Spectrum of retroperitoneal and genitourinary paraganglioma: Experience at a North Indian tertiary care center

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Introduction

Genitourinary and retroperitoneal paragangliomas are infrequent tumors with bizarre presentation. A high index of suspicion is required to make a diagnosis in young hypertensive individuals. Our aim is to study the varied clinical presentations and management of these paragangliomas. Herein, we share our experience of clinical presentation, diagnosis, and management of these paragangliomas.

Material and methods

Seventeen consecutive patients who underwent surgery for paraganglioma at our institute from August 2009 to July 2014 were included. Demographic, peri-operative, surgical, and follow up data were collected and analyzed.

Results

Mean age of presentation was 34.8 years with female predominance. The majority of the tumors were located in the retroperitoneum and urinary bladder. Most of them presented with classical symptoms of catecholamine excess and hypertension. Complete surgical resection could be performed in 13 cases. At a median follow up of two years, cases with R0 resection (no microscopic malignant cells) did not show recurrence. Among patients on chemotherapy, one died, another had partial response, and yet another had progressive disease.

Conclusions

Genitourinary and retroperitoneal paragangliomas are a disease of a young age group with variable clinical features at presentation. Appropriate pre-operative optimization and complete surgical resection provide the best chance of cure.

Key Words: genitourinary • malignant • paraganglioma • renal • retroperitoneal

INTRODUCTION

Retroperitoneal and genitourinary paragangliomas are rare neuroendocrine tumors arising from sympathetic chain ganglia. They arise from paraganglia, a network of chromaffin producing neural crest tissue that anatomically parallels the sympathetic and parasympathetic ganglia in the head, neck, thorax, abdomen, and pelvis. Clinical presentation is bizarre, requiring a high index of suspicion for diagnosis to avoid catastrophic perioperative complications.

• To study the varied clinical presentations and surgical management of retroperitoneal and genitourinary paragangliomas.

• To identify the role of good perioperative management for optimal outcome of patients who underwent complete surgical resection.

• To address surgical challenges in performing complete surgical resection of these tumors.

• To study post operative course and follow up.

MATERIAL AND METHODS

We analyzed the data of 17 consecutive patients who underwent surgery for abdominal and genitourinary paraganglioma from August 2009 to July 2014 at our institution. All patients were admitted and evaluated by an endocrinologist and a urologist. Serum
### Table 1. Summary of 17 cases

| S no. | Gender | Site | Size (cm) | Comorbidities | Presentation | Hormonal analysis | Imaging | Surgery | Peri-operative | Remark |
|-------|--------|------|-----------|---------------|--------------|------------------|---------|---------|----------------|--------|
| 1     | 42/F   | Urinary bladder | 5x3.5 | Nil | Gross hematuria | U. Metanephrine 16 µg/day, U. Normetanephrine 178 µg/day | CECT | Partial cystectomy | Uneventful | Diagnosis: Shot in BP while TURBT |
| 2     | 44/F   | Urinary bladder | 4x5  | Nil | Gross hematuria | P. Metanephrine 20.8 µg/ml, P. Normetanephrine 61 µg/ml | CECT | Partial cystectomy | Uneventful | Diagnosis: Shot in BP while TURBT |
| 3     | 52/M   | Urinary bladder, Metastatic | 10x8 | HTN | Classical, Gross hematuria | P. Metanephrine 39.8 µg/ml, P. Normetanephrine 1100 µg/ml | CECT DOTATATE | RC with IC | Uneventful | Adjuvant chemotherapy |
| 4     | 14/M   | Urinary bladder and inter-aorto-caval | 3.8x3 | Nil | Classical, Micturitional headache | P. Metanephrine 73.8 µg/ml, P. Normetanephrine 1479 µg/ml | CECT DOTATATE | Mid line Partial cystectomy with excision of inter-aortocaval lesion | Uneventful |
| 5     | 16/M   | Prostate Metastatic | 2.4x2.2 | HTN | Classical, Micturitional headache, Obstructive uropathy, LUTS | P. Metanephrine 24 µg/ml, P. Normetanephrine 1153 µg/ml | CECT DOTATATE, PET CT | Midline transperitoneal Excision | Uneventful | Diagnosis: true-cut Trans-rectal biopsy, Adjuvant chemotherapy |
| 6     | 26/F   | Pelvis | 8x6.4 | DM, HTN | Classical, Micturitional headache | P. Metanephrines 680 µg/ml | CECT DOTATATE | Lower midline Excision with Partial cystectomy | Uneventful | Mimicking Bladder phaeochromocytoma |
| 7     | 45/F   | Pelvis | 5x5   | Nil | Vague pain lower abdomen | P. Metanephrine 15.3 µg/ml, P. Normetanephrine 101 µg/ml | CECT DOTATATE | Lower midline transperitoneal Excision | Uneventful |
| 8     | 40/F   | Left Intra-Renal | 12x10 | DM, HTN | Gross hematuria | N/A | CEMRI | Lt Radical nephrectomy by left subcostal transperitoneal | Uneventful | Diagnosis: intraop shot in BP |
| 9     | 17/F   | Para-aortic | 12x10 | HTN, HCV+ | Classical | P. Metanephrine 27 µg/ml, P. Normetanephrine 153 µg/ml | CECT DOTATATE | Lap transmesocolic excision | Uneventful |
| 10    | 23/F   | Left renal hil | 4x3   | HTN | Classical | U. Metanephrine 135 µg/day, U. Normetanephrine 7218 µg/day | CECT DOTATATE, PET CT | Midline transperitoneal Excision | Uneventful | Renal preservation |
| 11    | 35/M   | Right renal hil | 5x4   | Nil | Classical | U. Metanephrine 43.5 µg/day, U. Normetanephrine 700 µg/day | CECT DOTATATE, PET CT | Midline transperitoneal Excision | Uneventful | Dense adhesion to great vessels Intraop IVC injured → repaired |
| 12    | 36/F   | Retroperitoneum, metastatic | 8.4x6.4 | HTN | Flank pain | P. Metanephrines 660 µg/ml | CECT DOTATATE, PET CT | Midline transperitoneal R2 Excision with right nephroureterectomy | Dense adhesion to great vessels Intraop IVC injured → repaired |
| 13    | 53/F   | Inter-aorto-caval | 12x7.5 | HTN | Classical | P. Metanephrines 124 µg/ml | CECT PET CT | Midline transperitoneal Excision | Uneventful | Rt lower limb DVT in post operative period |
| 14    | 21/M   | Retroperitoneum, Multiple | 8x5 | 2x2 Multiple subcentimetric | HTN | Pain abdomen | U. Metanephrines 338 µg/day | CECT DOTATATE | Midline transperitoneal R2 Excision | Dense adhesion to great vessels |
| 15    | 20/F   | Retroperitoneum, Multiple | 6.8x3.8 | 5.2x3 Multiple subcentimetric | Classical | P. Metanephrine 20 µg/ml, P. Normetanephrine 139 µg/day, U. Normetanephrine 667 µg/day | CECT PET SCAN, PET CT | Midline transperitoneal Excision | Uneventful | Left poorly functioning kidney secondary to poor flow |
| 16    | 55/M   | Retroperitoneum | 6x5  | HTN | Headache | U. Metanephrine 739 µg/day | CECT DOTATATE | Midline transperitoneal Excision | Uneventful | CABG and Excision in single sitting |
| 17    | 54/F   | Para-aortic | 6x4   | DM, HTN | Pain abdomen | Dyspnea | U. Metanephrine 9.09 µg/day, U. Normetanephrine 1967 µg/day | CECT PET SCAN, PET CT | Left subcostal transperitoneal Excision with nephrectomy | Uneventful | Small nonfunctioning left kidney |

P: Plasma, U: Urine, Metanephrines: Metanephrine+ normetanephrine, HTN: Hypertension, DM: Diabetes mellitus, HCV: Hepatitis C virus, EC: Ethylenediamine, BP: Blood pressure, TURBT: Trans urethral resection of bladder tumour, RC: Radical cystectomy, ICI: Ileal conduit, CCD: Continent cutaneous diversion, CECT: Contrast enhanced computed tomography, CEMRI: Contrast enhanced magnetic resonance imaging, PET: Positron emission tomography, MIBG: Meta-iodobenzylguanidine, DOTATATE: Amide of the acid DOTA, CABG: Coronary artery bypass graft, LUTS: Lower urinary tract symptoms, DVT: Deep vein thrombosis, IVC: Inferior vena cava, Lap: Laparoscopic, N/A: Not Available
and/or urinary free and/or total metanephrine levels were measured in 16 patients. Cross sectional imaging was by tri-phasic CECT of abdomen and pelvis or MRI. $^{18}$ Fluorodeoxyglucose positron emission tomography ($^{18}$FDG PET) scan was performed on 5 patients, while $^{68}$Ga DOTA-TATEPET was performed on 11 patients. Preoperatively, patients were monitored with at least twice-daily blood pressure measurements (both supine and standing). The target blood pressure was achieved in all patients (except one) with use of sequential $\alpha$ and $\beta$ blocker for two weeks. All patients were infused 2 litres of normal saline the night before surgery to prevent rebound hypotension in postoperative period as per the institution’s protocol. All cases were operated by a single surgeon. Two patients underwent laparoscopic surgery, while the rest were operated by open approach. Follow up data was collected from outpatient department (OPD) visits, telephonic consultations, as well as re-admissions.

RESULTS

Table 1 gives an overview of 17 cases included in our study. Age of presentation ranged from 16 to 53 years with mean age being 34.8 years. Female preponderance was noted (F:M = 3:1). Ten patients had elevated catecholamine levels. Presentation varied according to the site as shown in table 1. The patient with prostatic paraganglioma presented with hematuria, micturitional headache, and hypertension. On subsequent evaluation (CT, DOTATATE, $^{123}$I MIBG), he was found to have obstructive uropathy (serum creatinine 3 mg/dl) and solitary metastasis in the left humerus. After bilateral percutaneous nephrostomy (PCN), the serum creatinine became normal and patient was taken for radical cystoprostatectomy with continent cutaneous diversion (CCD).

Another young female presented with classical symptoms having a past history of eclampsia, in which the

Figure 1. CECT of abdomen and pelvis showing well enhancing lesion arising from the left lateral wall of the urinary bladder (a). DOTATATE scan of the same patient showing a second lesion in the inter-aortocaval region (b). Another patient with pelvic paraganglioma mimicking urinary bladder mass on CECT scan (c). Intra-operative photograph of the same patient showing pelvic paraganglioma sparing the bladder wall (d). BN – bladder neck, T – tumor, UB – urinary bladder.
baby was delivered by caesarean section. On evaluation, she was found to have pelvic paraganglioma seems to involve urinary bladder. This patient was taken up for surgery with the plan of radical cystectomy if needed, but complete excision of lesion could be performed with preservation of the urinary bladder and ureter (Figure 1).

All retroperitoneal cases which underwent open surgery were approached by a midline incision. For two patients with multiple retroperitoneal paragangliomas, small bowel mesentery was lifted up in a manner similar to retroperitoneal lymph node dissection (RPLND). In two patients, lesions were densely adherent to great vessels, retroperitoneum, and sacral promontory, so R2 resection (macroscopic residual tumor) could be performed (Figure 2). In one patient, the lesion was encasing the right ureter with gross hydronephrosis (HDUN) and thinned out renal parenchyma; en-bloc nephroureterectomy was performed (Figure 3).

Mean operative time was 87 minutes (range: 60–240), and 60 minutes in each laparoscopy case. Blood loss ranged from 50 ml to 900 ml, with less loss in both laparoscopy cases. Adjuvant chemotherapy comprising of cyclophosphamide, vincristine, and dacarbazine (CVD) was administered in 3 patients. In the postoperative period, blood sugar level became normal in all functional tumors except one patient with left renal paraganglioma. In the post-operative period, hypertensive drugs were not needed in 5 patients and 6 could be managed with single drug.

**Follow up**

Follow up data was available for fifteen patients. All patients were advised for follow up with serum/± urine

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**Figure 2.** CECT abdomen showing retroperitoneal paraganglioma with loss of fat planes with aorta (a). Intra-operative photograph showing aortic encasement by the tumor (b). Tumor was densely adherent to the retroperitoneum and aorta and an R2 resection could be done with preservation of major vessels (c). Gross specimen of the resected tumor (d). A – aorta, IVC – inferior vena cava, T – tumor.

**Figure 3.** DOTATATE PET scan of retroperitoneal paraganglioma in pelvis showing good uptake (a). Intraoperative photograph showing gross hydronephrosis on right side secondary to ureteric encasement by the tumor (b). Gross specimen (c). K – kidney, T – tumor, U – ureter
metanephrines levels yearly and cross-sectional imaging when required. The patient who underwent radical cystoprostatectomy with focal radiotherapy for humeral metastasis and adjuvant chemotherapy, showed partial response at 4 months of follow up. Two other patients on chemotherapy showed disease progression, with one dying a year after radical cystoprostatectomy. Patients who had undergone R0 resection did not show tumor recurrence at a median follow up interval of 2 years.

**DISCUSSION**

The classic symptoms in functional paragangliomas occur secondary to episodic release of excess catecholamine into circulation. They include headaches, palpitations, anxiety, and diaphoresis. Hypertension can be paroxysmal (48%) or persistent (29%). Blood pressure may be normal in up to 13% of patients. Non-specific symptoms, such as weakness and chronic fatigue, are also quite common confounding the diagnosis of paragangioma. Due to their bizarre clinical manifestations with a low prevalence, the timely and accurate diagnosis of paragangliomas may be challenging [1-5]. Urologic symptoms, such as episodic hematuria with characteristic headache, hypertension, palpitations, diaphoresis, syncope, or blurred vision after voiding or during cystoscopy, are characteristic of urinary bladder paragangioma [6, 7, 8]. In this study, the presentations were variable (Table 1). Emphasis on pre-operative diagnosis is needed because in the past, reported mortality rates were up to 50%, when surgery was usually done without prior catecholamine blockade. In the current era, it is less than 3% [9]. Paragangliomas usually occur in the third to fifth decades with equal gender distribution. In our patients, the average age of presentation was 34.8 years, which is same as reported in literature; however, female predominance was noted in a ratio of 3:1. Age of presentation may predict the tumor’s catecholamine phenotype and underlying genetic mutation. Patients with an established mutation or hereditary syndrome may manifest at a younger age with an average age of presentation in the third decade, in contrast to those with sporadic disease, who usually present in the fifth decade. Also, epinephrine secreting tumors tend to manifest at a later age [3, 10]. Pelvic paraganglioma can rarely present as non-functioning kidney with accelerated hypertension [11].

Biochemical testing is the first step in the evaluation of patients suspected of pheochromocytoma/paraganglioma. If biochemical tests are positive for high metabolic activity, appropriate imaging is undertaken to localize the source. Though functional imaging is not necessary in the preoperative workup of all paragangliomas, it may be needed to differentiate a paraganglioma from a neurogenic tumor, lymph node disease, or a mesenchymal tumor in the retroperitoneum. Moreover, since genetic status is often not available before surgery, biochemical testing may be considered for large lesions (>5 cms), young age (<40), and multiple lesions [12-16].

On plain CT images, lesions may show uniform attenuation, but in general, they are non-uniform with solid or cystic complex masses and may contain calcification. In contrast phase, these lesions typically enhance avidly, although the cystic area, if any, may remain unenhanced. Urinary bladder paraganglioma appears as a well-defined nonpapillary, well enhancing heterogenous lesion. Paragangliomas usually demonstrate low signal on T1-weighted and high signal on T2-based contrast agents. Cystic degeneration and hemorrhage within these lesions can cause further diagnostic challenges on MR imaging. Intra-renal paragangliomas may mimic renal cell carcinoma on pre-operative imaging [17]. The molecular structure of MIBG resembles that of norepinephrine, showing high affinity for the norepinephrine transporter system. $^{131}$I-MIBG causes low radiation dose, superior image quality, and high sensitivity in comparison to $^{131}$I-MIBG. Still, because of low sensitivity and specificity, this modality is valuable for familial syndromes with multiple neuroendocrine tumors at different sites, multifocal tumors, and relapsing and metastatic disease [18]. PET provides images with high spatial and contrast resolution, and improved image quality allows for detection of small lesions anywhere in the entire body. The most commonly used radiopharmaceutical for PET is 2-[fluorine18] fluoro-2-de-oxy-D-glucose (FDG) which has poor specificity for pheochromocytomas. To overcome this, noradrenergic transporter systems were targeted by PET tracers. This involves the use of $^{18}$F-fluorodopamine ($^{18}$F-DA), 18F-dihydroxy phenylalanine (DOPA), $^{11}$C-epinephrine, $^{11}$C-hydroxyephedrine (HED), $^{68}$Ga-DOTA compounds, and somatostatin receptor (SSTR) analogues. All these functional imaging studies have shown higher sensitivity and specificity in their initial experiences; however, metastatic lesions could not be picked up well. Data with $^{68}$Ga labeled agonists are still in infancy, but have bee found to be sensitive in the detection of rapidly progressing metastatic paraganglioma, especially in those with no or little avidity for MIBG. We performed $^{18}$FDG PET in 5 patients and $^{68}$Ga-DOTA PET in 11 patients and lesions were picked up by both. In 2 patients, FDG-PET and DOTATATE PET both were performed and latter was superior for localization [4, 12, 13, 19, 20].
To rule-out cardiomyopathy, preoperative cardiac evaluation and echocardiography is recommended. For catecholamine blockade, sequential α and β antagonists are the most commonly used drugs, alternatives being calcium channel blockers and the tyrosine hydroxylase inhibitor metyrosine. Preoperatively, patients should be monitored with at least twice-daily blood pressure measurements (both seated and standing to evaluate for orthostatic hypotension). In our patients, we used sequential α and β blocker. With regard to anesthetic care, fentanyl, ketamine, and morphine should be avoided because of their potential to stimulate catecholamine release. The use of atropine is discouraged because of its potential to cause tachycardia. Anesthetic gases with the least amount of cardiac depressant effects are preferred, while halothane and desflurane are generally avoided. Higher plasma norepinephrine concentrations, large tumor size (>4 cm) and postural hypotension following α-adrenergic blockade are associated with an increased risk of intraoperative hemodynamic instability. Intraoperative acute hypertensive crises can be managed with intravenous administration of esmolol, sodium nitroprusside, phentolamine (short acting α-blocker), or nicardipine. We used esmolol and sodium nitroprusside infusion because of the rapid onset of vasodilatory properties and shorter duration of action. In cases of atrial and ventricular arrhythmias, intravenous esmolol and lidocaine, respectively, are the agents of choice [2, 3, 7, 21].

Complete surgical excision is central to addressing paragangliomas. In the current era, most of pheochromocytomas and many paragangliomas are being treated with minimally invasive procedures whenever feasible. Laparoscopy is not advisable for locally invasive and/or large tumors or where organ resection is required. Unfortunately, open surgical approaches, although extremely effective, are associated with significant postoperative discomfort and recuperation. Minimally invasive surgical approaches were born out of the desire to address secondary issues related to surgery, including incisional pain, convalescence, and cosmesis. In our patients, only two could be removed laparoscopically, while the rest needed open surgery because of their size, location, and complexity. One patient with left intrarenal lesion was planned for laparoscopy, but attendants and the patient opted for open radical nephrectomy. Trans-mesocolic excision has been reported in literature. In our series, two patients (left renal hilar and paraaortic) were operated laparoscopically by transmesocolic approach with great caution to prevent renal vessels and ipsilateral ureter injury. Three ports were placed in each patient. In cases of locally invasive and/or metastatic lesions, options include palliative tumor resection to reduce tumor burden and excess catecholamine related symptoms [22]. Involvement of adjacent organ may require en bloc removal such as in one of our case, where right nephro-ureterectomy was performed because of invasion of the ureter with upstream hydrourereteronephrosis and adhesion to the great vessels and retroperitoneum. Left nephrectomy was performed for one patient with left para-aortic paraganglioma with a small nonfunctioning kidney. Bladder tumors with classical symptoms and radiological suspicion should be worked up for paraganglioma. Endoscopically, these tumors appear well circumscribed, solid looking, and solitary, with normal overlying mucosa anywhere in the bladder. In our patients, lesions were solid looking, solitary, and located in the base and trigone region in one, left lateral wall in one, and in the dome region. One was metastatic. For bladder paraganglioma, partial or radical cystectomy with pelvic lymph node dissection is the treatment depending upon size and location of lesion. We were able to save the bladder in two patients. Pelvic paragangliomas may appear arising from the urinary bladder on pre-operative imaging. Intra-operative identification of this scenario shall prevent inadvertent injury to urinary bladder with complete surgical excision [23]. In females, it is a rare, but very important, differential diagnosis of a tubo-ovarian mass [24]. Retroperitoneal multiple lesions are among the most difficult cases for surgery in the view of vicinity and adherence to great vessels and their branches. In our series, two retroperitoneal tumors could not be removed completely [4, 8].

Hypotension and hypoglycemia are the most common immediate postoperative complications. Patients need continuous intraoperative vital and blood sugar monitoring and for at least 48 hours following surgery. Data regarding follow up is scarce. Recent reviews suggest lifelong follow-up of patients with extra-adrenal pheochromocytoma, with yearly follow up in the initial 10 years [3]. Evaluation at follow up includes history and physical examination, blood pressure measurement, catecholamine level testing, and cross sectional imaging.

For patients with metastatic disease or incomplete excision, options include CVD regimen (cyclophosphamide 750 mg/m^2 body surface on day 1, vincristine 1.4 mg/m^2 body surface on day 1, and dacarbazine 600 mg/m^2 body surface on day 1 and 2, repeated every 21 days). However, benefits of CVD therapy for metastatic pheochromocytoma appears to be short-term and do not include an increase in patient survival. Other options are temozolomide, temozolomide with thalidomide, or targeted radio-
therapy with $^{131}$I-MIBG. Treatment of metastatic and inoperable paragangliomas with mTOR inhibitor, tyrosine kinase inhibitors, and interleukins are under trial [2, 25].

CONCLUSIONS

1. Paragangliomas are very infrequent lesions with bizarre presentation and wide area of location. If taken for surgery without diagnosis and preparation, high risk of catastrophic events may happen secondary to hypertensive crisis.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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