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Original article

Paragangliomas of the urinary bladder: A report of 6 cases and review of the literature

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ABSTRACT

Objective: Extra-adrenal pheochromocytomas are known as paragangliomas. The majority of extra-adrenal tumors occur intra-abdominally along the sympathetic chain. However, they may also occur in the urinary tract, including the urinary bladder.
Materials and methods: In this study, we report a clinical series of six patients diagnosed with bladder paragangliomas in our hospital over the past two decades, and review the literature regarding this unusual disease.
Results: Among the six cases, two were male and four were female. The most common presentation was painless gross hematuria, with five of the six patients (83.3%) having this chief complaint. Two patients presented with hypertension and one with palpitations. Two had malignant bladder paragangliomas, and one died within one year after the diagnosis. Four patients received transurethral resection of the bladder tumors, and one patient developed tumor recurrence within one year of follow-up.
Conclusion: Bladder paraganglioma is an extremely rare tumor with a high recurrence rate, and the most common presenting symptom in our series was painless gross hematuria. Large, polypoid, and multiple tumors indicate malignancy.

1. Introduction

Pheochromocytomas are catecholamine-secreting tumors derived from adrenal glands and the sympathetic nervous system. Extra-adrenal pheochromocytomas, known as paragangliomas, account for about 15% of all pheochromocytomas[1]. Bladder paragangliomas are extremely rare, accounting for less than 0.06% of all bladder tumors and less than 1% of all pheochromocytomas.[1–3] The most common symptoms of bladder paragangliomas are hypertension, headache, hematuria and palpitations, with characteristic micturition attacks, *i.e.*, secretion of catecholamines causing paroxysmal hypertension, palpitations, and micturition syncope.[3]

These tumors are typically benign, however, approximately 10% possess the capacity to invade and thus are deemed malignant even though they lack mitoses and cellular dissociation that are usually associated with malignant tumors. However, only when the primary tumor infiltrates locally into the non-nervous system or grows in organs without embryo residual ganglia such as the liver, spleen, lungs, brain, bones, and lymph nodes, can the diagnosis of malignant paraganglioma be made.[1] Herein, we present a series of six cases with bladder paragangliomas, and describe the clinical presentations, surgical interventions, pathological reports, and clinical outcomes. We also review the literature to provide more information and understanding of this rare disease.

2. Materials and methods

We retrospectively reviewed the pathological and clinical database of the National Taiwan University Hospital by International Classification of Diseases (ICD-9) code for the past 25 years. Six cases of bladder paragangliomas were identified. We present the patients' characteristics, initial clinical presentations, treatment courses, post-operative pathological reports, recurrence, and survival.

3. Results

Among the six cases of bladder paragangliomas, four were female and two were male with an average age of 52.6 years (range

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21 to 68 years). The general clinical characteristics are listed in Table 1. The most common presenting symptom was painless gross hematuria (5/6). Hypertension was noted in one-third of the patients, and one patient suffered from palpitations. The characteristic micturition attack occurred in only one patient with palpitations and headache during voiding.

Two patients received partial cystectomy for large tumors with the pathological results showing malignant bladder paraganglioma. Case number 1 was a 21-year-old male, who presented with multiple, large, polypoid malignant bladder paragangliomas with tumor invasion to extra-vesical fat tissue. He initially underwent partial cystectomy for suspected extra-vesical tumor extension, and since then he has received regular cystoscopy, annual urine/plasma Vanillomandelic acid (VMA) examinations (Figure 3), and abdominal/pelvic magnetic resonance imaging follow-up for ten years and six months to date. Twenty-four-hour urine VMA showed a dramatic drop in VMA level after the partial cystectomy until now. He is still well without recurrence. Case number 2 was a 53-year-old female patient with concurrent, multiple, large, polypoid malignant bladder paragangliomas with invasion to the uterus, vagina and bilateral ovaries. She underwent partial cystectomy, total hysterectomy and bilateral salpingo-oophorectomy. However, the post-operative course was complicated with vesicovaginal fistula which developed three months after radical surgery, and she died 21 months after the diagnosis of the disease. The death cause was urosepsis. No adjuvant therapy was given.

The other four patients received transurethral resection of the bladder tumor (TUR-BT) for small bladder paragangliomas. One of them was a 68-year-old male patient who was diagnosed with a bladder tumor incidentally while undergoing transurethral resection of the prostate (TUR-P). He received TUR-BT, and the pathology revealed a benign bladder paraganglioma (Table 1, case number 6). Post-operative follow-up computed tomography one year after the operation revealed one intra-mural tumor (Figure 1a and 1b). He received a second TUR-BT (Figure 2) and the pathology also showed paraganglioma of the bladder. The other three patients underwent TUR-BT with a smooth recovery course and no evidence of recurrence. These patients were all noted with normal blood pressure post-operatively.

The specimens of the two malignant bladder paragangliomas (Case 1 and 2) were large polypoid tumors, both rich in blood supply and broad-based. The specimens of the four benign paragangliomas (Case 3 to 6) were round or ovoid tumors. Only one patient had pre-operative and post-operative VMA/catecholamine data. The 21 year-old male was noted with early onset of hypertension with elevated urine norepinephrine 1009ug/24hr and elevated urine VMA 16.8mg/24hr pre-opearatively. Post-operative urine norepinephrine and VMA were 4.3ug/24hr and 3.8ng/24hr. Significantly decreased urine norepinephrine and VMA were noted after partial cystectomy. In the pathology reports of our patients, we noted positive s-100, positive chomogranin, positive synaptophysis and negative cytokeratin. Vimentin was not specifically stained by our pathologists.

4. Discussion

Pheochromocytomas are derived from the adrenal gland, and extra-adrenal pheochromocytomas are named paragangliomas, which account for 15–20% of all paragangliomas. Paragangliomas can occur anywhere from the head and neck to the pelvic region. Paragangliomas have also been reported in peri-renal and prostate glands in the genitourinary systems.[2] Dana et al. reported 236 extra-adrenal benign paragangliomas, and only two originated from the bladder. Bladder paraganglioma is a rare tumor that was first described by Zimmerman in 1953.[3] The incidence of bladder paraganglioma is less than 0.06% of all bladder tumors and less than 1% of all pheochromocytomas. Some of these tumors display functional characteristics and properties, such as normal urine or serum epinephrine levels, unlike pheochromocytomas, due to a lack of phenylethanolamine N-methyltransferase, the converting enzyme from norepinephrine to epinephrine. The most common presentations are painless gross hematuria and hypertension, headaches, and palpitations.

Our findings revealed a trend of female and middle-age predominance, which is compatible with previous studies.[4–6] Our results also share some common unique characteristics of bladder paragangliomas described by previous articles. First, the most common presenting symptom was painless gross hematuria,[7,8] and the supposedly characteristic micturition attack was only observed in 16.6% of our patients, which is consistent with previous studies.[7,9] The most well-known pathological finding refers to the “Zellballen” pattern, in which immunohistochemical staining is usually positive for synaptophysin and chromogranin, with S-100 being highlighted in sustentacular cells (Figure 4).

The diagnosis of primary, malignant, non-urothelial bladder tumor has been defined by WHO.[10] Bladder paraganglioma is an extraadrenal tumor of neural crest derivation that classically demonstrates groups of fairly uniform, polygonal cells (Zellballen).[11] With WHO criteria, paragangliomas are defined as malignant or benign in consideration of invasion of adjacent tissues and metastasis. It is controversial to diagnose and to predict malignant behavior in paraganglioma with histopathologic characteristics and scoring system.[12] In a previous case report and literature review, immunohistochemical staining for chromogranin, synaptophysin, and CD 56 were positive.[13]

More than 180 cases of bladder paragangliomas were reported before 2007, less than 30 of which were malignant.[14] However, there are no definite pathological criteria for malignancy at present, and only the clinical behavior can distinguish benign cases from malignant cases. In our experience, large, multiple, polypoid and broad-based tumors are more likely to be malignant, while small, single, round or ovoid tumors are more likely to be benign. Deng

Table 1
Clinical characteristics of 6 patients with bladder paraganglioma.

Case	Sex/Age	Presentation				Tumor appearance	Management	Pathology	Follow-up (mo)	Outcome
		Hematuria	HTN	Palpitation	Micturition attack					
1	M/21y	+	+	+	+	Multiple, large, polypoid	TUR-BT, partial cystectomy	Malignant paraganglioma	122	No recurrence
2	F/53y	+	+	–	–	Multiple, large, polypoid	Partial cystectomy, ATH and BSO	Malignant paraganglioma	28	Died
3	F/59y	+	–	–	–	Single, small, ovoid	TUR-BT	Paraganglioma	60	No recurrence
4	F/59y	+	–	–	–	Single, ovoid	TUR-BT	Paraganglioma	89	No recurrence
5	F/56y	+	–	–	–	Single, round	TUR-BT	Paraganglioma	26	No recurrence
6	M/68y	–	–	–	–	Single, round	TUR-BT	Paraganglioma	19	Bladder recurrence

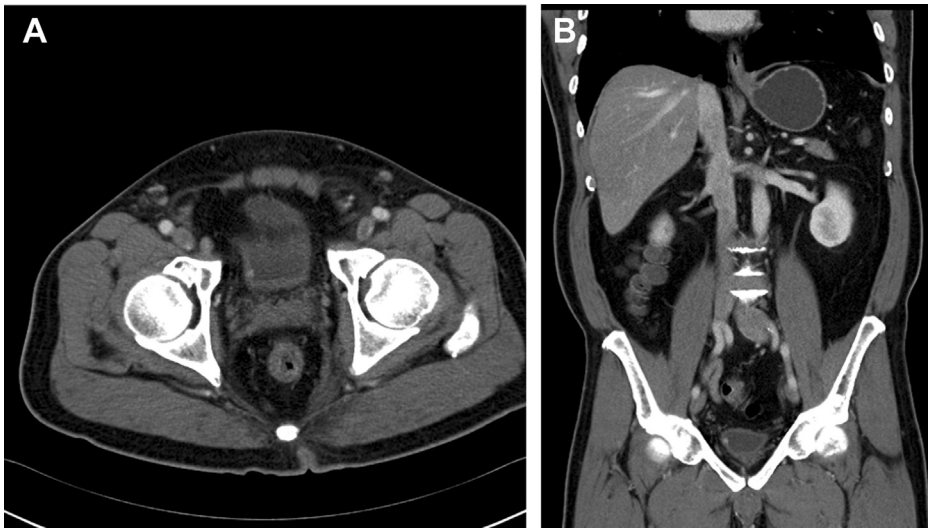

Figure 1. A 68-year-old male received TUR-BT for bladder paraganglioma, and a follow-up CT scan 1 year post-operatively showed recurrence of the bladder paraganglioma in the right lateral wall (arrow), with no extra-vesical invasion.

et al reported that large, multiple, tumors with an incomplete surface and pelvic lymphadenopathy are the major characteristics for malignant bladder paragangliomas.[4] Not all the patients received MRI. Most of them were noted with incidentally found bladder tumors due to hematuria. And most of them received abdominal and pelvic CT due to bladder tumor noted by cystoscopy.

Many experts advocate complete surgical removal as the standard management for paragangliomas, including partial cystectomy or radical cystectomy.[4,5,7,9] It is believed that paragangliomas of the bladder originate from the intra-mural portion of the bladder wall, and that it is therefore difficult to remove the tumor entirely with TUR-BT only. Furthermore, TUR-BT may result in fluctuation of blood pressure either with irrigation of distilled water or saline intra-operatively, or electrical stimulation during resection and cauterization.[15,16]

However, some surgeons still perform TUR-BT and follow the patients regularly for small tumors at special tumor locations. The advantage of a minimally invasive modality is a shorter recovery period.[17] According to a previous case series, bladder paraganglioma is a tumor with a high recurrence rate regardless of the treatment modality.[9] Deng et al described one of three patients with a benign bladder paraganglioma which recurred after TUR-BT despite the small tumor size.[4] This is similar to the 68 year-old male patient in our series who had tumor recurrence one year after TUR-BT. These two cases highlight the high recurrence rate even for small-sized, benign tumors, so once the diagnosis of bladder paraganglioma has been made, a much more extensive treatment modality such as partial or radical cystectomy should be preferred. Complete removal of the total tumor mass is optimal, however for small tumors or peri-ureteral orifice lesions, TUR-BT with regular computed tomography and urine VMA follow-up is another treatment option.

Tsai et al. suggested that post-operative follow-up protocols should include annual cystoscopy, plasma or urine catecholamine analysis and an 131I-MIBG scan.[17–19] Young et al regarded annual

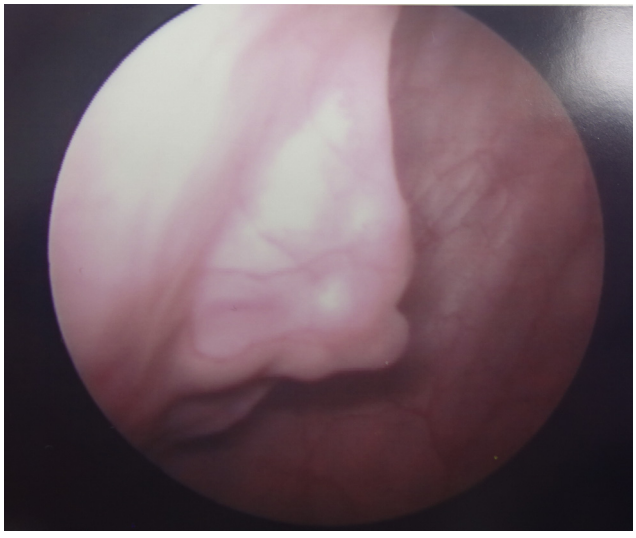

Figure 2. The second cystoscopic finding of the 68-year-old male after the CT scan revealing tumor recurrence. One ovoid tumor, slightly protruding from the submucosa area, was noted. The second pathology was still bladder paraganglioma.

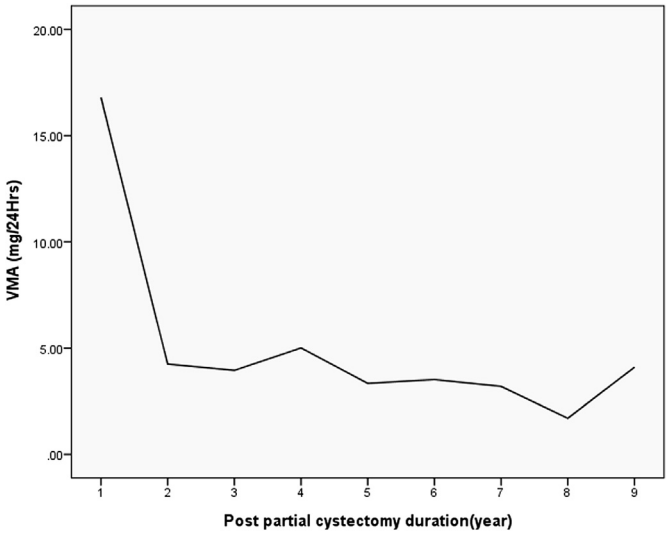

Figure 3. A 21-year-old male patient with malignant bladder paraganglioma. He received initial TUR-BT and partial cystectomy for the large tumor and extra-vesical invasion. He received regular annual 24-hour urine VMA tests which revealed no elevation post-operatively.

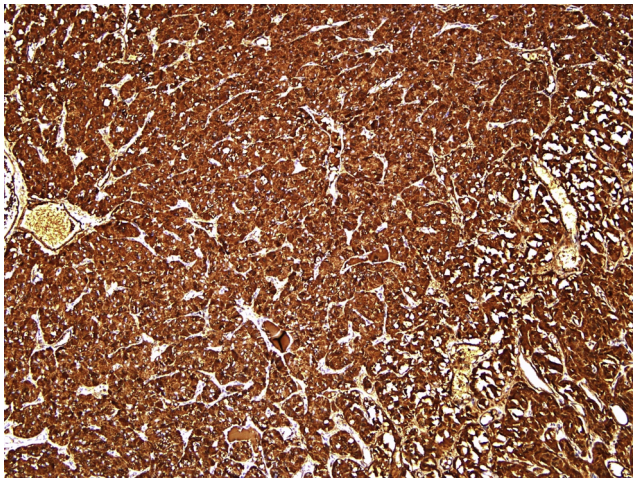

Figure 4. The pathology specimen of benign bladder paraganglioma of a 56-year-old female. She was diagnosed with a bladder tumor due to gross hematuria. The specimen was positive for synaptophysin (40×) and it showed the Zeballen pattern.

urine and serum VMA to be the best tools for detecting clinical recurrence or distant metastasis.[20] Life-long follow-up is necessary to detect late recurrences as suggested in previous studies.[21]

5. Conclusion

In summary, we report the high recurrence rate of bladder paraganglioma, even with benign or small tumors. If bladder paraganglioma is diagnosed, especially with a large tumor size, partial or radical cystectomy with life-long follow-up is strongly recommended.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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