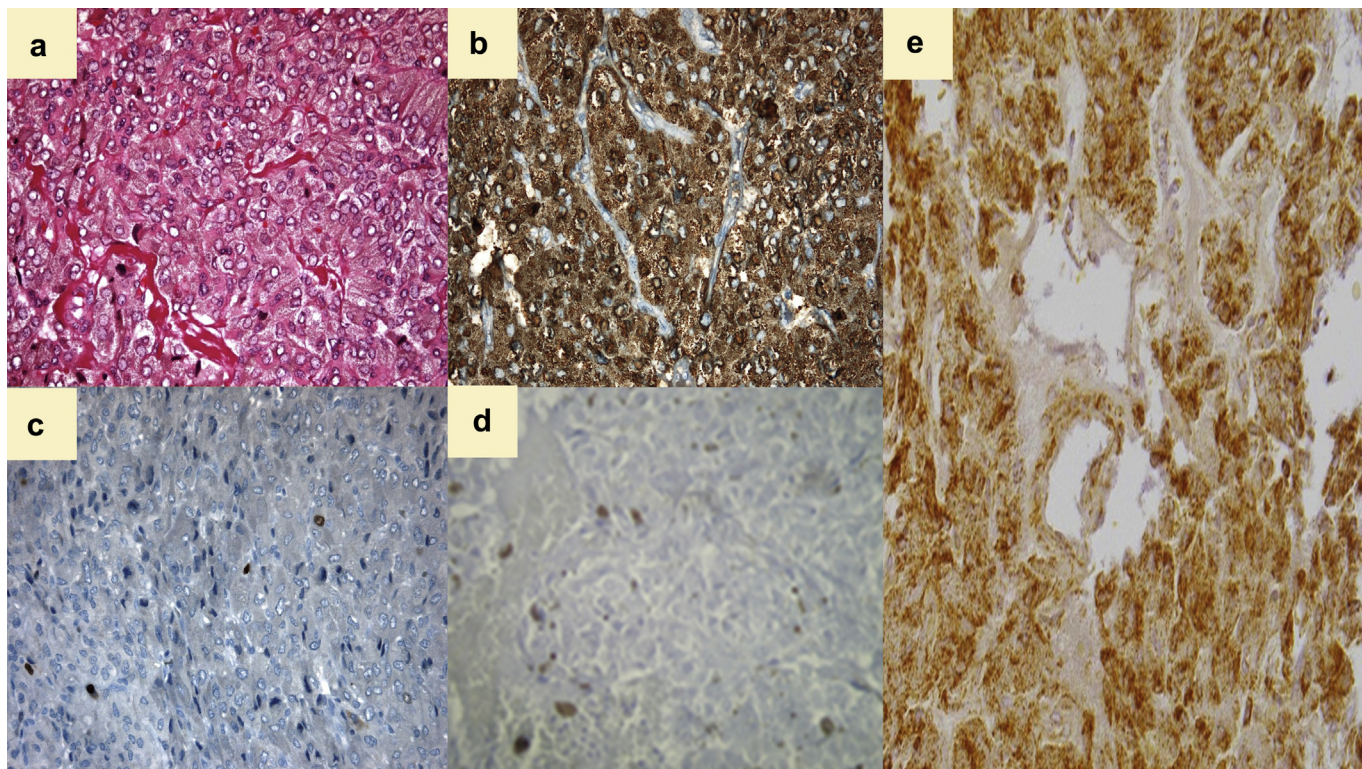
Figure 3. (a) Well-defined, partially encapsulated nodule composed of nests, cords, and trabeculae of cells with abundant granular cytoplasm and mildly atypical nuclei. (b) Immunohistochemistry for chromogranin A is strongly positive. (c) Immunohistochemistry for Ki-67 reveals low mitotic activity. (d) S100 staining is very weak and shows only a few sustentacular cells. (e) Succinate dehydrogenase subunit B (SDHB) staining reveals positive expression of SDHB.

together as a single concentration by early spectrophotometric assays and carries a sensitivity of 77%.[6] Newer high-performance liquid chromatography assays allow separate measurements of normetanephrine and metanephrine levels, termed "fractionated" metanephrines.[9] This has a much higher sensitivity (97%). Furthermore, as measurement of plasma-free metanephrines carries the highest sensitivity, it is the recommended test of choice in cases with a high index of suspicion. Nevertheless, despite sensitive tests, a relatively high false-negative rate has been noted in PPGLs of the bladder, which tested biochemically negative in up to 15% of cases in a meta-analysis.[1] False-negative results occur more commonly in small tumors, dopamine-producing tumors, and some tumors with *SDHx* mutations.[10] Notably, more than one-third of bladder PPGLs reportedly produced dopamine along with norepinephrine/normetanephrine.[11] As dopamine and its breakdown product, methoxytyramine, are not routinely included by laboratories in urinary catecholamine testing, dopamine-producing tumors may be overlooked. Urinary dopamine testing should be specifically requested when evaluating PPGLs.

Following positive biochemical testing, the next step in evaluation is localization with computed tomography/magnetic resonance imaging or functional imaging. Meta-iodobenzylguanidine (MIBG) is the preferred functional imaging test,[5] although its sensitivity is affected by certain factors. Sensitivity of standard [^{131}I] MIBG is 85%, compared to 98% using [^{123}I] MIBG.[12] In addition, medications such as nasal decongestants, antihypertensives (including labetalol), antidepressants, antipsychotics, and cocaine can interfere with MIBG uptake.[13] Such substances need to be withheld for 1 to 3 days before testing. Finally, MIBG scintigraphy has been reported to have low sensitivity in cases related to von Hippel–Lindau disease, *SDHx* mutations, or metastatic PPGLs.[14] Factors contributing to negative MIBG imaging in our patient may have been the use of [^{131}I] MIBG and labetalol.

Even after establishing a diagnosis of PPGL, a further layer of complexity in management arises from the inability to determine malignant potential. Classic histologic features suggestive of malignancy, such as nuclear pleomorphism, necrosis, mitotic rate, and local invasion can be seen even in benign paragangliomas.[15] According to the 2004 World Health Organization (WHO) criteria, the only established indicator of malignant behavior is metastatic spread.[16] It is now recognized that the tumor genotype can ascertain metastatic potential; tumors with *SDHB* mutations carry a higher malignant risk.[17] Deficient (abnormal) immunohistochemistry for

Table 2. Teaching points

Measurement of plasma-free metanephrines is the test of choice in patients with high pretest probability of PPGL
The sensitivity of MIBG imaging can be affected by the radioisotope type, certain medications, and the underlying genetic composition of the tumor
The diagnosis of malignancy cannot be made through histologic assessment and is defined by the presence of metastases
Genetic testing is recommended in all patients with PPGLs because of a relatively high prevalence of underlying germline mutations
Immunohistochemistry can be complementary to genetic testing

MIBG, meta-iodobenzylguanidine; PPGL, pheochromocytomas and paragangliomas.

SDHB is a sensitive and specific indicator of germline mutations in genes responsible for the assembly of the SDHB protein (*SDHA, SDHB, SDHC, SDHD,* and *SDHAF2*).[18] It can therefore be complementary to genetic testing.

The substantial genetic influence underlying PPGLs is being widely recognized. Approximately 40% of all PPGLs are thought to be caused by a hereditary etiology, in which an inherited or germline mutation occurs in 1 of 17 genes. These include well-studied disorders such as von Hippel−Lindau (VHL), multiple endocrine neoplasia type 2 (MEN2), neurofibromatosis type 1 (NF1), and the hereditary paraganglioma-pheochromocytoma caused by mutations in *SDHA, SDHB, SDHC, SDHD,* and *SDHAF2*. Newer genes for which clinical management has yet to be established include *TMEM127, MAX, EPAS1, FH, KIF1B, EGLN1, EGLN2, MDH2,* and *IDH*.[19] With increased recognition of the genetic contribution in PPGLs and the importance of identifying at-risk family members, genetic screening is now recommended in all PPGL patients.[5] The highest frequency of mutations in PPGLs occur within *VHL* and *SDHx* genes.[20] In bladder PPGLs in particular, *SDHB* mutations have been reported in more than 50% of the patients.[11] This is important, because *SDHB* mutations demonstrate high metastatic potential.[21] Defining a patient's genetic profile is thus potentially paramount in identifying the patient's prognosis, management, and surveillance, as well as for screening of family members.

In our patient, a *SDHx* mutation was suspected, given that *SDHB*-related PPGLs are more often extra-adrenal,[22] are associated with a negative family history,[22] and may be associated with false-negative MIBG imaging results.[4] Although immunohistochemistry staining was not suggestive of an *SDHx* mutation, there are reports of interobserver variability.[23] However, subsequent genetic testing was negative, implying that a somatic mutation is more likely. Alternatively, a gene mutation in 1 of the newer genes such as *EPAS1, KIF1B,* and *EGLN1* may be possible. The testing of these genes and their implications for management are still being elucidated.

CONCLUSION

Bladder PPGLs are rare and are clinically challenging to diagnose due to potentially false-negative biochemistry and functional imaging results. Consequently, a high index of suspicion must remain when evaluating typical symptoms. Factors influencing test characteristics should be considered and explored. A substantial proportion of PPGLs may have an underlying hereditary etiology, and warrant genetic testing to guide surveillance and management (see Table 2).

DISCLOSURE

All the authors declared no competing interests.

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