Paragangioma of urinary bladder, an innocent rarity or a nightmare: A case series report and review

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Abstract

Urinary Bladder Paraganglioma is rare form of extra-adrenal pheochromocytoma, accounting for less than 0.05% of all bladder tumours, commonly presenting with painless hematuria, headache, palpitation and micturitional syncope. Missed diagnosis of this rare condition puts patient at considerable risk, precipitating intraoperative hypertensive crisis, due to catecholamine release triggered by handling of tumour. The purpose of our presentation is to stimulate the physicians dealing with cases of bladder tumors that, with the characters of bladder tumors mentioned in the article, one should entertain a differential diagnosis of Bladder Paraganglioma, investigate to confirm the diagnosis and take appropriate measures to avoid an intraoperative mishap. We report three cases of Urinary Bladder Paraganglioma managed at a tertiary care hospital and discuss clinical features, pathology and review the previously published literature.

Keywords: Bladder; paraganglioma; pheochromocytoma

Introduction

Urinary bladder paraganglioma are the commonest extra-adrenal pheochromocytoma in Genitourinary System, reported first by Zimmerman in 1953[1]. They arise from extra-adrenal para-ganglia and are composed of specialised neural crest-derived cells which are catecholamine-secreting chromaffin cells[2]. Urinary bladder Paraganglioma account for 0.05% of all bladder tumours and 6% of extra-adrenal pheochromocytoma [3]. In the genitourinary tract, the most commonest site is urinary bladder (79.2%), followed by the urethra (12.7%), renal pelvis (4.9%), and ureter (3.2%) [4, 5]. Patients sometimes present with atypical signs and symptoms which make establishing a pre-operative diagnosis difficult.

Case presentation

After approval from local ethics committee, Hospital records of three patients who were diagnosed with urinary bladder paraganglioma during period January 2014 to December 2021 were perused with an aim to study the clinical features, diagnosis and treatment received. The details are summarised in Table 1.

Three patients were diagnosed as urinary bladder paraganglioma on postoperative histopathology.

Out of three patients, two were male and one female. The age of patients ranged from 20-60 years. All three patients presented with painless gross hematuria. Only one patient retrospectively recalled history of micturitional syncope. One patient presented with clot retention. Only one amongst the three was Hypertensive.

All the patients underwent preliminary investigations, including hematological, biochemical, Ultrasound & Urine cytology after hospitalization. Preoperative Ultrasound showed nodular, hyper echoic, vascular intravesical lesion ranging in size from 2.5 to 4.5 CMs (Figure 1). Contrast enhanced CT (CECT) (figure 2a & 2b) showed nodular, intensely enhancing lesions, limited to the bladder.

The patient who had presented with clot retention was taken up for emergency clot evacuation and was found to have a nodular lesion which was biopsied. The other two patients were subjected to Transurethral resection of bladder tumour (TURBT). Two patients developed hypertensive crisis during resection of tumour which was managed with Nitroglycerine drip and settled after 4 hours. The resection of tumour was stopped in these two patients due to hypertensive crisis.

To our surprise, Histopathological examination revealed Paraganglioma. Post operatively Serum Metanephrines and Urinary VMA were sent, which turned out to be normal in all three patients.
All three patients were advised partial cystectomy. However one patient refused surgery and was lost to follow up. The other two patients were followed up with history, physical examination, Ultrasound and Cystoscopy. There were no recurrences

**Discussion**

Paraganglioma of urinary bladder is rare tumour accounting for less than 0.05% of all bladder tumours and 1% of catecholamine secreting neoplasms. Though sporadic in incidence, an increasing percentage of cases are being diagnosed as part of familial genetic syndromes and in certain familial syndromes, the risk of malignant transformation reaches as high as 50% [6]. Paraganglioma are extra-adrenal pheochromocytomas arising from the embryonic rests of chromaffin cells within the urinary bladder wall, often present in young women in their second to fourth decade of life [7]. Most of the bladder paraganglioma are solitary and localised to submucosa of dome or the trigonal regions [8, 9]. Depending upon the catecholamine secretion, these tumours can be functional or nonfunctional, the former making up 83% of all paraganglioma [10]. Most frequently these tumours present with symptoms of heightened catecholamine secretion like hypertension, palpitations, headache, micturation syncope and sometimes those symptoms due to tumour itself like haematuria and difficulty in voiding. The functional symptoms present in only 50% [11]. In our series only one patient had a history of micturition syncope and another was hypertensive. The functional symptoms get triggered by defeation, sexual activity, ejaculation, bladder instrumentation. In our series two patients, two developed severe hypertension during transurethral resection of tumour which settled on stopping the resection and starting nitroglycerine.

Hematuria as a presenting symptom is seen in about 50-60% of cases [12]. In our case series all three patient presented with Hematuria. A seemingly nonfunctional bladder paraganglioma, presenting only with gross hematuria is often managed as any other bladder tumour till the hypertensive crisis gets triggered intraoperatively by tumour handling.

In 83% of cases of paraganglioma show elevated levels of urinary metanephrines and serum catecholamine [13, 14] in our series none of the patients had elevated catecholamines or their urinary metabolites. Yamamoto et al reported that only 28.9% could be diagnosed preoperatively and rest were managed as urothelial bladder tumours [15].

Paraganglioma appear as highly vascular solid lesion on ultrasound (Figure1). On contrast enhanced CT scan these tumours appear as polypoidal, sessile tumours which show intense enhancement due to rich capillary network and delayed washout [16] which was seen case in two of our patients (Figure 2a & 2b). CECT also helps to delineate extra-vesical extension and pelvic lymphadenopathy. On MRI the paraganglioma appears as multilobulated lesions, heterogeneously intense to bladder muscle on T1, with an admixture of hyper-intense & hypo-intense foci appearing as classical Salt & Pepper appearance [17] suggestive of paraganglioma. These feature help in raising a suspicion that a nodular polypoidal lesion in bladder could be paraganglioma, investigate further and try to avoid hypertensive crisis during the resection of tumour. Suspecting an uncommon pathology like a paraganglioma of bladder, should lead to measurement of catecholamines and urinary metanephrines and to prepare patient before resection of bladder tumour. CT and MRI are highly sensitive (90-100%), but relatively less specific (70-80%) [18].

1131 or 1123 Metidobenzylguanidine (MIBG) helps in localisation of metastastic disease and multifocal tumours. Due to non-availability of facility none of our patient underwent 1131 MIBG scan. Compared to 1131 MIBG, 1123 MIBG has better sensitivity (90% v/s 85.7%), but both have equal specificity of 100% [19].

Under microscopy the tumours are polygonal with granular eosinophilic cytoplasm and arranged in organoid pattern separated by fibrovascular stroma, which is described as typical Zelleballen pattern (Figure-4). On immunohistochemistry, the cells stain for S-100, chromogranin, Nonspecific enolase, and Synaptophysin. Though there are no reliable histological criteria to distinguish a malignant lesion from benign, malignancy is suspected in those tumors showing local invasion and distant metastases. Only 15% of paraganglioma are metastatic and show local invasion [8, 9].

In the absence of uniform standard management protocol, the treatment options include Transurethral resection of tumour (TURBT) and Partial or Total cystectomy with pelvic lymphadenectomy, latter restricted to those cases with proven metastasis [20]. Patients with functional tumours with symptoms of catecholamines release like,
hypertension, palpitations and micturational syncope need pre-operative stabilization with control of hypertension, volume repletion before the surgery. Nonselective alpha-blocking agents e.g. Phenoxybenzamine are preferred to control the hypertension. Those patients in whom a pre-operative diagnosis is not possible and hence are poorly prepared, are exposed to great risk due to intraoperative catecholamine release triggered by tumour handling [21]. Though the tumour can be resected transurethrally, due to involvement of the bladder muscle wall, partial cystectomy is preferred [22, 23]. Two of our patients underwent partial cystectomy (Figure.3).

Fig 1: Ultrasound examination showing hyperechoic mass (arrow)

Fig 2a: Computed Tomography showing bladder mass. (arrow)

Fig 2b: Nodular mass with Intense enhancement. (arrow)

Fig 3: Intra-operative photograph showing nodular tumour in bladder

Fig 4: Solid arrow showing Nest of Tumour cell Hollow arrow showing fibrovascular septa- “classical Zellballen Pattern” (40x magnification)

Conclusions
Paraganglioma of urinary bladder are a rare form of extra-adrenal pheochromocytoma, which need a high index of suspicion to make a preoperative diagnosis. Majority of them are functional and a lack of pre-operative diagnosis and preparation expose these patients to greater risk & morbidity, arising out of hypertensive crisis, triggered by sudden release of catecholamines on tumour handling.

List of Abbreviations: Not Applicable

Conflict of Interest
Not available

Financial Support
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