International Journal of Research in Medical Sciences
Kriplani A et al. Int J Res Med Sci. 2022 May;10(5):1183-1190
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20221193

Case Series

Urinary bladder paraganglioma: a clinical dilemma in diagnosis and management: our experience at a tertiary care center

Akshay Kriplani, Deep Jain, Mayank Kulshreshtha, Suraj Jayadeva Reddy, Shruti Pandit, Bathi Sourabh Reddy, Gurvansh Singh Sachdev, Vivekanand Kedarlingayya Hiremath, Arun Chawla*

Department of Urology and Renal Transplant, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India

Received: 28 February 2022
Revised: 29 March 2022
Accepted: 31 March 2022

***Correspondence:**
Dr. Arun Chawla,
E-mail: chawlaurology@gmail.com

ABSTRACT

Urinary bladder paraganglioma (UBP) are rare neuroendocrine tumors with variable biological behavior. High index of suspicion in the preoperative evaluation would enable the clinician to formulate appropriate management of the rare tumors. Clinical and pathological data of seven cases evaluated and treated as per a devised protocol for suspected bladder paraganglioma from 2008 to 2019 was retrospectively reviewed. Among the seven cases, UBP's were predominantly seen in middle aged men. Most of these presented with storage symptoms (85.71%; n=7) and gross painless hematuria (42.85%; n=3). Three patients were hypertensives and post-micturition syncope was seen in two patients. Among the seven patients two patients had functionally active tumors confirmed by elevated urinary and serum markers for catecholamine excess. Functional tumors, nonfunctional tumors involving uretero-vesical junction or broad based polypoidal tumor were considered for partial cystectomy. Other small nonfunctional tumors underwent trans-urethral resection of bladder tumour (TURBT). Follow up protocol included repeat ultrasound, check cystoscopy and completion TURBT at one month and annually thereafter. Repeat urinary catecholamines at 1 month was done in functional UBP. Cystoscopic examination of a bladder lesion which are solid, sessile and predominantly intramural, a prior to a definitive planned surgery may differentiate UBP from urothelial cancer. Most of the non-functional UPB are diagnosed by histopathological examination. In symptomatic cases, functional evaluation with biochemical estimation of catecholamine excess allow better treatment planning and avoiding intraoperative hemodynamic instability. Due to high recurrence rate life-long follow-up despite complete excision is strongly recommended.

Keywords: Bladder paraganglioma, TURBT, Partial cystectomy, Histopathology

INTRODUCTION

UBP's are tumors of chromaffin cells, derived from the embryonic neural crest cells, originating from the sympathetic paraganglia in the bladder wall.[1-3] They may be classified into functional or non-functional tumors depending on the ability to actively secrete catecholamines.[4-6] Functional tumors commonly present with headache, palpitations, hematuria, visual disturbances, paroxysmal hypertension and post-micturition syncope.[7,8]

Bladder mass identified on ultrasound is better characterized on CECT or MRI. In case of functional tumors functional imaging techniques with metaiodobenzylguanidine (MIBG) scintigraphy also localizes other concomitant extravesical paragangliomas.[4,5] Once diagnosed with classical

histological features in the resected specimen, immunohistochemistry is important to distinguish paraganglioma from nested variant urothelial carcinoma because of their histo-morphological overlap.[6]

Most UBP's are benign, however, approximately 10% can be malignant. Presence of metastasis or ability to infiltrate locally or into organs without embryonal residual ganglia such as the liver, spleen, lungs, brain, bones, and lymph nodes suggests malignant potential.[9]

CASE SERIES

Clinical and pathological data of seven cases evaluated and treated as per a devised protocol for suspected bladder paraganglioma from 2008 to 2019 was retrospectively reviewed.

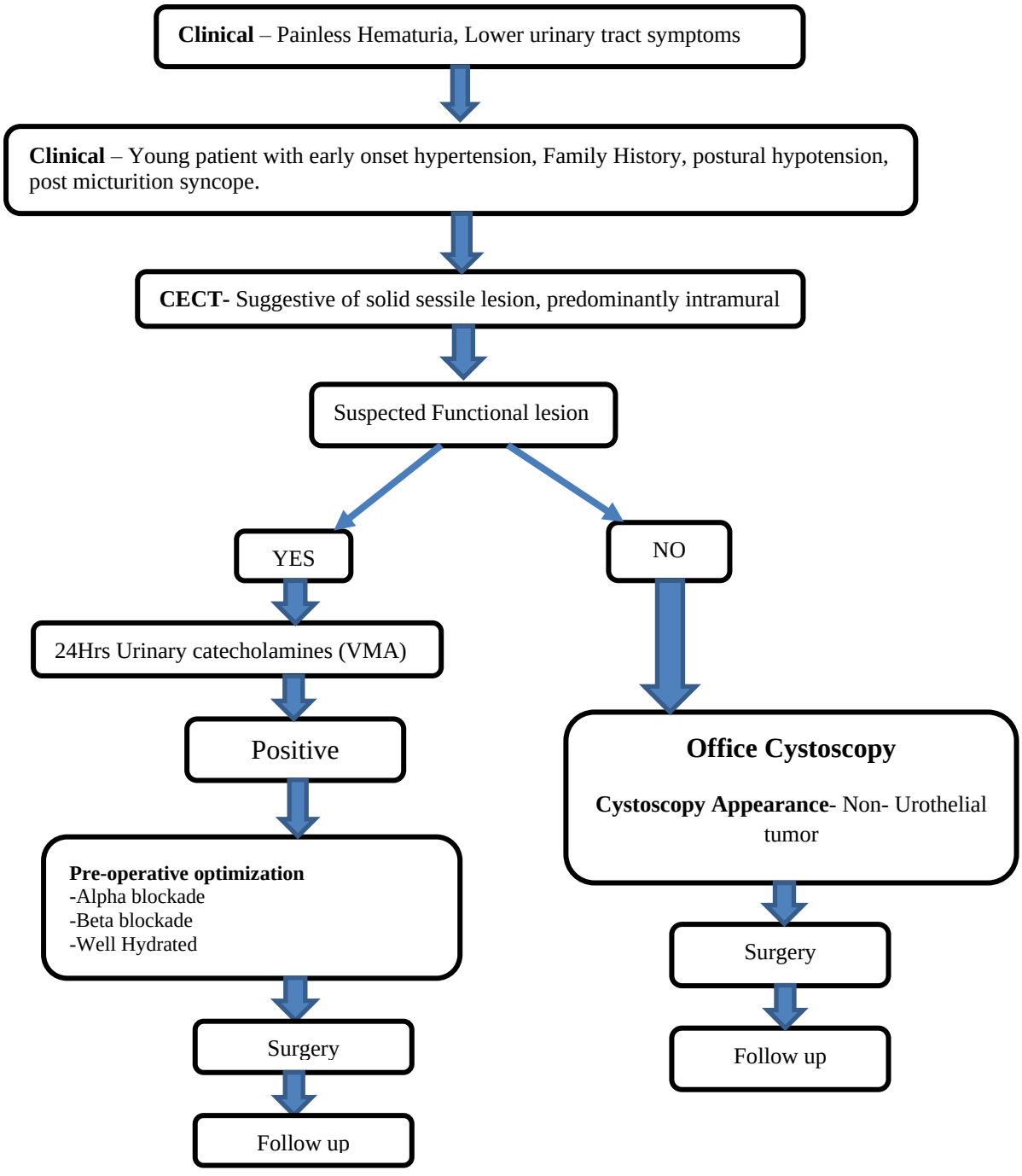

Figure 1: Scheme of evaluation as followed in our institute.

Table 1: Follow up protocol for UBP in our institute.

Duration	Functional UBP	Non-functional UBP
1 month	Clinical examination; USG abdomen; 24 hr urinary metanephrines	Clinical examination; USG abdomen; Cystoscopic±completion TURBT
Annually for 5 years	Clinical examination; USG abdomen; 24 hr urinary metaneprines	Clinical examination; USG abdomen; Cystoscopic+completion TURBT

The clinical profile of seven patients has been described in Table 1 and 2. The mean age of presentation was 38.42 years with a male to female ratio of 6:1.

The most common presentation was storage voiding symptoms (85.71%) followed by gross painless hematuria (42.85%). Three patients were known hypertensives and the classical presentation of post-micturition syncope was present in two patients. Bladder tumors were characterized on CECT. Two patients were found to have functional tumors with elevated 24 hours urinary catecholamines. Urine cytology for malignant epithelial cells was negative in all patients. Functional tumors were optimized with adequate catecholamine blockade with alpha and beta blockers. Non-functional tumors were managed by transurethral resection (case 2, 4 and 7). Cystoscopy revealed five of these patients (case 1, 2, 4, 5 and 7) to have tumors in the posterior wall and two of them had lateral wall lesions (case 3 and 6) with either normal.

Lesion involving the right ureteric orifice (case 1) was considered for distal ureterectomy with partial cystectomy and right ureteric reimplantation. Preoperatively diagnosed functional tumor (case 3) was considered for partial cystectomy. Despite adequate pre-operative optimization, a mere attempt of cystoscopy in the other patient with functional tumour (case 6) led to an attack of paroxysmal hypertension intraoperatively compelling the procedure to be abandoned. Two similar episodes on repeat cystoscopies (after further optimization) demotivated the patient for definitive treatment and was lost on follow up. The general follows up protocol included repeat ultrasound at 1 month with check cystoscopy and restaging TURBT with repeat urinary catecholamines, thereafter followed up annually.

The clinical profile of seven patients has been described in Table 1 and 2. The mean age of presentation was 38.42 years with a male to female ratio of 6:1. The most common presentation was storage voiding symptoms (85.71%) followed by gross painless hematuria (42.85%). Three patients were known hypertensives and the classical presentation of post-micturition syncope was present in two patients. Bladder tumors were characterized on CECT. Two patients were found to have functional tumors with elevated 24 hours urinary catecholamines. Urine cytology for malignant epithelial cells was negative in all patients.

Functional tumors were optimized with adequate catecholamine blockade with alpha and beta blockers. Non-functional tumors were managed by transurethral resection (case 2, 4 and 7). Cystoscopy revealed five of these patients (case 1, 2, 4, 5 and 7) to have tumors in the posterior wall and two of them had lateral wall lesions (case 3 and 6) with either normal. Lesion involving the right ureteric orifice (case 1) was considered for distal ureterectomy with partial cystectomy and right ureteric reimplantation. Preoperatively diagnosed functional tumor (case 3) was considered for partial cystectomy.

Despite adequate pre-operative optimization a mere attempt of cystoscopy in the other patient with functional tumour (case 6) led to an attack of paroxysmal hypertension intraoperatively compelling the procedure to be abandoned. Two similar episodes on repeat cystoscopies (after further optimization) demotivated the patient for definitive treatment and was lost on follow up. The general follow up protocol included repeat ultrasound at 1 month with check cystoscopy and restaging TURBT with repeat urinary catecholamines, thereafter followed up annually.

Table 2: Clinical characteristics of the seven cases of urinary paragangliomas

Characters	Case-1	Case-2	Case-3	Case-4	Case-5	Case-6	Case-7
Age (years)/gender	12/M	45/M	42/M	48/M	28/M	46/M	48/F
Presenting complaints							
Dysuria/frequency	-	+	+	+	+	+	+
Hematuria (gross, painless)	+	-	+	-	+	-	-
Hypertension (HTN)	-	-	+	-	-	+	+
Palpitations	-	-	-	-	-	-	-
Post-micturation syncope	-	-	+	-	-	+	-

Table 3: Tumor characteristics, surgical management and follow-up.

Characters	Case-1	Case-2	Case-3	Case-4	Case-5	Case-6	Case-7
Imaging (USG)	Solitary bladder mass 4×3 cm Right postero-lateral bladder wall, right HUN	Solitary bladder mass 2.5×1.5 cm Right posterior bladder wall (Figure 5)	Solitary bladder mass 7×5 cm Dome and right lateral bladder wall	Solitary bladder mass 2×2 cm Posterior bladder wall	Solitary bladder mass 2×3 cm Posterior bladder wall	Diffuse bladder wall thickening 5×3 cm right lateral wall	Solitary bladder mass 1.8×1.3 cm base of the bladder
Imaging findings	4×3 cm Circum-scribed Homo-genous Hyper-enhancing distal ureter and bladder wall (Figure 2)	2.5×1.5 cm Circum-scribed Homo-genous Hyper-enhancing right posterior bladder wall	8.4×5.7 cm Polypoidal Hetero-genous Hyper-enhancing dome and right lateral bladder wall (Figure 6)	3×3 cm Circum-scribed Homo-genous Hyper-enhancing posterior bladder wall	2×3 cm Polypoidal Homogenous Hyper-enhancing posterior bladder wall	Irregular hetero-geneously hyper-enhancing wall thickening of right lateral wall (Figure 8)	1.8×1.3 cm Circum-scribed Homo-genous Hyper-enhancing
Urine cytology	-ve	-ve	-ve	-ve	-ve	-ve	-ve
24 Hr Urinary catecholamines (VMA) (normal value≥15 years; adults<8.0 mg/24 hrs)	Not done	Not done	+ve 25 mg/24 hr	Not done	Not done	+ve 20 mg/24 hr	+ve 22 mg/24 hr
Cystoscopy	Ovoid mass protruding from right ureteric orifice edematous overlying mucosa	Solitary, ovoid lesion Right posterior wall, 2.5 cm cranial to the right ureteric orifice normal overlying mucosa	Solit-ary, poly-poid, vascu-lar lesion-dome and right lateral wall Edem-atous over-lying mucosa	Solitary, papillary lesion-posterior bladder wall, supra-trigonal normal overlying mucosa	Solitary, broad based polypoidal mass with odematous overlying mucosa-posterior bladder wall (Figure 7)	Attempted thrice after adequate optimi-zation but abandoned due to hyper-tensive crises	Solitary, ovoid lesion trigonal region normal overlying mucosa
Manage-ment	Distal ureterectom y with partial cystectomy. Right ureteric reim-plantation (Figure 3)	TURBT	Partial cystectomy	TURBT	Partial cystectomy	Patient refused	En bloc excision
Histo-pathology	Para-ganglioma S-100 +ve;	Para-ganglioma S-100 +ve;	Para-ganglioma S-100 +ve;	Para-ganglioma S-100 +ve;	Para-ganglioma S-100 +ve;	--	Par-gangliom-

Continued.

Characters	Case-1	Case-2	Case-3	Case-4	Case-5	Case-6	Case-7
	Synapto-physin +ve; chromogranin +ve (Figure 4)	synaptophysin +ve; chromogranin +ve	Synapto-physin +ve; chromo-granin +ve Ki67-32%	Chromo-granin +ve	Synapto-physin +ve; chromogranin +ve		asynaptophysin +ve S-100 -ve
Follow-up (F/u) (months)	60	72	48	24	36	Lost to F/u	3

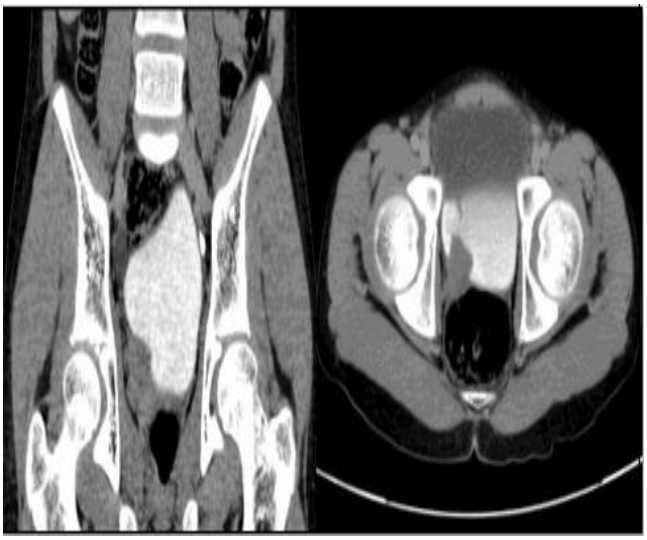

Figure 2: CT cystogram finding of case CT cystogram showing a 4×4 cm mass in distal ureter extending into the bladder around the vesicoureteric junction.

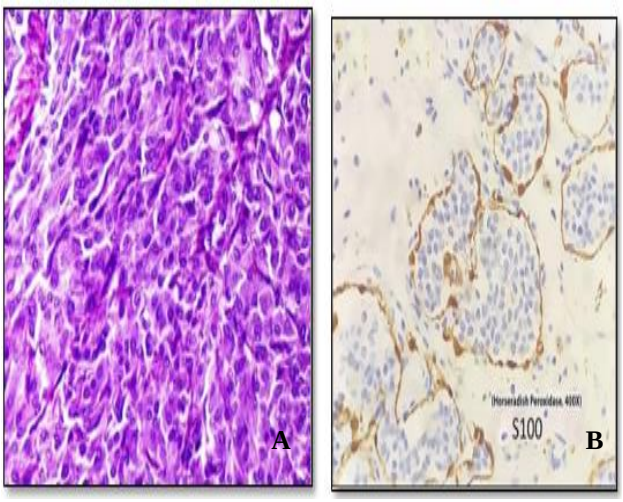

Figure 4: Histopathology and immunohistochemistry in case 1 (A) packed nests of polygonal to ovoid cells (Zellballen with abundant pattern) cytoplasm with anisonucleosis (400X H and E staining) eosinophilic.

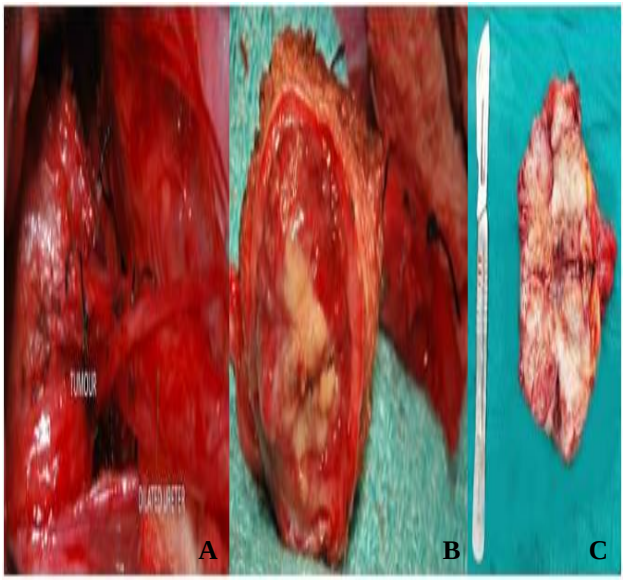

Figure 3: Case 1: (A) intra-operative and excised specimen; (B) with cut section; and (C) after distal ureterectomy with partial cystectomy.

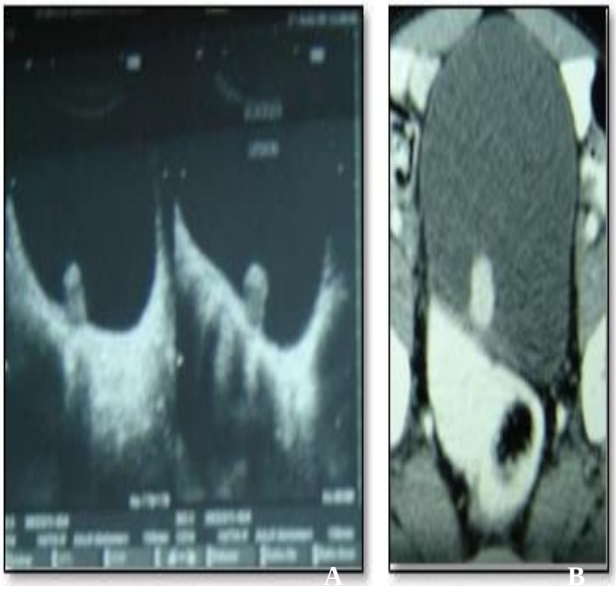

Figure 5: (A) USG and; (B) CECT image showing a 2.5×1.5 cm polypoidal enhancing mass over right posterior wall of the urinary bladder.

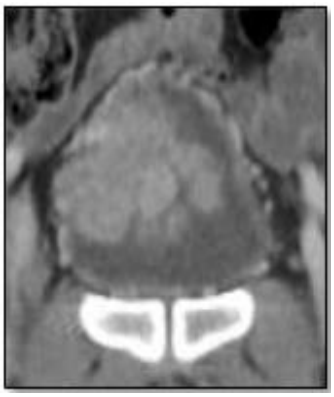

Figure 6: CECT finding of case 3- polypoidal enhancing growth of 8.4×5.7×4.9 cm in the dome and right lateral bladder.

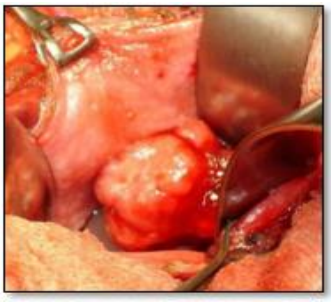

Figure 7: Intra-operative image in case 5- image of the posterior bladder wall polypoidal growth during partial cystectomy.

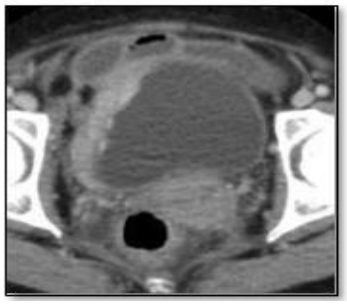

Figure 8: CECT finding in case 6- CECT image showing irregular heterogeneously hyper-enhancing wall thickening of right lateral wall.

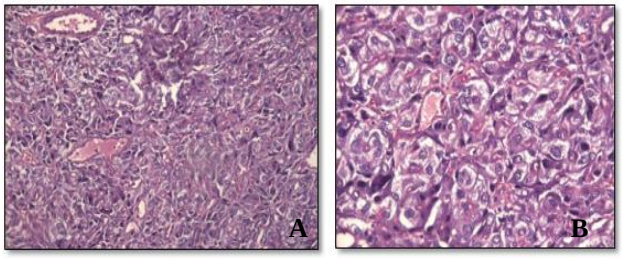

Figure 9: Classical histopathological feature in paraganglioma- H and E staining: Zellballen rrangement of polygonal cells (A) 20×; and (B) 400×.

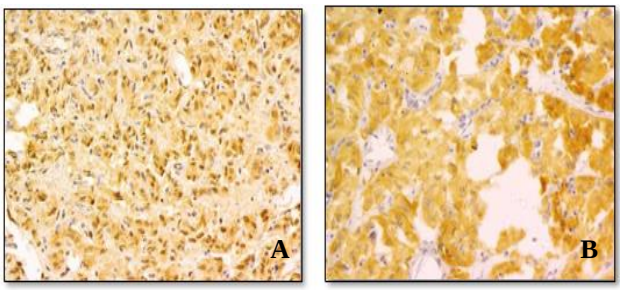

Figure 10: Classical immunohistochemistry in paraganglioma immunoreactivity of (A) chromogranin at 200× and; (B) synaptophysin (at 400×) in the tumor cells.

DISCUSSION

UBP's are rare bladder mesenchymal tumors with variable biological behavior. With around 200 cases described in world literature, they account for <0.05% of all bladder tumors, <1% of all pheochromocytomas and < 6% of all extra-adrenal pheochromocytomas.[2-5] Male predominance in our patient cohort is contrary to female predominance reported in literature.[7,8,10,11] Presentation in young patients ranging from 12-48 years is similar to the reported increased prevalence in the middle-age group.[7,8,10,11] Common differentials being urothelial carcinomas are common in men between 50-70 years of age.[12]

Most of the times, diagnosis of UBP is missed preoperatively. Differentiating non-functional UBP from urothelial cancer of bladder is difficult and often made by histopathological examination. In the presence of young age, hypertension, micturition syncope, early onset hypertension serves as cues for more detailed evaluation of preoperative diagnosis of UBP. In particular, in the cases where micturition attack was noted, a preoperative diagnosis was made in over 80% of the cases.[22]

Majority of the patients in our case series, presented with storage lower urinary tract symptoms. It was difficult to attribute these storage symptoms to a bladder mass of a certain size or particular location in bladder. Symptoms may be due to intramural origin of these tumors. Gross painless hematuria seen in three patients is presumed to be due to the inflammatory mucosal changes with increased vascularity or rupture of microvasculature. Hematuria was considered one of the most common clinical features in both functional and non-functional tumors and overlaps diagnosis of urothelial cancers.[10,14,20] Most of these tumors included in our study presented as nonfunctional tumors and the diagnosis was confirmed by histopathological examination.[7,8] Functional tumors presented with features of catecholamine excess such as headache, paroxysmal hypertension or postmicturition syncope.[8] Post micturition syncope is hypothesized to occur due to release of catecholamines in circulation during bladder contraction causing vasoconstriction and hypertension which is short lived followed by bradycardia and vasodilatation leading to hypotension due to peripheral pooling.[23] In our series

history of hypertension, post micturition syncope and elevated urinary VMA contributed to the diagnosis of functional tumours in three patients.

Four patients (57.14%) presented with well circumscribed homogenous hyperenhancing mass on CECT, whereas two patients (28.57%) presented with polypoidal mass. One patient presented with irregular heterogeneously hyperenhancing wall thickening. These imaging features are nearly identical to the hyperenhancing masses reported in literature.[6,9] This appearance of smooth intramural lesions should be differentiated from urothelial tumors which appear as irregular intraluminal filling defects.[12] However, no imaging features to differentiate functional from non-functional tumors have been described. MIBG study is highly specific for the detection of paragangliomas, while MR imaging is the most sensitive. On MRI, the tumour shows a characteristic salt-and-pepper appearance and heterogeneously hyperintense in T2 are noted.[10] None of our patient had MRI or MIBG done.

UBPs can be differentiated from urothelial carcinoma, squamous cell carcinoma, and adenocarcinoma, with a glossy and continuous mucosa seen on cystoscopic examination.[24] Posterior wall was the commonest site. Literature evidence suggests a similar appearance of single to multiple, small, ovoid tumors being the most common cystoscopic feature.[7,10] This appearance can be differentiated from urothelial tumors which are usually irregular papillary masses, pedunculated or sessile with increased vascularity but differentiation from solid flat tumors may be difficult. Most of the urothelial tumors are present on the base of the bladder (80%) and can invade the bladder wall or adjacent viscera.[12]

Complete surgical removal is the standard management for paragangliomas, and depending upon size and location includes partial or radical cystectomy.[11,13,14] Paragangliomas are intramural bladder tumors and adequacy of transurethral resection is questionable. Furthermore, over distention by bladder irrigation during TURBT or electrical stimulation during resection can result in fluctuation of blood pressure, in functional tumors.[15,16] However, TURBT for small tumors is also considered as an accepted practice considering its shorter recovery period.[17] In the present series, partial cystectomy with 5 mm margin, after adequate optimization with initially with alpha blocker and later with add on beta blockers was done in the preoperatively diagnosed functional tumour (case 3). Patient with distal ureteric involvement (case 1) and broad based polypoidal mass (case 5) were also considered for partial cystectomy with distal ureterectomy, after endoscopic evaluation. Other three patients (case 2, 4 and 7) underwent transurethral resection as per protocol for bladder tumors. After complete tumour excision, deep biopsy was separately sent for evaluation to ensure adequacy of resection with negative margin status. Multiple, large or polypoidal tumors or preoperatively diagnosed functional tumors form the basis to consider partial cystectomy as a primary procedure.[7,10] Most solitary, small, peri-ureteral orifice non-functional tumors are considered for TURBT and diagnosed as paraganglioma on histopathology.[7,10]

Post-operative follow-up protocols should include ultrasound, annual cystoscopy, serum or urine catecholamine analysis and 131I-MIBG scan.[13,18] Mean follow-up in our series is of 40.5 months. As a follow up strategy in our patients undergoing TURBT, a completion TURBT at 1 month to ensure complete resection was done in all which included a resection biopsy from the bed, similar to urothelial bladder tumours. All patients in our cohort had a negative biopsy. Annual follow up with ultrasound, check cystoscopy and urinary catecholamines diagnoses early recurrence. Apart from the patient lost to follow up, all patients have normal ultrasound and check cystoscopy in their annual check-up. Life-long follow-up is necessary to detect late recurrences.[19]

The characteristic histological feature includes packed nests of polygonal to ovoid cells with abundant eosinophilic cytoplasm with anisonucleosis arranged in the classical 'Zellballen' pattern (Figure 8). Immunohistochemical staining is usually positive for synaptophysin and chromogranin, with S-100 being highlighted in sustentacular cells was demonstrable in all the cases (Figure 9). No reliable histologic findings can distinguish benign from malignant paraganglioma. In our cohort all patients had similar histopathological features.

CONCLUSION

UBP are rare tumours with varied spectrum of presentation. Clinically and radiologically, it is difficult to differentiate UBP from urothelial tumors. In symptomatic cases, functional evaluation with biochemical analysis allows better treatment planning and avoiding intraoperative hemodynamic instability. In absence of functional symptoms, the presence intramural, solid, sessile tumors on CECT and non-urothelial appearance on cystoscopy should raise suspicion of UBP. Complete resection of the tumor by partial cystectomy and transurethral resection followed by completion TURBT prevents local recurrence. Long term follow-up is needed to detect recurrences early.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Priyadarshi V, Pal DK. Paraganglioma of urinary bladder. Urol Ann. 2015;7(3):402-4.
2. Monappa V, Jaiprakash P. Bladder paraganglioma- A report of two cases. African J Urol. 2018;24:70-2.
3. Ranaweera M, Chung E. Bladder paraganglioma: A report of case series and critical review of current literature. World J Clin Cases. 2014;2(10):591-5.

4. Kappers MH, Meiracker AH, Alwani RA, Kats E, Baggen MG. Paraganglioma of the urinary bladder. Neth J Med. 2008;66(4):163-5.
5. Vyas S, Kalra N, Singh SK, Agarwal MM, Mandal AK, Khandelwal N. Pheochromocytoma of urinary bladder. Indian J Nephrol. 2011;21(3):198-200.
6. Baez JC, Jagannathan JP, Krajewski K, O'Regan K, Zukotynski K, Kulke M, et al. Pheochromocytoma and paraganglioma: imaging characteristics. Cancer Imaging. 2012;12(1):153-62.
7. Chang YK, Chiang NI, Chen CH, Wang SM. Paragangliomas of the urinary bladder: A report of 6 cases and review of the literature. Urological Sci. 2015;26:111.
8. Menon S, Goyal P, Suryawanshi P, Tongaonkar H, Joshi A, Bakshi G, et al. Paraganglioma of the urinary bladder: a clinicopathologic spectrum of a series of 14 cases emphasizing diagnostic dilemmas. Indian J Pathol Microbiol. 2014;57(1):19-23.
9. Lee KY, Oh YW, Noh HJ, Lee YJ, Yong HS, Kang EY, et al. Extraadrenal paragangliomas of the body: imaging features. AJR Am J Roentgenol. 2006;187(2):492-504.
10. Deng JH, Li HZ, Zhang YS, Liu GH. Functional paragangliomas of the urinary bladder: a report of 9 cases. Chin J Cancer. 2010;29(8):729-34.
11. Ranaweera M, Chung E. Bladder paraganglioma: A report of case series and critical review of current literature. World J Clin Cases. 2014;2(10):591-5.
12. Loveys FW, Pushpanathan C, Jackman S. Urinary Bladder Paraganglioma: AIRP Best Cases in Radiologic-Pathologic Correlation. Radiographics. 2015;35(5):1433-8.
13. Young WF. Paragangliomas: clinical overview. Ann N Y Acad Sci. 2006;1073:21-9.
14. Cheng L, Leibovich BC, Cheville JC, Ramnani DM, Sebo TJ, Neumann RM, et al. Paraganglioma of the urinary bladder: can biologic potential be predicted? Cancer. 2000;88(4):844-52.
15. Quist EE, Javadzadeh BM, Johannesen E, Johansson SL, Lele SM, et al. Malignant paraganglioma of the bladder: a case report and review of the literature. Pathol Res Pract. 2015;211(2):183-8.
16. Vassilatou E, Argeitis J, Nika H, Grapsa D, Smyrniotis V, Pafiti A. Malignant paraganglioma of the urinary bladder in a 44-year-old female: clinicopathological and immunohistochemical study of a rare entity and literature review. Eur J Gynaecol Oncol. 2007;28(2):149-51.
17. Liu Y, Dong SG, Dong Z, Mao X, Shi XY. Diagnosis and treatment of pheochromocytoma in urinary bladder. J Zhejiang Univ Sci B. 2007;8(6):435-8.
18. Tsai CC, Wu WJ, Chueh KS, Li WM, Huang CH, Wu CC, et al. Paraganglioma of the urinary bladder first presented by bladder bloody tamponade: two case reports and review of the literatures. Kaohsiung J Med Sci. 2011;27(3):108-13.
19. Tsai SY. Bladder pheochromocytoma: a case report. Urol Sci. 2004:15.
20. Beilan JA, Lawton A, Hajdenberg J, Rosser CJ. Pheochromocytoma of the urinary bladder: a systematic review of the contemporary literature. BMC Urol. 2013;13:22.
21. Zhou M, Epstein JI, Young RH. Paraganglioma of the urinary bladder: a lesion that may be misdiagnosed as urothelial carcinoma in transurethral resection specimens. Am J Surg Pathol. 2004;28(1):94-100.
22. Kurose H, Ueda K, Uegaki M, Ogasawara N, Kumagae H, Chikui K, et al. Paraganglioma of the urinary bladder: Case report and literature review. IJU Case Rep. 2020;3(5):192-5.
23. Sunil VN, John K, Nawahirsha S, Iyyadurai R. Micturition syncope: a rare presentation of bladder paraganglioma. BMJ Case Rep. 2020;13(9):235353.
24. Male M, Ye T, Tao J, Chen ZQ, Peng E. Differentiating Nonfunctional Paraganglioma of the Bladder from Urothelial Carcinoma of the Bladder: Pitfalls and Breakthroughs. Biomed Res Int. 2019;2019:1097149.

Cite this article as: Kriplani A, Jain D, Kulshreshtha M, Chawla A, Reddy SJ, Pandit S, et al. Urinary bladder paraganglioma: a clinical dilemma in diagnosis and management- our experience at a tertiary care center. Int J Res Med Sci 2022;10:1183-90.