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Metastatic Retroperitoneal Paraganglioma: Case Report and Review of the Literature

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Abstract

Paragangliomas are rare neuroendocrine tumors with 500 to 1600 new cases in the United States each year. The clinical presentation may range from asymptomatic to the classic triad of episodic diaphoresis, headache, and palpitations. Surgery is the hallmark of treatment when tumors are amenable to resection. When patients are found to have metastases, systemic therapies may be employed. In this case report, we present a patient found to have a large retroperitoneal paraganglioma with nodal metastases.

Clinical History and Workup

The patient is a 68-year-old male who presented to the emergency room with 3 weeks of worsening abdominal, back, and supra pubic pain, associated with unintentional weight loss as well as intermittent night sweats and nausea. He denied any urologic symptoms, such as dysuria or hematuria. His past medical history is significant for type 2 diabetes mellitus, hypertension controlled on enalapril, and hyperlipidemia. His surgical history is significant for a left orchiectomy due to testicular torsion. His medication, social, and family history were otherwise unremarkable. Physical exam revealed a soft, non distended abdomen with left upper quadrant tenderness but no palpable masses. Routine laboratory studies and urinalysis did not demonstrate any abnormalities. Computed Tomography (CT) scan of the chest, abdomen, and pelvis with oral and intravenous contrast revealed a 10 cm × 6 cm heterogeneous mass adjacent to the right kidney with concern for kidney cancer or retroperitoneal sarcoma (Figure 1). Subsequent MRI of the abdomen demonstrated a 10.9 cm × 7.2 cm × 8.8 cm mass adjacent to the right renal lower pole. It was noted that the mass had displaced the ureter and renal pelvis anteriorly to the right and flattened the inferior vena cava (Figure 2). Bone scan was negative for metastatic disease. The patient went to the operating room with the urology and surgical oncology teams where he underwent an exploratory laparotomy, right radical nephrectomy, resection of retroperitoneal mass and retroperitoneal lymph node dissection. His postoperative course was unremarkable.

Surgical Pathology

Grossly, the specimen measured 11 cm in greatest dimension, involved the renal hilum and compressed the mid to lower pole of the kidney. It had a variegated red tan cut surface with areas of necrosis. Ureteral and vascular margins were negative for tumor, as was the renal parenchyma. Paraganglioma resection margins were also negative. On histology, the lesion was composed of round to oval cells with occasional nucleoli and fine granular cytoplasm, arranged in small nests with intervening thin vascular fibrous stroma. By immunohistochemistry, the tumor was positive for synaptophysin, chromogranin, and GATA3, while S100 highlights sustentacular cells. The morphology and immunoprofile support the diagnosis of paraganglioma. While all 6 out of 6 para-caval lymph nodes were negative for tumor, 3 out of 4 pre-caval lymph nodes demonstrated metastatic paraganglioma (not contiguous with the main tumor) (Figure 3).

Discussion

Pathophysiology

Paragangliomas are a subset of rare neuroendocrine tumors that originate from extra-adrenal sympathetic and parasympathetic nerve tissues within para-ganglia. Paragangliomas are grouped based off their origin in the parasympathetic's or the sympathetics. Parasympathetic paragangliomas typically arise from tissue in the head and neck, including the carotid body, vagus nerve, and jugular foramen; less than 5% of these tumors are malignant. In contrast, paragangliomas

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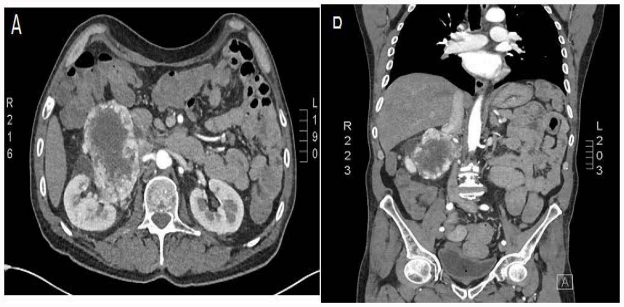

Figure 1: CT of the chest, abdomen and pelvis with PO and IV contrast A) Transverse and B) coronal views demonstrating 10 cm × 6 cm heterogeneous mass adjacent to the right kidney.

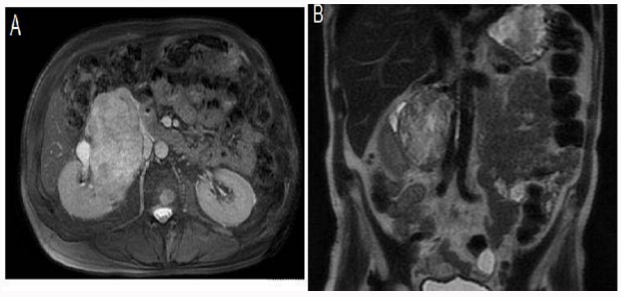

Figure 2: MRI of abdomen with IV contrast A) Transverse and B) coronal views demonstrating 10.9 cm × 7.2 cm × 8.8 cm mass adjacent to the right renal lower pole displacing the ureter and renal pelvis anteriorly and flattening the inferior vena cava.

are considered by many to be extra-adrenal pheochromocytomas. Collectively pheochromocytomas and paragangliomas are referred to as PPGLs. Paragangliomas arise from chromaffin tissue outside of the adrenal medulla and secrete neuropeptides and catecholamines [1,2]. Sympathetic paragangliomas are most common in the para-aortic region of the abdomen, pelvis, and chest [3]. Genetic mutations underlie 25% to 40% of paragangliomas, with germline mutations in the Succinate Dehydrogenase (SDH) family being the most common. Patients with a mutation in the B subunit of SDH, known as SDHB, are more likely to have metastatic disease. Other frequent mutations include VHL, RET, and NF1 [4,5]. Moreover, the development of PPGLs may be linked with one of five types of paraganglioma syndromes, or PGL1-5. Each syndrome is distinguished by a different mutated subunit of SDH and has a characteristic incidence of PPGLs as well as renal cell carcinomas, gastrointestinal stromal tumors, pituitary tumors, and thyroid cancers [5].

Clinical features

Hypertension is the most common clinical feature in those with PPGLs. While only a minority of patients present with the classic Symptomatology of palpitations, headaches, and diaphoresis, the triad is rather sensitive (90.9%) and specific (93.8%) in diagnosis. Other signs and symptoms are non-specific and may include abdominal and chest pain, nausea, weakness, unexplained arrhythmias or hypertension during surgeries and procedures, weight loss, the development of metabolic disorders, or orthostatic hypotension. In severe cases, patients may experience hypertensive crises or multisystem organ failure [3,5].

Diagnosis

Clinicians may consider workup for PPGL in patients with symptoms, adrenal incidentalomas or other suspicious imaging findings, and genetic predispositions [3,6]. When there is suspicion for PPGL, the patient should undergo biochemical testing for plasma free metanephrines and urinary fractionated metanephrines. After engaging in shared decision making, genetic testing for SDH mutations may be recommended as well [6]. CT of the chest, abdomen, and pelvis is recommended as the first-line imaging study. MRI is typically reserved for those with likely metastatic PPGL or those with contraindications to undergoing a CT scan. Positron Emission Tomography (PET) scan and ^{123}I-MIBG scintigraphy may also be used to evaluate for metastatic disease [6].

Natural history of disease and prognosis

The natural history of PPGLs is heterogeneous and ranges from indolent to the development of rapid metastases [7]. 10% of pheochromocytomas and 25% of paragangliomas are malignant [3]. Approximately 10% to 26% of PPGLs become metastatic with a 5-year overall survival rate ranging between 20% and 70% in comparison to 90% for those without metastatic disease [8,9]. The diagnosis of malignant PPGLs requires documentation of metastases into non-chromaffin tissues, according to the World Health Organization (WHO) [10]. Therefore, PPGLs may invade into local structures without being deemed malignant, although they may be considered to have malignant potential [9]. To date, there are no known biomarkers that reliably distinguish benign from malignant PPGLs. Some groups have associated a higher malignant potential with younger patient age, larger tumor size, and particular secretory profiles [9]. Several models have been created for predicting which PPGL tumors are likely to metastasize but have limitations in their clinical utility. The first of these algorithms, known as Pheochromocytoma of the Adrenal Gland Scaled Score (PASS), is a 12 parameter scoring system for detecting malignant potential in pheochromocytomas; however, it does not apply to paragangliomas and has had poor concordance amongst pathologists [11]. Subsequently, the Grading System for Adrenal Pheochromocytoma and Paraganglioma (GAPP) score was created for both pheochromocytomas and paragangliomas. It incorporates multiple elements of the PASS as well as other biochemical factors [9,12]. The modified GAPP (M-GAPP) adds in genetic testing for loss of SDHB and has had some ability to predict

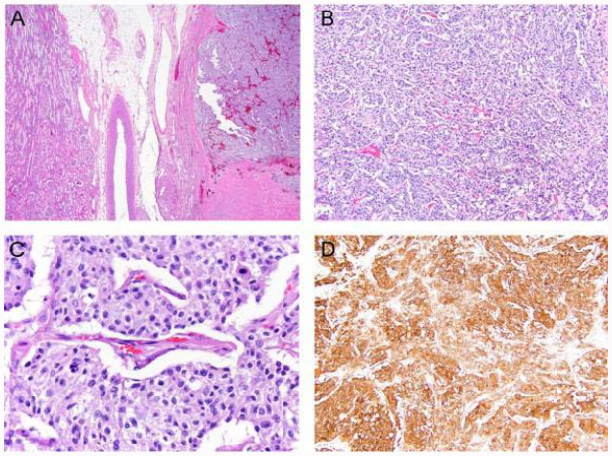

Figure 3: Histology of metastatic paraganglioma A) Lesion (right) in relation to normal renal parenchyma (left) (20x magnification). B) Lesion showing nest of cells arranged in typical "zellballen" pattern with thin delicate vascular network (100x magnification). C) On higher magnification, occasional atypical mitoses are identified (400x magnification). D) Synaptophysin immunostain shows strong membrane positivity (100x magnification).

metastasis in a small series [12]. Most recently, the Age, Size, Extra-adrenal location, and Secretory type (ASES) score was developed for PPGLs and takes into account patient age, tumor size, extra-adrenal location, and secretory profile [9]. Its reported negative predictive value of 96.5% demonstrates its potential to identify tumors with low malignant potential. Larger validation studies are needed before integrating them in everyday practice.

Treatment

Treating PPGLs involves managing effects of hormone secretion and tumor debulking to prevent progression and improve overall survival [7,8]. The hallmark of curative treatment of PPGLs is surgical resection. Recent guidelines recommend minimally invasive adrenalectomy for pheochromocytomas <6 cm and open resection of paragangliomas [6]. Resection of PPGLs should include local resection of affected structures as well as lymphadenectomy when appropriate. Surgical debulking has been demonstrated to improve overall survival, possibly by limiting metastatic potential. Additionally, tumor removal helps improve associated hypertension by removing the source of excess catecholamine secretion. Preoperatively, patients should undergo properly timed alpha and beta blockades to prevent adverse hemodynamic events [7]. According to guidelines by the National Comprehensive Cancer Network (NCCN) all patients should undergo close postoperative monitoring with serum biochemical markers and blood pressure measurement within three months after surgery and then biannually for the first three years [13]. CT and PET scans may also be used to monitor for recurrence or progression at the discretion of the clinician. For patients with metastatic disease, localized radiopharmaceuticals and systemic therapies may be utilized [8]. The current gold standard for these patients is Cyclophosphamide, Vincristine, and Dacarbazine (CVD), which may decrease tumor size, improve blood pressure, and contribute to improved overall survival [7,14]. In addition, case reports have shown an improvement in progression-free survival with the use of temozolomide and lanreotide after progression on CVD [14]. In terms of radiotherapy options, ^{131}I-MIBG, a norepinephrine analog labeled with a radioactive isotope, can be used for both diagnosis and treatment of metastatic PPGLs. One meta-analysis of 243 patients with metastatic PPGL treated with varying doses of ^{131}I-MIBG demonstrated 3% complete response, 27% partial responsive, and 52% stable disease [7,15]. In patients with metastatic tumors expressing somastatin receptors, peptide receptor radio ligand therapy with ^{177}Lu-dotatate has been shown to improve quality of life and achieve either partial response or stable disease in up to 80% of patients with neuroendocrine tumors [16]. Sunitinib, a tyrosine kinase inhibitor which inhibits angiogenesis and cell proliferation, is another drug that has been recently investigated in the treatment of metastatic PPGL. A retrospective study of 17 patients with metastatic PPGL treated with sunitinib demonstrated an overall improvement in hypertension, reduction in tumor size, and disease stabilization [7,17]. Currently, randomized control trials are underway looking at a variety of biological molecules including sunitinib (NCT01371201), as well as cabozantinib (NCT02302833), lenvatinib (NCT03008369), pembrolizumab (NCT02721732), ipilimumab/nivolumab (NCT02834013), and dovitinib (NCT01635907) for the treatment of metastatic PPGLs [7,18].

Conclusion

PPGLs are a rare group of diseases with varying clinical presentations and carry a high morbidity and mortality when not appropriately diagnosed and treated. While cure is feasible by surgical resection in some localized tumors, there are fewer options for those with metastatic disease. As advances in surgical technique and systemic therapies develop, randomized clinical trials will be essential in elucidating the optimal treatment plan for these patients.

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