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# Malignant Intrarenal/Renal Pelvis Paraganglioma with Co-Occurring SDHB and ATRX Mutations

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## Abstract

Paragangliomas are rare neuroendocrine tumors which originate from embryonic neural crest cells. These tumors may arise from parasympathetic or sympathetic paraganglia, may secrete catecholamines, and can occur in varied anatomic locations, with some locations being less common than others. Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes are characterized by paragangliomas and pheochromocytomas and have been associated with germline heterozygous mutations in *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127*. Herein, we report a case of a middle-aged male who was diagnosed with an intrarenal/renal pelvis paraganglioma after presenting in hypertensive crisis with palpitations, headache, and diaphoresis. He was later found to have extensive metastatic disease, as well as genetic testing that showed biallelic inactivation of *SDHB* and a co-occurring somatic *ATRX* mutation. Respectively, these germline and somatic mutations have been associated with increased risk of metastatic spread and clinical aggressiveness. Despite multiple surgical resections and various treatment modalities, the patient eventually elected for palliative care measures and died of disease. Together, the findings seen in this patient are unique and serve as an appropriate catalyst for discussing the unusual locations, interesting genetic profiles, and metastatic risk factors that may be associated with paragangliomas.

**Keywords** Paraganglioma · Metastatic · SDHB · ATRX · Intrarenal/renal pelvis

## Case Report

A 48-year-old male with a clinical history of hypertension presented to the emergency department in hypertensive crisis (BP 220/120 mmHg) and expressed symptoms of palpitations, headache, and diaphoresis. After an extensive workup, the patient was found to have elevations in plasma and urine metanephrines, as well as 24-h urine catecholamines and vanillylmandelic acid. His subsequent CT and MR imaging showed an 8.5 cm heterogeneous mass in the right renal sinus with possible invasion into the renal vein and inferior vena cava (IVC) and was suspicious for renal cell carcinoma. However, in view of unremarkable bilateral adrenal glands and clinical history, a clinical diagnosis of intrarenal paraganglioma was favored. The patient was medically managed with plans for surgical excision in a few months. Prior to surgery, a repeat perioperative CT scan showed an L2 vertebral body lesion, which was concerning for metastasis. Despite this finding, surgical resection of the primary lesion was still felt warranted in order to reduce overall tumor burden, and the patient had a radical resection of the tumor en bloc with the right kidney, adrenal gland, and IVC.

On gross examination, a variegated, fleshy, myxoid tumor (7.5 × 6.0 × 4.5 cm) was identified at the mid and lower pole of the kidney with involvement of the perinephric and hilar fat. The vascular margins and adrenal gland were free of neoplasm (Fig. 1a). The tumor was shown to penetrate the renal capsule and involve the perinephric fat, hilar fat, and renal vein (Fig. 1b–c). On microscopy, the tumor showed a typical zellballen pattern, consisting of nests of polygonal cells separated by peripheral capillaries (Fig. 1d). Prominent nuclear pleomorphism, conspicuous nuclear atypia, and larger irregular nests were also focally identified (Fig. 1e). By immunohistochemistry,

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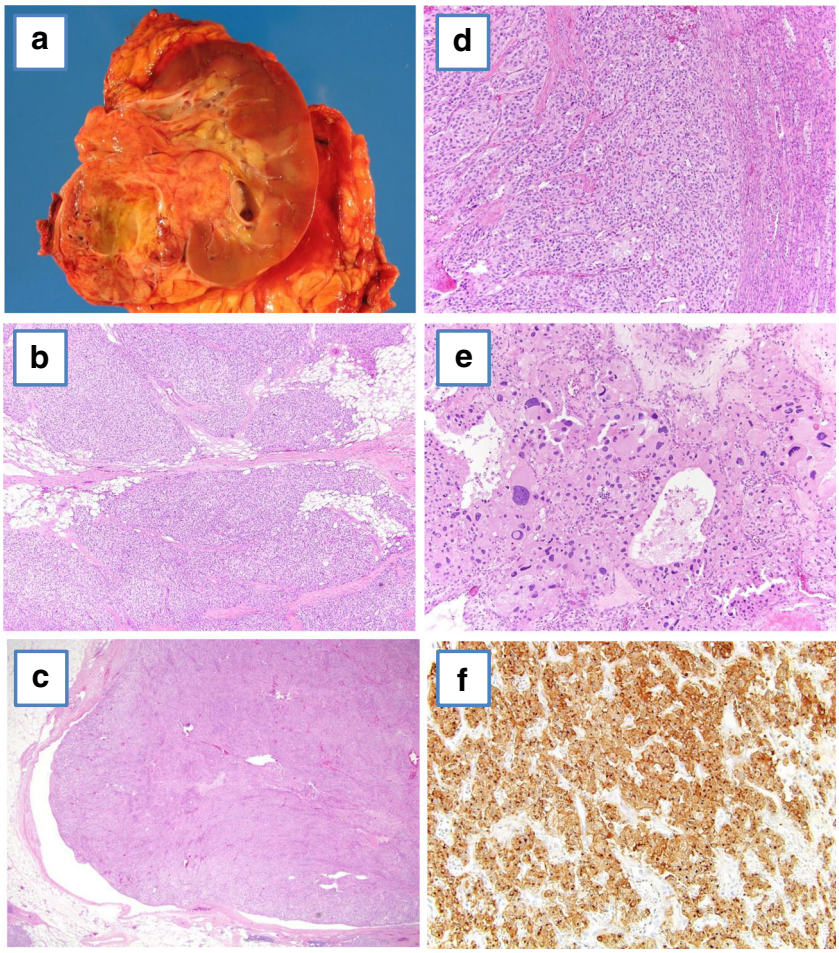


**Fig. 1** Malignant succinate dehydrogenase (SDH)-deficient paraganglioma arising in renal pelvis. Gross photo (**a**) showing a 7.5 cm multilobular, variegated, fleshy and myxoid tumor involving lower and mid pole of kidney, invading into the hilar fat (**b**) and extending into the renal vein (**c**). Interface between kidney parenchyma and tumor (**d**) forming nests and balls of amphophilic cells separated by a fibrovascular septae. Focal areas of nuclear pleomorphism and degenerative atypia (**e**). Immunostaining for neuroendocrine markers synaptophysin (**f**) and chromogranin were strongly positive, confirming diagnosis of extra-adrenal pheochromocytoma/paraganglioma

neoplastic cells were uniformly positive for chromogranin and synaptophysin, further confirming the diagnosis of paraganglioma (Fig. 1f). Additionally, S100 immunostaining highlighted scattered sustentacular cells in the majority of the tumor with zellballen pattern and lack of expression in the areas of irregular nested pattern. Ki-67 was also performed and showed an average proliferative index of 6.5% (range 3–10%).

Because of known heritable susceptibility genes associated with paragangliomas, germline and somatic genetic testing were performed. As a result, the patient was found to have a germline, pathogenic splice site mutation in *SDHB (*NM_003000:c.541-2A>G*)*, with somatic loss of heterozygosity, resulting in biallelic inactivation of succinate dehydrogenase B (Fig. 2). Additional mutations were present, including a somatic mutation in *ATRX* (p.T320Ifs*12, NM_000489.4:c.959del).

The patient recovered after surgery, but his blood pressure began to gradually increase. A PET scan at 1-month follow-up showed increased uptake in the retroperitoneal bed of the resection site, as well as evidence of hypermetabolic metastases to multiple vertebrae, bilateral scapulae, the left pubic bone, and the left inferior fourth rib. Because of these findings, he was started on cyclophosphamide, vincristine, and dacarbazine (CVD) chemotherapy.

The patient responded well to CVD and was followed clinically for 2.5 years. Unfortunately, he began to experience recurrent episodic symptoms of headache, nausea, palpitations, tremors, and diaphoresis, which correlated to elevated urinary catecholamines, as well as CT/PET scans showing prominent T3/T4 and paracaval lesions. He was restarted on CVD therapy, but during a subsequent routine CT scan, it was discovered that he had further progression of his T3 metastatic lesion, as well as an incidental, right-sided saddle pulmonary embolus. His pulmonary embolus, thought secondary to hypercoagulability of malignancy, was appropriately treated, but an MRI showed epidural extension of the T3 lesion with impending spinal cord compression. In response, the patient was switched to sunitinib, and his T3 lesion was resected. On histology, his T3 level epidural tumor was morphologically and immunohistochemically similar to his prior radical resection, confirming the diagnosis of metastatic SDH-deficient paraganglioma (Fig. 3a–c).

He continued sunitinib for almost 2 years, but eventually stopped due to toxic side effects, worsening laboratory biomarkers, and interval progression of metastases seen in multiple

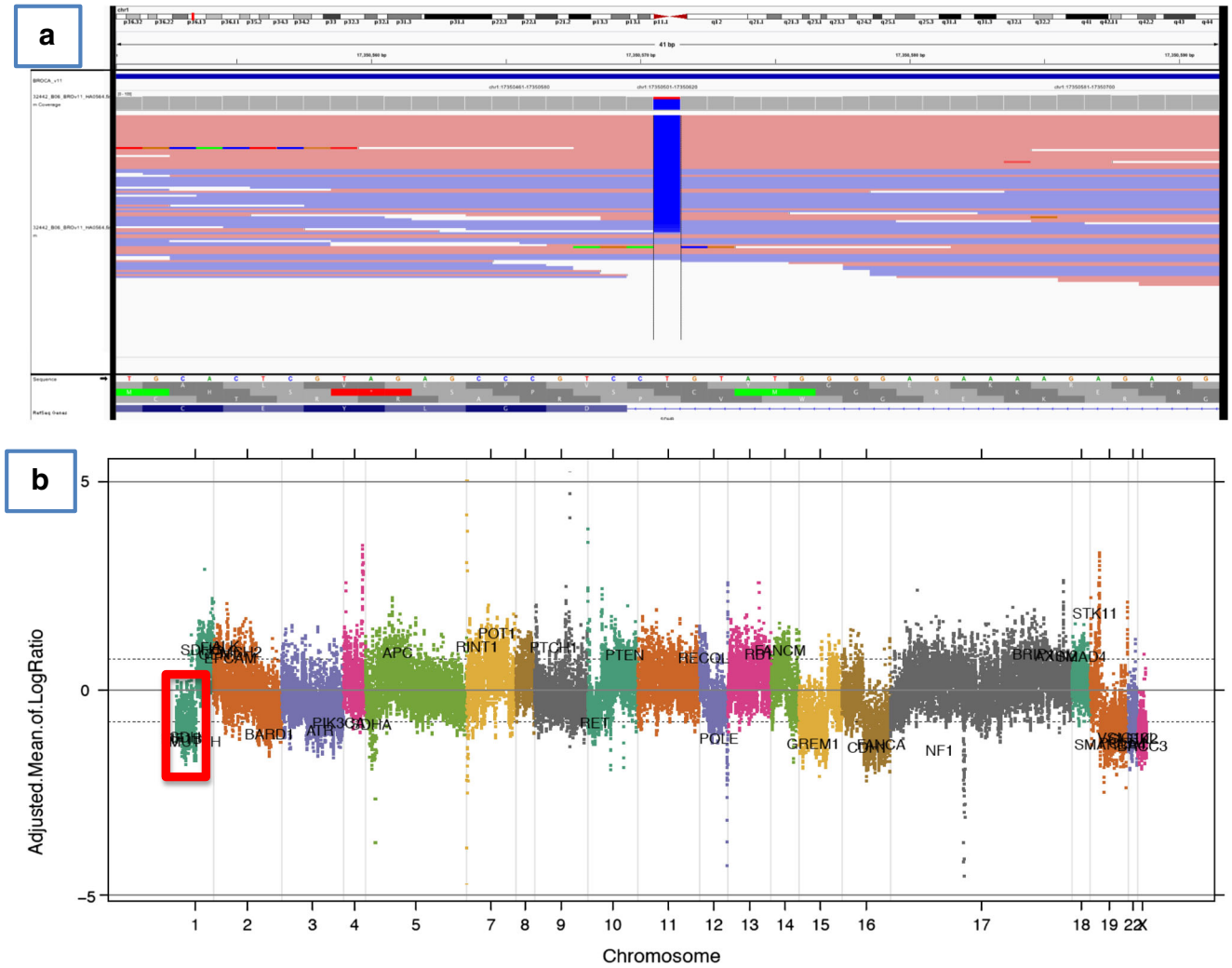


**Fig. 2** (**a**) Integrated Genomics Viewer (IGV) representation of *SDHB* splice site mutation (NM_003000:c.541-2A>G) in malignant paraganglioma metastases. (**b**) Copy number variant (CNV) plot of 87 genes captured in the BROCA panel in malignant paraganglioma metastases. Single copy loss of the region of chromosome 1, containing *SDHB,* is highlighted by the red box. Additional CNVs include copy loss of portions of chromosome 15, 16, 19, and 22. A single copy of X is present in this male patient. Intronic regions are lost in portions of chromosomes 12 (*POLE*) and 17 (*NF1*)

vertebrae, the left fourth rib, and an aortocaval lymph node. He was soon after started on a phase 1 trial drug (Pfizer B7401001, PF-06664178 (TROP 2)) and continued this for 9 months before presenting to the emergency department with acute-onset leg weakness and instability. MR imaging at that time showed a large epidural mass along the posterior T2–T4 vertebral bodies, which required resection.

The patient tried many other medications and multiple doses of external beam radiation therapy over the next 2 years, but he continued to show progression of disease with multiple PET/CT scans demonstrating vertebral metastases. He also had another operation during this period, this time for an L2 lesion compressing his thecal sac (Fig. 3d–f). A few months later, the patient suffered a pathologic fracture of his left scapular coracoid process and was stopped on a phase 1 clinical trial. At a follow-up appointment, the patient decided that he would only pursue palliative measures without further efforts made toward cancer-directed therapy and succumbed to disease 9 years after the primary diagnosis.

## Discussion

There are approximately 500–1600 new cases of pheochromocytomas/paragangliomas (PCCs/PGs) in the USA each year, PGs accounting for only about 15% of this total [1]. PGs may arise from either parasympathetic paraganglia or from sympathetic paraganglia. Parasympathetic PGs occur in the head and neck (e.g., carotid body, middle ear, vagus nerve, and larynx), while sympathetic PGs occur along the prevertebral and paravertebral sympathetic chains (predominately in the abdominopelvic region) [2].

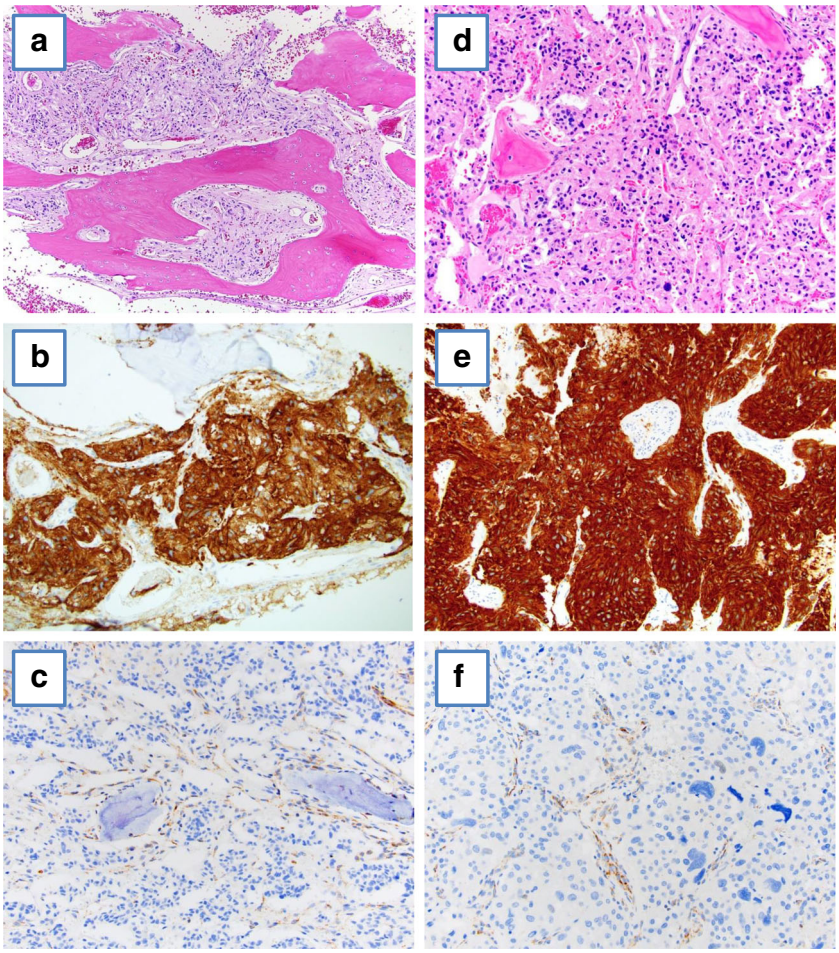


**Fig. 3** Metastases of malignant succinate dehydrogenase (SDH)-deficient paraganglioma to epidurum (a–c) and L3 spine (d–f). Histology of metastatic tumor (a, d) shows infiltrating nests and sheets of amphophilic cells filling marrow spaces. Both metastases were diffusely and strongly positive for neuroendocrine marker synaptophysin (b, e) and consistently negative for SDHB (c, f)

While parasympathetic PGs are rarely functional, sympathetic PGs are more likely to secrete catecholamines, potentially leading to clinical signs and symptoms such as hypertension, headaches, palpitations, and diaphoresis. The patient presented in this case study was shown to have a functional renal pelvis tumor, consistent with an extra-adrenal sympathetic PG.

Although PGs often develop at somewhat predictable locations, these tumors may occur at any body site where paraganglia reside during or after embryonic development. These include the periadrenal, paraaortic, and paracaval regions, as well as within organs such as the thyroid, parathyroid, gut, lungs, liver, and heart [2]. PGs of the genitourinary tract are rare, most frequently diagnosed in the bladder (~ 80%), urethra (~ 15%), and less commonly in the renal pelvis (~ 5%) [1–5]. In fact, there have been fewer than 20 cases of intrarenal/renal pelvis PGs described in the literature, including the current report [3–5]. The vast majority of reported intrarenal PGs are functional (> 80%), and up to 50% of cases presented as either locally aggressive tumors involving adjacent organs and requiring extensive surgery or with metastases, although median follow-up in many reported cases was short [1–5].

Our case report is unique due to 9-year follow-up, detailed morphologic characterization of primary intrarenal mass and metastatic tumors, and next-generation sequencing of both germline and neoplastic tissues. This is important given the high susceptibility of PGs to germline mutations [1]. Mutations in at least nineteen genes have been associated with heritable PGs, with the majority of mutations effecting autosomal dominant, tumor suppressor genes, but with incomplete penetrance. Due to the variability in penetrance and clinical presentation, the current recommendation is for all patients (regardless of family history) to undergo genetic testing for at least the most frequent germline mutations [1, 6].

The most common cause of hereditary PGs is seen in germline mutations coding for succinate dehydrogenase subunits (SDHx) [1]. Functioning in both the Krebs cycle and the electron transport chain, succinate dehydrogenase (SDH) is an enzyme embedded within the inner mitochondrial membrane that consists of four subunits, i.e., SDHA, SDHB, SDHC, and SDHD [6]. Germline mutations in *SDHB* are the most common (occurring in 7% of patients with PCCs/PGs), followed by *SDHD* (5–6%), *SDHC* (1–2%), and *SDHA* (1%) [1]. Though the mechanism of tumorigenesis is not entirely understood,

biallelic inactivation of any *SDHx* gene is thought to impair function of the entire SDH complex, resulting in the disruption of the Krebs cycle and electron transport chain, leading to the generation of reactive oxygen species and the accumulation of succinate within the cell. This leads to the expression of hypoxia-sensitive transcription factors and associated target genes in a "pseudohypoxic pathway" [1]. Reactive oxygen species and elevated succinate are also thought to alter other molecular pathways to cause additional mutations, as well as induce hypermethylation of histones and promoter regions of many genes that lead to tumorigenesis [1]. Biallelic inactivation of any SDH subunit may be detected via loss of expression of SDHB by immunohistochemistry, as seen in the patient of this case report (Fig. 3). This is due to instability of the SDH complex, which releases SDHB into the cytoplasm to be rapidly degraded in the setting of biallelic inactivation of SDHA, SDHC, or SDHD [6]. This phenomenon allows SDHB to act as a surrogate marker for any SDHx inactivation in PCCs/PGs, which can be a useful screen to identify patients that should undergo germline genetic testing [6]. If SDHB expression is lost by immunohistochemistry, an additional stain for SDHA may also be performed to potentially demonstrate if this is in fact the underlying SDH subunit mutation. Genomic testing of patients with SDHx loss should undergo germline testing of all SDHx genes in a stepwise or comprehensive manner.

While PGs have a strong association with inherited susceptibility gene mutations, somatic mutations may also occur and lead to sporadic tumors. Furthermore, co-occurring somatic mutations can enhance tumorigenesis and the progression of disease in patients with heritable PGs. One described somatic mutation associated with PCCs/PGs is in *ATRX*. Found on the X-chromosome, the ATRX gene has previously been described as a driver mutation in pancreatic neuroendocrine tumors, neuroblastomas, and gliomas, as well as the primary insult in the germline disease X-linked alpha thalassemia mental retardation syndrome [7]. *ATRX* codes for a protein involved in chromatin remodeling at telomeres, and mutations are often associated with alternative lengthening of telomere (ALT) pathways, as well as additional tumorigenesis mechanisms, which prevent senescence [1]. Additionally, it has been shown that the presence of *ATRX* mutations has been associated with clinically aggressive behavior, especially when occurring in the context of a *SDHB* mutation [8]. With regard to PCCs/PGs, somatic *ATRX* mutations are seen in 4–13% of tumors [7, 8], while somatic *SDHx* mutations are rarely observed. In a study that utilized whole exome sequencing of 21 PCCs/PGs, two out of seven tumors with germline *SDHB* mutations also had deleterious variants identified in *ATRX* [7].

The risk of metastases in extra-adrenal sympathetic paragangliomas ranges from 2.5-50% with lesions commonly occurring in the lymph nodes, bones, liver, and lungs, as well as rarely in the peritoneum, pleurae, and gonads [1]. The wide range observed for metastatic risk is based primarily on classic factors such as large tumor size (> 5 cm), but has also been associated to be increased in tumors harboring specific mutations [1]. Prior to 2017, risk of metastatic spread was the criteria used to distinguish between benign and malignant PGs. The most recent update to the WHO classification [1], however, no longer classifies any PG as benign, as all PGs have metastatic potential and/or can be multifocal [2]. Due to this recognized possibility of multifocal disease in syndromic PGs, one should keep in mind that multiple anatomic lesions may not be actual metastases, but instead represent independent primary lesions. An exception is the presence of PG lesions within the bones or brain, which can be surmised to be metastatic because paraganglia do not reside in the bones or brain during development, as is described in the current report. *ATRX* mutations seem to be also key drivers in metastatic PGs and, as previously alluded to, have been shown to be an independent risk factor of poorer prognosis and associated with reduced overall survival [8]. It has been suggested that screening for *ATRX* mutations, especially in those with *SDHx*-mutated tumors, may aid in evaluating risk of metastatic potential [8]. Further identification and elucidation of these specific genetic PG subtypes may help future diagnosis, treatment, and clinical follow-up of these patients.

Various grading systems using histopathologic criteria to predict the metastatic potential of PCC/PGs have also been proposed. The Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP) is one tool meant to aid clinicians [9]. The GAPP criteria scores tumors from 0 to 10 points based on histological pattern, cellularity, presence of comedo-type necrosis, capsular/vascular invasion, Ki67 proliferative index, and catecholamine type (well-differentiated, 0–2 points; moderately differentiated, 3–6 points; poorly differentiated, 7–10 points) with a higher score correlating to a greater risk of metastasis. Retrospectively, applying these criteria to the primary tumor of this case report shows the histology to be consistent with an irregular zellballen pattern due to a mixture of variably sized tumor nests with a focal loss of sustentacular cells on S100 staining (1 point). This irregular zellballen pattern was present in a multifocal fashion alternating with areas of typical zellballen architecture (Supplementary Figure 1A–D). The tumor cellularity was calculated under high-power magnification (× 400) in two fields, averaging 240 cells/U (1 point). The Ki67 proliferative index in two of the most highly labeled areas were counted manually in 500 cells at an average of 6.5% (range 3–10%, 2 points) (Supplementary Figure 1E). An area of coagulation necrosis and scar formation was seen, but comedo-type necrosis was not identified (0 points) **(Supplementary Figure 1F)**. Capsular invasion was demonstrated (1 point), and the elevated norepinephrine and dopamine without elevated epinephrine levels led to classification of a functional norepinephrine-type tumor (1 point). These findings gave the primary tumor a retrospective GAPP score of 6/10 (moderately differentiated).

Interestingly, an updated scoring system called the modified GAPP score (M-GAPP) was developed to further improve predictive ability in PCC/PG metastatic risk [10]. M-GAPP incorporates loss of SDHB immunohistochemical staining with 5 GAPP parameters (histologic pattern, comedo-type necrosis, vascular invasion, Ki67 proliferative index, and catecholamine type). In this case report, the primary tumor M-GAPP score was retrospectively found to also have a high risk of metastatic potential (score 5/6). This case further highlights that validated histopathological grading systems may be useful tools for clinicians in evaluating prognosis and follow-up of patients with PCC/PG tumors.

## Conclusion

PGs are rare neuroendocrine tumors that are particularly uncommon when they occur in the intrarenal/renal pelvic region. Additionally, the clinically aggressive course and extensive metastatic burden seen in this particular patient was unique and correlates with genetic findings, including biallelic inactivation of *SDHB*, as well as a mutation in *ATRX*. These mutations are associated with increased metastatic potential and reduced overall survival, especially when they co-occur, such as in this report.

This distinctive case serves to highlight the unusual locations, unique genetic findings, and potential metastatic risk associated with PGs with the hope of further generating awareness of these remarkable tumors.

### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflicts of interest.

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