Original Article

JHSMR Journal of Health Science and Medical Research

The Usual Story of an Unusual Site: A Case Series of Urinary Bladder Paraganglioma from a Single Institution

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Received 4 May 2025 ● Revised 19 July 2025 ● Accepted 25 July 2025 ● Published online 2 February 2026

Abstract:

Objective: Bladder paragangliomas (PUB) are extremely rare. The incidence is <0.06% of all bladder tumors and <1% of all pheochromocytomas. The importance of accurate diagnosis is crucial for effective patient treatment.

Material and Methods: This study encompassed 9 cases of bladder paragangliomas, identified over a duration of 6 years. Analyses of the epidemiological features, symptoms, imaging, laboratory tests, treatments, pathology, immunohistochemistry (IHC), and follow-up outcomes were executed.

Results: Among the 9 cases of PUB, 5 were female and 4 male, with ages ranging from 24 to 73 years. The most common presenting symptom was painless gross hematuria (67%), followed by micturition attack (22%), and hypertension (11%). Radiologically, the tumors were well circumscribed, solitary, and broad-based. Most patients underwent transurethral resection of the bladder tumor (TURBT). The characteristic Zell Ballen pattern of tumor cells, separated by a delicate fibrovascular network and supported by small sustentacular cells, was evident on microscopy. All tumors were classified as T2, per the 8th edition American Joint Committee on Cancer Staging System (AJCC) staging system. Based on histmorphology, various differentials were considered. On IHC, tumor cells were immunoreactive for synaptophysin, chromogranin, with S100 highlighting sustentacular cells, thereby confirming the diagnosis of PUB. MIB1 ranged from 1-10%. Two patients were lost to follow-up. Duration of follow-up ranged from 3 months to 78 months (6.5 years). All the patients were disease and symptom-free at the follow-up.

Conclusion: PUB is a rare condition. Characteristic clinical presentation, histologic features, and application of immunohistochemistry are all important to differentiate this tumor from other bladder tumors, ensuring patients receive the appropriate treatment.

Keywords: bladder paraganglioma, paraganglioma, urinary bladder, Zell Ballen

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J Health Sci Med Res
doi: 10.31584/jhsmr.20261309
www.jhsmr.org

Introduction

Paragangliomas (PGLs) are defined as neuro-endocrine neoplasms originating from neural crest–derived progenitor cells within the paraganglia, distributed along the prevertebral and paravertebral sympathetic chains, sympathetic nerve plexuses, and fibres. PGLs can occur in various locations, including the lower abdomen, retroperitoneum, pelvis, and bladder wall, and are closely associated with the presence of paraganglia[1].

PGLs can be functional and nonfunctional. PGLs are mostly sympathetic with functional activity, leading to excess catecholamines and hence clinical symptoms[1].

Urinary bladder paragangliomas (PUB) are the PGLs arising in the urinary bladder and are extremely rare. PUB constitutes <0.06% of all bladder neoplasms and <1% of all pheochromocytomas[2].

Zimmerman et al. first documented it in 1953, marking the beginning of its recognition in medical literature. Since then, numerous individual case reports and a limited number of case series have been published, contributing to a growing but still scarce body of knowledge on this rare tumor[3].

When Adrenaline/Noradrenaline is in excess, it induces symptoms like sweating, palpitation, anxiety, paroxysmal hypertension, and tachycardia[1]. Symptoms of PUB include hypertension, headache, haematuria, palpitations, and micturition attacks. Micturition attacks are episodes of sudden-onset hypertension, accompanied by palpitations and fainting (syncope) during urination, due to the release of catecholamines in PUB patients[2].

The diagnosis of malignant paraganglioma is accurate when the primary paraganglia infiltrates locally into the non-nervous system or grows in organs in which there are no residual ganglia, such as the liver, spleen, lungs, brain, bones, and lymph nodes[2].

Histomorphological features can overlap with urothelial carcinoma and its variants, especially the nested variant. Correlation of clinical information, histopathology, and appropriate ancillary techniques is required for the correct diagnosis and treatment modality[4].

In this study, we present a case series involving 9e patients diagnosed with bladder paragangliomas, detailing their clinical symptoms, the surgical procedures performed, pathological findings, and their clinical progress or outcomes. Also, a detailed review of the literature was conducted for a better understanding of this rare disease.

Material and Methods

A retrospective review of our institute's pathological and clinical electronic database identified 9 cases of bladder paragangliomas over a 6-year period.

The key aspects of the clinical diagnosis and treatment were determined by examining epidemiological characteristics, symptoms, imaging findings, laboratory results, treatment approaches, pathological features, immunohistochemical analysis, and follow-up outcomes.

Between January 2018 and August 2024, 308 patients were diagnosed with bladder neoplasms at our institute, of which 9 were confirmed as PGL. This included all biopsies, referral review cases, and resected specimens. It excluded cases with inadequate material. Patients were determined as having functional and nonfunctional PUBs based on their clinical complaints of episodic symptoms in spells or paroxysms. Appropriate surgical intervention was performed in 7 cases at our Institute, while 2 were review cases. Tumor size was grossly measured based on its maximum diameter. The essential points of diagnosis and treatment for PUB were analyzed, including epidemiological data, clinical presentations, imaging findings, treatment strategies, pathological characteristics, immunohistochemical profiles, postoperative recovery, and follow-up results. To assess therapeutic outcomes, long-term follow-ups were conducted through patient reexaminations and telephone interviews. Follow-up duration was measured from the date of surgery to the last recorded assessment or disease progression.

All patients provided informed consent, and the study was approved by our Institute's Ethics Committee (IRC/2025/P11).

Results

Clinical features

Amongst 9 nine cases of PUB, 5 patients were female and 4 were male, with a mean age of 44.3 years (range: 24–73 years). The general clinical characteristics are detailed in Table 1. The most frequently observed symptom was painless gross hematuria, occurring in 67% of cases. Hypertension (HTN) was documented in 1 patient (11%). Additionally, 3 patients (22%) experienced characteristic micturition attacks, presenting with palpitations and syncope during voiding. Reports for biochemical testing for metanephrine levels were untraceable/unretrievable from the database.

Radiological and surgical characteristics

All cases were preoperatively assessed radiologically. In 3 cases, radiological reports were unavailable. Usually, tumors are well circumscribed. Most tumors were solitary and broad-based; 2 tumors were polypoidal. Size (maximum dimension) ranged from 2 cm to 5 cm. One was in the dome of the urinary bladder, 1 in the base of the urinary bladder, and 4 were in the corpus of the urinary bladder. computed tomography (CT) scan images in the coronal and axial planes showing intraluminal well-defined solid ovoid lesions on the anterolateral left wall of the urinary bladder can be seen in Figure 2.

Two cases out of 9 were referred; slides were reviewed for diagnosis before beginning treatment. 6 patients underwent transurethral resection of the bladder tumor (TURBT). One patient received a partial cystectomy for a large tumor. Post-operative stay for the 6 patients ranged from 3–6 days.

The radiological and surgical details of these 9 patients are listed in Table 2.

Pathologic characteristics

In 8 cases, TURBT was done. Grossly, the tissue comprised multiple grey-tan soft pieces, with an average size of 2.5 cm (size range: 1–8 cm in dimension). In 1 case, a partial cystectomy was done, and grossly, the residual tumor measured 2.5 cm in its greatest dimension, with a homogenous yellow cut surface.

Table 1 General clinical details of 9 patients

Patient number	Sex	Age (years)	Clinical features		
			Hypertension	Hematuria	Micturition attack
1	Female	53	–	–	+
2	Male	24	–	+	–
3	Female	35	–	–	+
4	Male	38	–	+	–
5	Female	45	–	+	–
6	Female	55	–	+	–
7	Male	73	+	–	–
8	Female	44	–	+	–
9	Male	32	–	+	+

Legend: This table describes patient characteristic like demographics and clinical symptoms.

Table 2 Radiological and surgical details of 9 patients

Patient number	Surgery type	Radiology		
		Number	Site	Size (cm)
1	TURBT	Single	Left lateral wall	4
2	TURBT	Single	Base of urinary bladder	4
3	Partial cystectomy (post TURBT)	Single	Dome of urinary bladder	2
4	TURBT	Not available	Not available	Not available
5	TURBT (review)	Not available	Not available	Not available
6	TURBT	Single polypoidal	Posterolateral wall	5
7	TURBT	Single polypoidal	Anterobasal wall	3
8	TURBT (review)	Not available	Not available	Not available
9	TURBT	Single	Anterior wall	4

Legend: This table describes the type of surgery, size, number and location characteristic of the lesion.
TURBT=transurethral resection of the bladder tumor

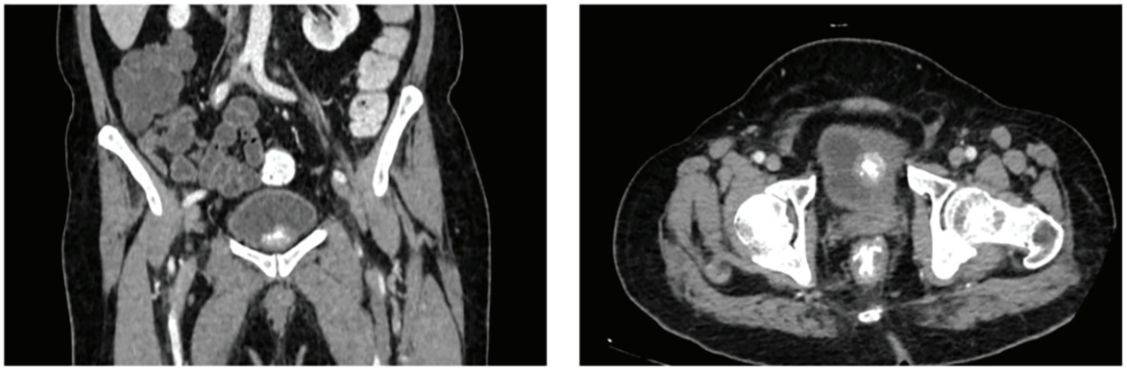


Figure 1 CT coronal and axial plains show intraluminal well-defined solid ovoid lesion present on the anterolateral left wall of the urinary bladder, which shows heterogeneous and avid contrast enhancement on the arterial phase with washout on delayed phase.

Microscopic examination showed tumor cells were arranged in a zell ballen (nesting) pattern with an interspersed delicate fibrovascular network and small sustentacular cells. The tumor nucleus had a round to oval shape with eosinophilic, granular to clear cytoplasm. Muscularis propria invasion was evident in 5 cases. Necrosis was evident in 4 cases. Lymphovascular emboli were seen in a single case. Occasional mitotic figures were seen in 3 cases. Atypical mitosis was absent in all the cases (Figure 2). All tumors were T2 stage (in accordance with the American Joint Committee on Cancer Staging System (AJCC) Cancer Staging Manual, 8th edition).

On IHC, tumor cells were immunoreactive for synaptophysin, chromogranin, with sustentacular cells being highlighted by S100. Epithelial and melanocytic markers (CKAE1/AE3, CK7, CK20, p63, HMB45, and Melan A) were uniformly negative. MIB1 was quantified manually, and it ranged from 1-10% (Figure 3). SDH-B staining was not performed because it is not available in our Institute.

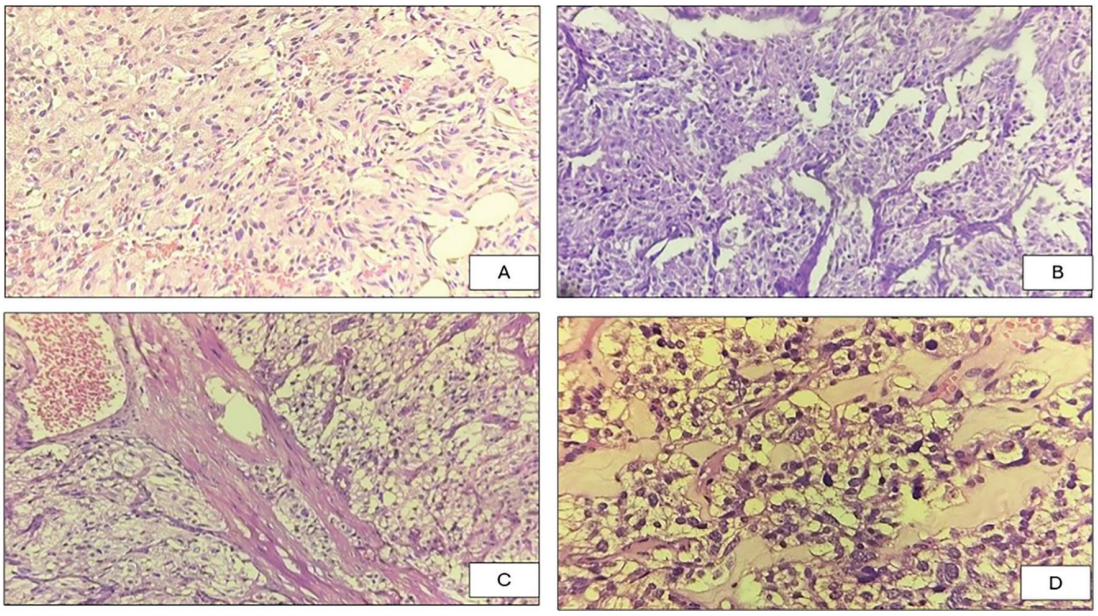


Figure 2 Microscopic images of bladder paragangliomas (PUBs) show (A) zellballen pattern arrangement of round to spindle shaped tumor cells. (B) Fibrotic stroma separating tumor cells. (C) Tumor cells have clear to eosinophilic cytoplasm. (D) Tumor cells have clear cytoplam and sclerotic stroma.

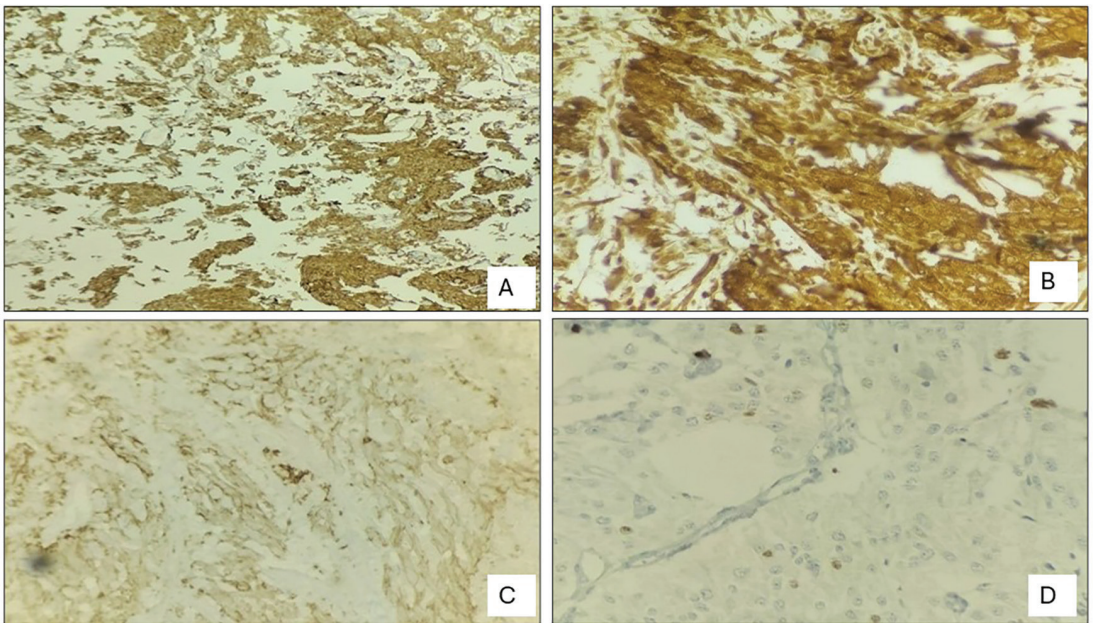


Figure 3 Immunohistochemistry (IHC) images show tumor cells being a diffuse strong positive for (A) synaptophysin and (B) chromogranin. (C) S100 stains tumor cells faintly, but sustencular cells are highlighted strongly. (D) MIB1 index is 3 % in this case.

Follow-up

Two of the 9 patients were lost to follow-up. One patient underwent a second surgery at our institute for a residual tumor from a previous surgery performed elsewhere. Duration of follow-up ranged from 3 months to 78 months (6.5 years). All the remaining patients were disease- and symptom-free at follow-up.

Discussion

The diagnosis of malignant PGL is accurate when the primary paraganglia infiltrate locally into the non-nervous system or grow in organs in which there are no residual ganglia, such as the liver, spleen, lungs, brain, bones, and lymph nodes[2].

Currently, there is no definitive marker to distinguish benign from malignant PUB. Malignancy is confirmed by metastasis to nonchromaffin tissues/organs like lymph nodes, liver, spleen, or bone. Around 10% of cases are malignant[5].

In Chang et al.'s case series of 6 patients, the average age was 52.6 years (range: 21-68 years)[2]. Belian et al.'s systematic review reported a mean age of 43.3 years (range: 11-84). Li et al.'s case series of 4 patients ranged from 28 to 54 years[8]. The average age in our study was 44.3 years (range: 24-73 years). Given the limited sample size, these findings are consistent with existing literature.

Chang et al. reported 6 cases, 4 were female and 2 were male[2]. In the systematic review by Belian et al., the male-female ratio was 1.07:1[6]. In a series of 4 cases by Li et al., all patients were females[8]. Our results correspond to the literature.

PUB are classified into functional and nonfunctional types based on the clinical characteristics. Functional PUBs present with disease-associated symptoms, resulting from elevated catecholamine levels and their metabolites in plasma and urine, along with positive MIBG or octreotide scintigraphy findings. These markers are absent in nonfunctional PUBs[1,5,7]. It is depicted in Figure 4.

According to the study by Zhai et al., the most common indicative symptoms were hematuria (36.4%), hypertension (31.8%), micturition syncope (27.3%), headache (18.2%), and palpitations (13.6%)[5]. In a systematic review by Beilan et al., 106 cases of PUB were reviewed from 1980 to 2012. The common symptoms of PUB in their study were hypertension (54.7%), micturition attack (52.8%), headache (48.1%), hematuria (47.2%), and palpitation (43.4%)[6]. In our case series, 5 patients had hematuria (67%), 2 had micturition-related symptoms (22%), and 1 had hypertension (11%) as a presenting complaint.

Around 55-60% of patients have the clinical symptoms of painless haematuria, with the majority of patients having microscopic hematuria. Hematuria is very nonspecific, as any bladder mass can present with the same symptom[7]. Catecholamine and its metabolites, metanephrine and vanillylmandelic acid (VMA), are secreted in either the blood or urine[7]. The study by Zhai et al. found significant elevation of catecholamines and their metabolites in the plasma and/or urine in 5 out of 17 patients (29.4%)[5]. In our series, 7 cases were nonfunctional and 2 were functional (with micturition attack). These cases were not suspected as bladder paraganglioma. The biochemical reports were unavailable/untraceable in both cases. In patients with clinical symptoms significant history of mictutrition attacks, PUB should be suspected in patients with radiological bladder masses by urologist & pathologist.

Paraganglia are present in the bladder wall, hence paraganglioma is found in all parts of the bladder[1]. Menon et al. reported no site predilection in their study[4]. Zhai et al. reported that the most common locations for a urinary bladder tumor were the body (6, 27.3%), apex (6, 27.3%), trigone (6, 27.3%), fundus (2, 9.1%), and the bladder neck (2, 9.1%)[5]. Our results were similar to the study by Zhai et al.

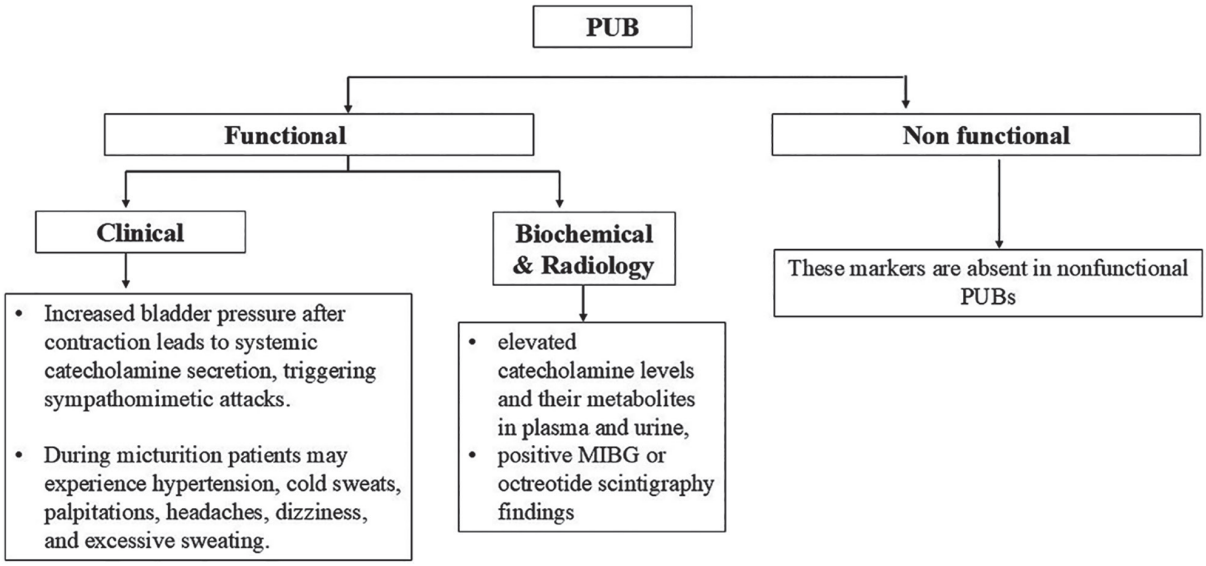


Figure 4 Classification of PUB based on clinical, radiological, and biochemical findings into functional and non-functional.

In the study by Zhai et al., the average tumor size ranged from 0.8–4.5 cm; Li H et al. reported that the size ranged from 0.6–3 cm, and in the study by Beilan et al., the average tumor size ranged from 1–9.1 cm[5,6,8]. In the study by Zhao et al., tumor size <3 cm reduced the perioperative hospital stay[10,11]. In our series, tumors ranged from 2 cm to 5 cm.

A study by Chang et al. also indicated TURBT with a shorter perioperative recovery[2]. In the case series by Zhai et al., TURBT constituted 27.3% amongst other diverse techniques like En Bloc transurethral resection with Thulium-Yag Laser (18.2%), Open Partial Cystectomy (27.3%), Laparoscopic Partial Cystectomy (18.2%), and Robot Assisted Laparoscopic Partial Cystectomy (9.1%). Their study also showed that the perioperative indoor stay of patients and complications related to surgery were lower in TURBT and En Bloc Transurethral Resection with Thulium-Yag Laser[5]. Beilan et al.'s systematic review showed that approximately 70% of patients underwent partial cystectomy as primary surgery for PUB[6]. In our study, duration did not vary according to surgery, which may be due to the smaller sample size. For the other studies and their surgical techniques, see Table 3.

Classically, on histomorphology, the cells are arranged in a nested pattern, giving a Zell Ballen appearance, supported by sustentacular cells along with a fibrous network rich in blood vessels. The tumor cells can have varied cytological and architectural appearances. Tumor cells can have an epithelioid to spindle shape, round-ovoid to polygonal nuclei with abundant granular eosinophilic to clear cytoplasm. Cellular architecture can be in nested, trabecular, or sheet-like patterns. Muscularis propria invasion is common in PUBs. Necrosis can also be seen[1–10].

Table 3 Surgical techniques used in the different studies[2,7,9]

Study	TURBT	Partial cystectomy
Li et al. (case series of 4 cases)	3	1
Zhao et al. (cases series of 29 cases)	15	14
Chang et al. (case series of 6 cases)	4	2
Our study	8	1

Legend: This table compares surgical technique utilized in different studies.
TURBT=transurethral resection of the bladder tumor

Studies have proved that the tumors located between the submucosa and muscle layers in the bladder are usually benign, whereas tumors invading perivesical and extra-vesical fat tissue have the potential to be malignant[2]. In the studies by Menon et al. and Zhou et al., muscularis propria invasion occurred in 72% and 7%, respectively[4,11]. In our study, all tumors were benign. In 5 cases (55.6%), there was an invasion into the muscular propria. The rest were superficial. In the study by Menon et al., focal necrosis was seen in 3 cases (21%)[4]. In the study by Zhou et al., tumor necrosis was present in 1 case (7%)[11]. In our study, necrosis was seen in 4 cases (44.44%). The findings might be discordant due to a smaller number of cases in the series.

The presence of a diffuse growth pattern, focal areas of clear cells, necrosis, and invasion of the muscularis propria in PUB, coupled with significant cautery artefacts, can closely resemble urothelial carcinomas, particularly the nested variant. Differential diagnoses for PUB include bladder granular cell tumors, carcinoid tumors, metastatic large cell neuroendocrine carcinoma, metastatic renal cell carcinoma (RCC), prostate cancer, and malignant melanoma[7-9].

Misdiagnosis often leads to the wrong treatment and prognosis. Urothelial carcinoma therapies are determined by stage. For muscle non-invasive carcinomas, intravesical Bacillus Calmette-Guerin (BCG), surveillance, and reTURBT are recommended. The recommended treatment for muscle-invasive urothelial carcinoma is radical cystectomy. For PUBs, the preferred treatment—regardless of muscle invasion—is transurethral resection of the bladder tumor (TURBT) or partial cystectomy with complete tumor removal. In rare cases of metastasis, chemotherapy and radiotherapy may be necessary[4].

In these circumstances, immunohistochemistry plays a key role in diagnosis. PUBs are immunoreactive for neuronspecific enolase, chromogranin, and synaptophysin. They are immunonegative for urothelial markers and cytokeratin but are positive for GATA3 (nuclear). The sustentacular cells are positive for S100 and SOX10.

Histomorphologically, the nested growth pattern with delicate vascular septae and clear to occasionally eosinophilic cytoplasm is seen in RCC, and by IHC, they are positive for CK, EMA, RCC antigen, and CD10. They are negative for neuroendocrine markers. Prostatic adenocarcinomas can be seen extending directly into the bladder with a nesting growth pattern, uniform nuclei, and prominent nucleoli. They are positive for CK, PSA, and AMACR. Melanoma is also a differential for paraganglioma, showing immunopositivity for Melan A, HMB-45, MiTF, and S100. Carcinoid tumors and other neuroendocrine tumors may have an insular growth pattern that may mimic zellballen, but these are exceedingly rare with immunopositivity for cytokeratin. Granular cell tumor can

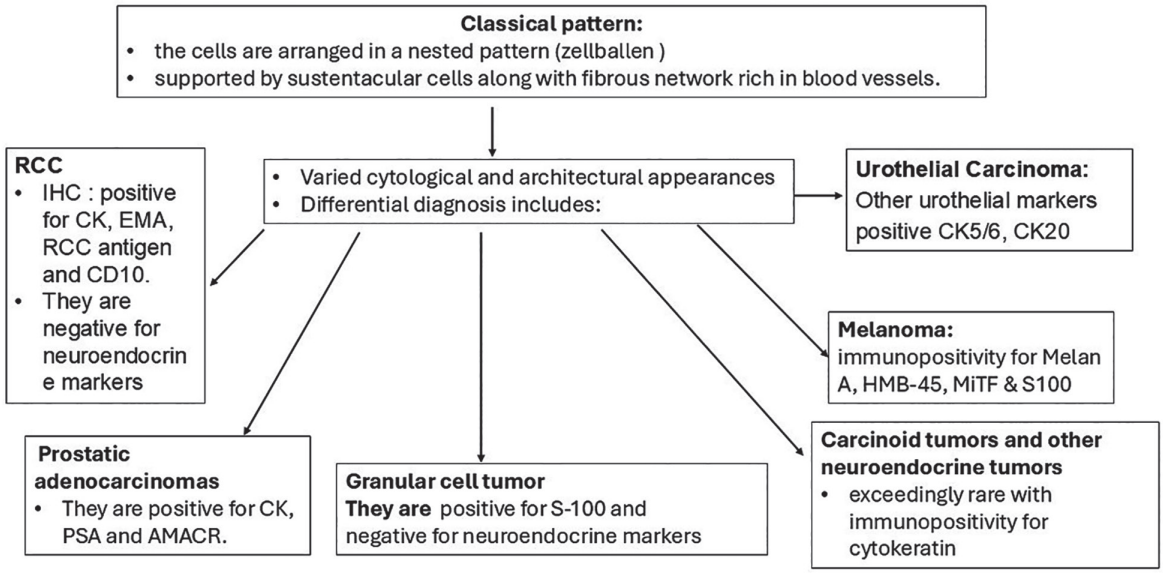
resemble PGL histomorphologically, but is positive for S-100 and negative for neuroendocrine markers, in contrast to the positive S-100 staining found only in the sustentacular cells of paragangliomas[4,7,11]. Our study had comparable results, as depicted in Figure 5.

Thirty percent of paragangliomas/pheochromocytomas are familial with germline mutations associated with von-Hippel Lindau (VHL) syndrome, MEN2 syndrome, NF1, RET oncogene, and recently elucidated succinate dehydrogenase (SDH) mutations of familial paraganglioma-phaeochromocytoma syndromes. These patients would be ideal candidates for genetic counselling, and further genetic testing of family members is advised. The SDH mutations in extra-adrenal paragangliomas are more likely to have malignant behavior. IHC surrogate markers for germline mutations are SDHA/B[2,4,5,7,9,10]. Due to the unavailability and financial constraints, we could not perform this test.

The Ki-67 index shows proliferative activity. In many studies, the Ki-67 proliferative index ranged from 1-10% in benign cases[5,8,10]. In a case series, the proliferative index exceeded 20% in a malignant metastatic paraganglioma[10]. Diagnosing a malignant tumor can be challenging and is frequently confirmed clinically by the detection of metastases[2,6,9]. In our study, the Ki-67 proliferation index was 1-10% and benign.

We should always consider a diagnosis of PUB when the patient is symptomatic (especially with Micturition attacks), the histology shows a nested pattern, and when sustentacular cells are highlighted by S100.

In accordance with the AJCC implemented in 2017, it was established that all sympathetic paragangliomas are classified as pT2 stage, regardless of size, to assist clinicians in selecting the appropriate therapies and follow-up care for patients[12]. The staging and survival data gathered



RCC=renal cell carcinoma, IHC=immunohistochemistry, CK=cytokeratin, EMA=epithelial memebrane antigen, CD10=cluster of differentiation 10, PSA=prostate specific antigen, AMACR=alpha methylacyl CoA racemase, PUB=bladder paragangliomas

Figure 5 Approach to diagnosis of PUB and its differential diagnosis with the help of morphology and IHC.

are anticipated to enhance the understanding of these tumors and contribute to advancements in patient care in the future. In a case series by Zhai et al., 72.7% were categorized as stage T2, 18.2% as stage T3, and 9.1% as stage T4[5]. In our series, all cases were staged as pT2, likely due to a smaller number of cases.

In the study conducted by Menon et al, follow-up data were available for only 6 out of 14 cases, with a follow-up period ranging from 8 to 120 months. Among these, 1 patient developed cervical lymph nodal metastasis at 120 months. The remaining 5 patients were asymptomatic with no evidence of disease recurrence[4]. In Zhai et al. (range: 6-130 months), 80% of patients had no evidence of disease[5]. In the study by Ranaweera et al. (range: 24-60 months), all 3 patients had no evidence of disease[7]. In a case series by Li et al. (range: 6-63 months), all 4 patients were asymptomatic and had no evidence of disease[8]. Our results are comparable to the other studies.

Conclusion

Bladder paragangliomas are uncommon, and accurate diagnosis is critical for optimal patient care. It is crucial for urologists and pathologists to be aware of this entity in order to prevent misdiagnoses. Differentiating this tumor from other bladder neoplasms necessitates a thorough evaluation of the clinical presentation, detailed assessment of histologic characteristics, and the strategic use of immunohistochemistry. These steps are essential for achieving an accurate diagnosis. Genetic testing and long-term follow-up ensure appropriate patient management.

Acknowledgement

We are immensely thankful to the institute, our patients, our family, and our friends.

Conflict of interest

None

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