REVIEW ARTICLE

Retroperitoneal Paraganglioma often Atypical: Short Case Series and Review of the Literature

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Abstract

Retroperitoneal paragangliomas (rPGL) are rare chromaffin cell tumors traditionally associated with symptoms of catecholamine excess; however, this notion is currently in question. Three cases of rPGL that were presented consecutively to our center over a period of 6 months are discussed. Each presented under completely different circumstances; the first was detected during diagnostic workup for weight loss; the second was found synchronously during workup for gynecological malignancy; and the third was diagnosed postoperatively following resection of an incidentally detected, asymptomatic retroperitoneal tumor. In all cases, typical symptoms were absent from the history. Recent advancements and ongoing gaps in understanding of this rare entity are reviewed including theories of tumor phenotype, the outdated notion of classical symptomatology, and the emerging importance of succinate dehydrogenase (SDH) gene mutations for apparent sporadic rPGL as well as disease prognostication. Pitfalls in diagnosis and management of this frequently silent but potentially catastrophic and malignant tumor are discussed. rPGL is a complex clinical entity that may not present with typical symptoms of catecholamine excess; a high index of suspicion of rPGL is necessary for all clinicians dealing with retroperitoneal tumors.

Keywords: Extra-adrenal pheochromocytoma, Paragangliomas, Pheochromocytoma, Retroperitoneal neoplasm.

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Introduction

Retroperitoneal paragangliomas (rPGL) are rare chromaffin cell tumors that share a histological profile identical to adrenal pheochromocytomas.[1] Traditionally, rPGL has been associated with so-called classical symptoms of catecholamine excess that include headache, sweating and palpitations,[2] however, several authors have noted the absence of these symptoms in rPGL.[3–7] We illustrate our experience in dealing with a series of three cases of rPGL that presented consecutively to our center, in all cases no typical symptoms were elicited in the history. An updated review of the current knowledge, challenges, and pitfalls in the diagnosis and management of this rare entity is presented.

Case Presentation

Case 1

A 72-year-old male presented with an unintentional weight loss of 16 kg over a 3-year period with no other symptoms, specifically no typical symptoms of catecholamine excess. His past medical history was significant only for hypertension controlled with an ACE inhibitor. Initial investigations including an upper and lower gastrointestinal endoscopy were negative. An abdominal CT scan was performed which demonstrated a 3 cm retroperitoneal mass medial to and separate from the left adrenal gland, which was further delineated using MRI (Fig. 1).

Plasma normetanephrine was significantly elevated, and scintigraphy using radioiodinated metaiodobenzylguanidine (^{123}I-MIBG) demonstrated high uptake in the mass consistent with left-sided rPGL. Following the preoperative alpha blockade, the patient underwent a posterior retroperitoneoscopic approach as described by Walz et al.[8] with an uncomplicated general anesthetic and minimal intraoperative fluctuation in blood pressure.

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Histopathological examination confirmed the diagnosis of rPGL, with characteristic features including ball and nest cellular architecture, trabeculated supporting network, and strong staining of neuroendocrine markers chromogranin and CD56. Testing for Succinate dehydrogenase subunits A and B (SDHA/SDHB) mutations by immunohistochemical staining was negative. There were no postoperative complications, total hospital stay was 3 days and metanephrine levels normalized on follow-up.

Case 2

A 75-year-old female presented with lower abdominal discomfort, anorexia, and weight loss of 3 kg over 1 month period. No symptoms of catecholamine excess were present on specific questioning. Her medical history was significant only for an acoustic neuroma

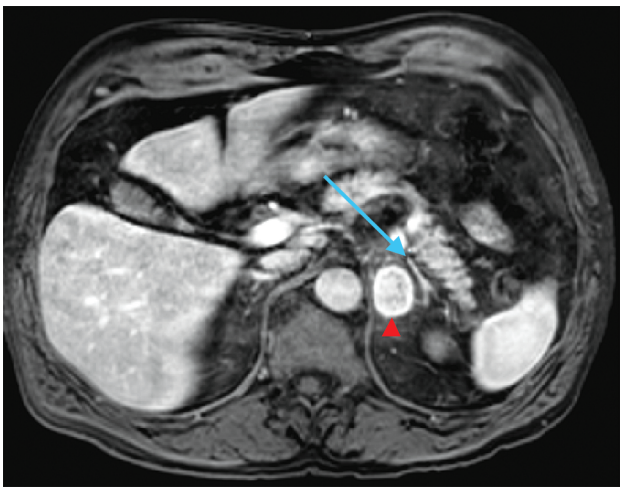


Fig. 1: Case 1, MRI transverse section demonstrating rPGL (arrowhead) superomedial to left adrenal gland (arrow)

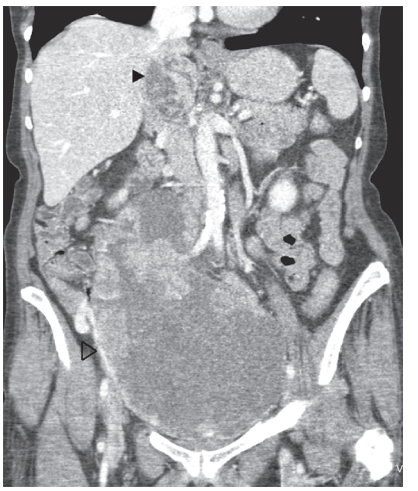


Fig. 2: Case 2, CT coronal section demonstrating rPGL (solid arrowhead) and pelvic tumor (clear arrowhead)

and hyperlipidemia for which she was on statin treatment. On examination, the patient was hypertensive with a BP of 170/90 and had a palpable abdominopelvic mass. Routine tests were unremarkable. A CT scan revealed two synchronous but separate tumors; the first was a large 20 cm mass within the pelvis, whilst the second was a 6 cm retroperitoneal cystic mass close to the right adrenal gland (Fig. 2).

A diagnosis of ovarian carcinoma with adrenal metastasis was initially made, however, on further workup levels of plasma metanephrine and normetanephrine were found to be elevated. ^{123}I-MIBG scintigraphy demonstrated high uptake in the retroperitoneal mass consistent with rPGL but with no uptake in the pelvic mass. A subsequent PET scan using somatostatin analog Lutetium-177-DOTA-D-Phe1-Tyr3-Thr8-octreotide (DOTATATE)[9] also demonstrated high uptake in the retroperitoneal mass with none in the pelvic mass.

The diagnosis was amended to likely right-sided rPGL with intercurrent pelvic tumor. Following the alpha blockade, the patient proceeded to have a laparotomy with removal of the retroperitoneal tumor with en-bloc adrenalectomy followed by the pelvic tumor with en-bloc salpingo-oophorectomy. Intraoperative fluctuations in BP were mild (10–20 mm Hg) and managed with sodium nitroprusside and noradrenaline.

Tumor histology confirmed the diagnosis of an rPGL adjacent to but separate from the right adrenal gland which was found to contain a small cortical adenoma. Immunohistochemistry was negative for SDHA/SDHB mutations. The ovarian tumor revealed an entirely separate diagnosis of ovarian clear cell carcinoma. The patient recovered well and proceeded to have adjuvant chemotherapy for her ovarian cancer.

Case 3

An 80-year-old man presented with a left perirenal mass incidentally detected on abdominal ultrasound performed for dyspepsia. He denied any associated symptoms, including specific symptoms of catecholamine excess. His past medical history was significant for coronary slow flow syndrome, paroxysmal AF, dyslipidemia, and hypertension which were treated with three different agents. The examination was unremarkable, and a CT scan was performed which demonstrated a 57×36 mm complex cystic mass anterior to the left kidney and inferior to the renal vein (Figs 3A and B).

Concerns of a retroperitoneal sarcoma were raised and due to the relations of the tumor to vital structures, the patient was referred to the urology service with the decision for open resection of the tumor. A midline laparotomy was performed and the mass was successfully resected without disruption of the left kidney or aorta. No fluctuation in blood pressure or heart rate was observed during induction of anesthesia, tumor dissection, handing, or subsequent resection.

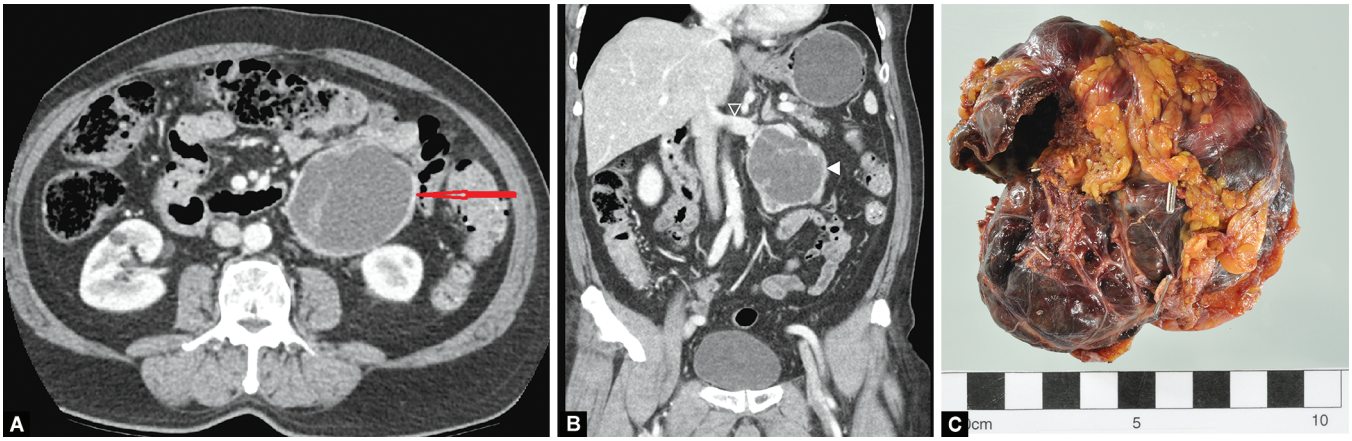
On macroscopic examination, an encapsulated tumor with extensive intratumoral hemorrhage was seen with histopathology revealing an unexpected diagnosis of rPGL (Fig. 3C). The postoperative course was complicated by an ileus, which was resolved with conservative management. The patient recovered well with no evidence of recurrence to date.

Discussion

Epidemiology and Genetics

Retroperitoneal paragangliomas is rare; retrospective series from around the world report an incidence of between 5 and 67 cases per decade.[10–16] Histologically identical to adrenal pheochromocytoma and occasionally referred to as 'extra-adrenal pheochromocytoma',[1] rPGL can arise anywhere along the paravertebral sympathetic ganglia and represent 14–22% of all catecholamine secreting tumors.[17,18] Commonest sites of occurrence are in the para-aortic, pericaval, and perinephric regions, as well as the chromaffin cell-bearing region anterior to the iliac bifurcation known as the organ of Zuckercandl;[14,15,19–21] occurrences in the urinary bladder, prostate, and spinal cord, have also been described.[20,22] For historical reasons, parasympathetic tumors of the head and neck are also confusingly referred to as paraganglioma; these non-chromaffin tumors have little biochemical, histological, or clinical features in common with rPGL[1] and are discussed elsewhere in the literature.

The genetics of chromaffin cell tumors are extensively studied; several complex and overlapping pathways for tumorigenesis have been described.[1,23] It is estimated that up to 30% of all tumors are hereditary; mutations in the susceptibility genes associated with multiple endocrine neoplasia 2A and 2B (RET proto-oncogene), neurofibromatosis type 1 (NF-1 tumor suppressor gene), and Von Hippel Lindau disease (VHL gene) have long been associated with increased incidence of rPGL and pheochromocytoma.[23]



Figs 3A to C: (A) Transverse CT demonstrating rPGL (arrow) anterior to left kidney; (B) Coronal CT demonstrating rPGL (solid arrowhead) and relation to the left renal vein (clear arrowhead); (C) rPGL, macroscopic appearance

Of emerging importance are the mutations in genes encoding the SDH complex of the mitochondrial respiratory chain (SDHA, SDHB, SDHC, and SDHD); SDHB mutations have been found in up to 28% of seemingly sporadic rPGL.[17]

Signs and Symptoms

The clinical presentation for rPGL is neither typical nor specific.[3] Local symptoms that have been described include back or flank pain, abdominal mass, symptoms from IVC compression, and hematuria.[13-15,22] The 'classical symptom triad' of headache, palpitations, and sweating is traditionally ascribed to chromaffin cell tumors,[2] however, rPGL series suggest that these tumors do not obey this pattern. A large Chinese series of 81 rPGL found symptoms of headache, palpitations, and sweating in only 26, 21 and 25% of patients, respectively.[19] Rates of classical symptoms have ranged from 33–42% in other published rPGL series.[13,15,21] A history of hypertension is present in up to 64% of rPGL[19] however, hypertension alone has little diagnostic specificity given its high population prevalence; in an outpatient setting, chromaffin cell tumors account for less than 0.5% of all causes of secondary hypertension.[24]

The variation in catecholamine secretion and symptomatology for rPGL are not understood. Prior immunohistochemical studies of chromaffin cell tumors found rPGLs had reduced or absent levels of the enzyme phenylethanolamine-N-methyltransferase (PNMT), the enzyme responsible for the conversion of noradrenaline to circulatory adrenaline.[25,26] The lack of PNMT was initially thought to result in a tumor phenotype that did not secrete adrenaline and was, therefore, clinically silent,[1,3] however rPGL with appreciable levels of PNMT have since been reported.[27]

Similar to our third case, large rPGL (8–10 cm diameter) presented without symptoms has also been reported in the literature;[4,6] a series of 43 chromaffin cell tumors found that silent tumors were significantly larger.[7] Reasons for the seemingly inverse association of large size and lack of symptoms are unknown. A 2007 immunohistochemical study of large asymptomatic rPGL found tumor levels of tyrosine hydroxylase (a critical enzyme in the catecholamine synthesis pathway) to be almost undetectable; all tumors in that series also exhibited an SDHB mutation.[5]

The postmortem diagnostic rate of chromaffin cell tumors is 0.05% in the autopsy series; in the majority of cases, the undiagnosed tumor was implicated in the cause of death.[28,29] Making an early accurate diagnosis is clearly vital; the absence of typical symptomatology should not be considered reassuring.

Incidental rPGL

At present, up to 47% of rPGL are detected as incidental findings in abdominal imaging studies for unrelated conditions;[14] the trend towards wider use of sensitive abdominal imaging modalities is paralleled by an increased rate of detection for smaller, asymptomatic rPGL.[16] Unfortunately, this is not accompanied by improved diagnostic accuracy. Features of rPGL on CT scans that include homogenous tissue density, avid contrast enhancement, cystic changes, and central necrosis are not unique to rPGL but are shared with several other retroperitoneal tumors including histiocytoma, neuroblastoma, and sarcoma.[21] In a review of imaging findings for rare retroperitoneal neoplasms, a paravertebral location was described as an important discriminating feature for rPGL;[30] indeed this finding was consistent for all three of our cases (Figs 1 to 3).

Earlier retrospective studies found equal or slightly higher sensitivity of MRI compared to CT for detection or localization of rPGL, however, blinding was not explicit in these studies.[31,32] A subsequent qualitative study found no benefit in the addition of MRI to CT in terms of improving diagnostic accuracy for rPGL.[20] Current consensus is that while CT and MRI share excellent sensitivity and anatomical definition, neither have sufficient specificity for rPGL.[33]

Workup

The suspicion of rPGL on abdominal imaging should prompt biochemical testing as the first line of investigation to substantiate this diagnosis. Measurement of plasma or urinary metanephrine/normetanephrine offers greater diagnostic accuracy compared to traditional measurements of catecholamines themselves (i.e., adrenaline and noradrenaline); this in turn is thought to be due to constant intratumoral production and secretion of the former as opposed to the highly episodic and variable secretion of the latter.[34]

Diagnosis should be further supported using functional imaging. The most commonly used modality is scintigraphy with radioiodinated metaiodobenzylguanidine (^{123}I-MIBG), a guanidine analog that shares a similar structure to noradrenaline thus, allowing its uptake by cells of neural crest origin. ^{123}I-MIBG scintigraphy has

a sensitivity and specificity of up to 83.3 and 87.5%, respectively for the detection of abdominal chromaffin cell tumors[35] making it an important diagnostic adjunct for rPGL. Positron emission tomography (PET) using somatostatin analogs has recently emerged as a highly specific for the diagnosis of neuroendocrine tumors. A 2013 systematic review found PET to be superior to ^{123}I-MIBG for detecting rPGL and metastatic disease.[36] In case 2, the use of ^{123}I-MIBG, as well as PET, confirmed the preoperative diagnosis of synchronous rPGL, allowing safe resection of two tumors of differing etiology.

Preoperative Pharmacologic Preparation

Despite lacking high-quality evidence[37] the use of preoperative preparation with alpha-blockers to avert intraoperative hypertensive crisis remains widely popular. The latest European Endocrine Society guidelines continue to recommend this[38] whilst North American guidelines extend this recommendation to include tumors with even apparently normal catecholamine levels.[39] At least one prospective study found no benefits and even potential harm from this practice. In a cohort study of patients with normotensive chromaffin cell tumors who elected voluntarily to have either alpha blockade versus no preoperative preparation, no hypertensive crises were seen and intraoperative blood pressures were not significantly different between groups; conversely, the use of vasopressors and colloid infusions were significantly greater for the group that had preoperative alpha blockade.[40]

In our third case, pharmacologic preparation was overlooked due to a lack of suspicion of rPGL fortunately without any noticeable detriment. Reports of pharmacologically unprepared patients undergoing uneventful operations to remove retroperitoneal tumors that were subsequently found to be rPGL are found throughout the literature.[6,41] We suspect such occurrences will likely remain under-reported due to publication bias. Important lessons from our third case are maintaining a high index of suspicion and actively consider rPGL as a differential for any retroperitoneal tumor. Workup should be performed judiciously. At present, evidence is lacking for the use of alpha blockade in undifferentiated retroperitoneal tumors (i.e., negative on workup); such cases should be considered on individual merit.

Surgical Management

Several approaches to rPGL have been described, with minimally invasive retroperitoneal approaches having comparable profiles of safety, learning curve, and oncological soundness.[8,11,14,42,43] The posterior retroperitoneoscopic approach described by Walz et al. has seen considerable success in addressing rPGL situated above the renal vessels, with key components of the technique being prone to patient positioning and greater insufflation pressures of 20–24 mm Hg.[8] It has become our approach of choice for uncomplicated adrenal tumors and was used successfully in our first case of right-sided suprarenal rPGL (Fig. 1).

Other techniques used for rPGL include the laparoscopic transperitoneal approach,[8,14] with recent reports from Japan documenting successful use of a single port technique in a series of nine rPGL.[43] Open surgery remains an option and was used in our more complex second and third cases. Technological advancements in surgical training such as remote telementoring that was recently used in a transcontinental setting to teach the posterior retroperitoneoscopic approach[44] will likely translate into wider and bolder applications of minimally invasive techniques to address rPGL as well as other retroperitoneal neoplasms.

Malignant rPGL

The differentiation between benign and malignant rPGL rests upon the presence of metastatic lesions at sites where chromaffin cells are not usually found.[1] Earlier aggregate scoring systems based on histological features including the presence of local invasion, necrosis, high cellularity, spindling, increased mitotic figures, and nuclear pleomorphism have not been shown to reliably predict progression to malignant disease. Similarly, a more recent scoring system that accounts for patterns of catecholamine secretion and level of tumor differentiation has remained to be externally validated.[18]

The presence of SDHB mutations has been revealed to be a potentially sensitive biomarker for malignant rPGL. Described earlier as an important cause of sporadic rPGL, at least two studies have also found increased that tumors expressing SDHB mutations are at greater risk of metastasis and poorer long-term survival.[18,45] Another series of 501 individuals with chromaffin cell tumors found germline mutations in SDHB in up to 21% of individuals who developed metastatic disease.[17]

Treatment of metastatic disease is similarly controversial and little established data exists.[38] Cytoreductive or palliative surgery may have a role in debilitating symptoms or life-threatening metastases, however, the rarity of this condition precludes high-quality comparative evidence. One series of vertebral metastasis of chromaffin cell tumors demonstrated uniformly poor outcomes in spite of palliative spinal surgery.[46] A less invasive option for palliation is therapeutic ^{131}I-MIBG, which has been shown in at least two prospective studies to improve survival in patients with metastatic disease and reduction in tumor size.[47,48] Cytotoxic chemotherapy has an unclear role and standardized regimes do not yet exist. One study found a regime of cyclophosphamide, vincristine, and dacarbazine to obtain complete and partial responses in 11 and 44% of patients, respectively. However, no difference in survival for the different response groups was observed.[49]

Follow-up and Genetic Testing

Retroperitoneal paragangliomas is traditionally associated with a greater risk of metastatic disease compared with adrenal pheochromocytoma; this has been recently confirmed in two large multicenter studies that found significantly higher rates of malignancy for rPGL (15[17] and 50%[18]) compared to adrenal pheochromocytoma (4.9[17] and 11%[18]). In the latter study, the median length of time to discover metastatic disease was 5.5 years.[18] Another series of 51 rPGL estimated a mean incidence of locoregional recurrence of 23% at ten years postprimary resection.[50] Given the indefinite timeframe of recurrences as well as the unreliability of typical symptoms, long-term follow-up for rPGL especially where SDHB mutations are detected is currently advocated.[23,38,50]

Clinical features such as young age, positive family history, metastatic disease, and syndromic presentations i.e., MEN2, VHL are clear indications to perform genetic testing; however, for the majority of apparent sporadic rPGL, genetic testing must be rationalized to detect the most likely susceptibility mutation using case-specific algorithms.[38] Developments in multi parallel

sequencing techniques, as well as increasing affordability and costs, will likely enable future clinicians to perform expanded screening for multiple susceptibility genes for all cases of rPGL. However, novel mutations of uncertain significance will likely be uncovered in this process providing challenges for interpretation and subsequent clinical decision making.[23]

Conclusion

Retroperitoneal paragangliomas is a rare but important diagnosis that demands the utmost clinical vigilance. Mechanisms for heterogeneity in tumor phenotypes are poorly understood, however, the so-called classical presentation can no longer be relied upon due to the highly variable and occasionally absent symptomatology. The possibility of rPGL should be considered in all cases of incidentally detected retroperitoneal tumors with workup including metanephrine levels and functional imaging using either ^{123}I-MIBG scintigraphy or labeled somatostatin analog PET scanning. Whilst the evidence is incomplete, the preoperative alpha blockade remains the standard of care for rPGL. Minimally invasive approaches to rPGL are effective and likely to increase with increasing propagation of techniques and surgeon proficiency. Histopathological criteria remain insufficient to differentiate benign from potentially malignant tumors in cases of isolated rPGL, however, detection of an SDHB mutation has emerged as a strong predictor for the development of metastasis. Optimal management for metastatic disease remains elusive as the rarity of rPGL precludes high-quality evidence. Until more definitive evidence becomes available, extended follow-up is recommended for all cases of rPGL.

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