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Case Report

Extra-adrenal pheochromocytoma at the organ of Zuckerkandl: a case report and literature review

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ARTICLE INFO

Article history:

Received 12 September 2016

Received in revised form

1 December 2016

Accepted 19 December 2016

Available online 21 March 2017

Keywords:

Paranglioma

Pheochromocytoma

Zuckerkandl

Octreotide

Neuroendocrine

ABSTRACT

Pheochromocytomas and paragangliomas are tumors that occur in characteristic locations and are commonly detected on imaging studies. A correct diagnosis is important because of differences in associated neoplasms, risk for malignancy, and need for genetic testing. In addition, associated complications, including death, can be avoided if appropriately recognized and treated. Here, we report a rare case of an extra-adrenal paraganglioma of the organ of Zuckerkandl.

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Introduction

Pheochromocytomas (PCCs) and paragangliomas (PGLs) are rare catecholamine secreting neuroendocrine tumors. The combined estimated annual incidence in the United States is approximately 500–1600 cases per year [1]. Both tumors classically present with paroxysmal attacks of headache, palpitations, and diaphoresis. During these episodes of catecholamine release, blood pressure is typically highly elevated and labile.

Eighty-five percent of these masses occur in the adrenal medulla; however, 15% occur extra-adrenally along the sympathetic chain [2]. Most extra-adrenal disease occurs in the subdiaphragmatic region, most commonly within the organ of Zuckerkandl. Because of their varied clinical presentations, imaging, and pathologic appearances, accurate diagnosis can be challenging; however, appropriate and timely diagnosis and treatment is essential in preventing severe complications such as myocardial infarctions, strokes, and death.

Competing Interests: The authors have declared that no competing interests exist.

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<http://dx.doi.org/10.1016/j.radcr.2016.12.009>

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Case report

A 52-year-old male patient with a known history of coronary artery disease and past myocardial infarction presented to the emergency department with complaints of a 2-month history of nonradiating midsternal chest tightness on exertion. In addition, he endorsed weakness, palpitations, and a 4–5-year history of diffuse abdominal pain. The patient was found to be tachycardic with a labile blood pressure, ranging from 147-183 systolic and 91-133 diastolic. Abdominal examination was unremarkable except for tenderness on palpation of the right upper quadrant and left lower quadrant. The patient was admitted for acute coronary syndrome rule out. Electrocardiogram showed normal sinus rhythm with no ST changes and negative troponins.

Imaging was obtained to further evaluate the abdominal pain. Computed tomography (CT) imaging of his abdomen revealed a heterogeneously enhancing soft tissue mass within the retroperitoneum between the infrarenal abdominal aorta and the inferior vena cava, which measured approximately $4.0 \times 4.4 \times 4.3$ cm. Differential considerations included primary malignancy, metastatic disease, or an extra-adrenal PCC (Figs. 1-4).

Laboratory work revealed an elevated urine 24-hour normetanephrine (5555, normal 122-676), urine metanephrines and normetanephrines (5665, normal 224-832), and 24-hour urine metanephrines were normal (210, normal 90-315). Endocrinology was consulted and ordered a magnetic resonance imaging (MRI) for further evaluation.

Further workup with an MRI of the abdomen with contrast was obtained for further characterization. It revealed the $4.0 \times 4.4 \times 4.3$ cm T1 hypointense, T2 hyperintense heterogeneously enhancing mass within the retroperitoneum along the distal abdominal with subtle scattered areas of restricted diffusion. In combination with clinical findings, it was thought that this could relate to an extra adrenal PCC within the organ of

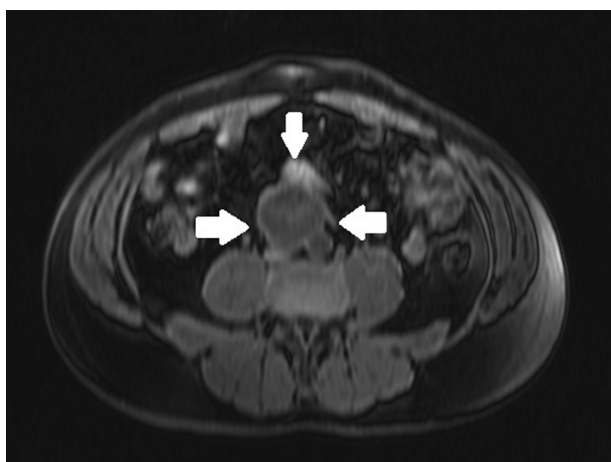


Fig. 1 – Axial unenhanced T1 fat saturation-weighted magnetic resonance (MR) image shows a heterogeneous retroperitoneal mass (arrows) adjacent to the distal abdominal aorta. The mass results in mass effect on the inferior vena cava.

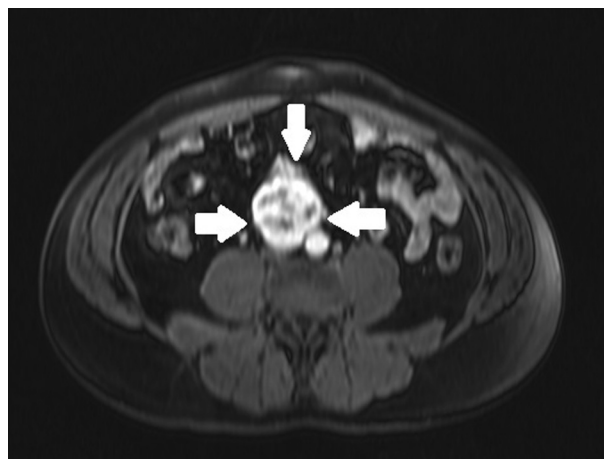


Fig. 2 – Axial contrast enhanced T1 fat saturation-weighted MR image demonstrates a mass (arrows) with peripheral enhancement with central nonenhancement.

Zuckerkanndl. Other differential possibilities included hypervascular metastases.

A whole body Indium 111 octreotide nuclear medicine scan was then performed along with single-photon emission computed tomography (SPECT) in which a focus of abnormal radiotracer uptake in the mid abdomen in the region of the previously described mass. Although, SPECT/CT is superior to SPECT in terms of diagnostic accuracy and localization of neuroendocrine tumors, that technology is not available at this institution [1]. Thus, through SPECT, the patient was diagnosed with an extra-adrenal PGL. He was then transferred to the surgical intensive care unit for blood pressure control before surgical removal.

The patient later underwent exploratory laparotomy with exploration of the retroperitoneum. A soft brown-tan mass

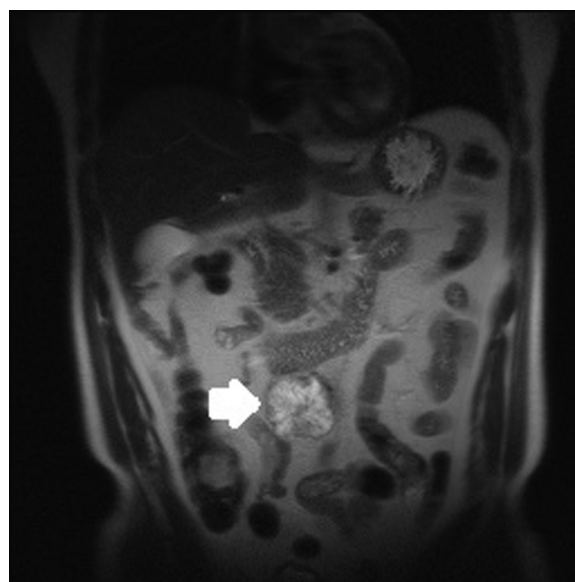


Fig. 3 – Coronal T2-weighted half-Fourier acquisition single-shot turbo spin-echo (HASTE) image demonstrates a predominantly hyperintense retroperitoneal mass (arrow).

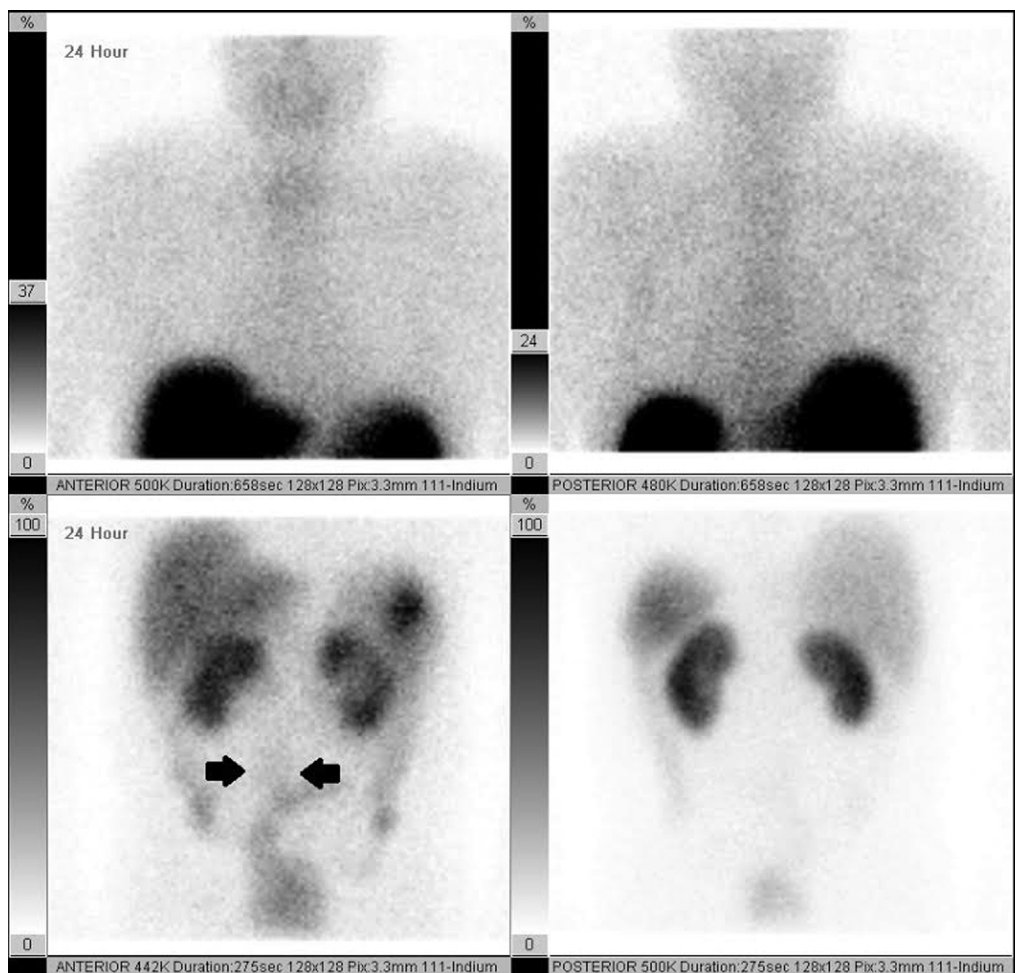


Fig. 4 – Whole body Indium 111 octreotide scan reveals a subtle focus of abnormal radiotracer uptake in the mid abdomen (arrows) in the region of the previously described mass.

directly on top of the vena cava and to the right of the aorta was resected and sent to pathology. Pathology found the tissue was consistent with a benign PGL. He recovered well from the operation and was eventually discharged in a stable state. Follow-up with the outpatient cardiology clinic revealed resolution of any chest pain or palpitations and his blood pressure was well controlled. Finally, it was recommended that patient have genetic testing performed given the extra-adrenal location. Through this, it was determined that there was not a genetic component to this patient's case.

Discussion

The paraganglionic system develops early in gestation and is of neural crest origin. It is composed of the adrenal medulla and a diffuse collection of extra-adrenal paraganglia. PGLs are rare neuroendocrine tumors that arise from the extra-adrenal autonomic paraganglia. They are closely related to PCC, which are catecholamine-producing tumors derived from chromaffin cells of the adrenal medulla [2].

PGLs are further categorized into parasympathetic and sympathetic subtypes based on their anatomic location and

secretory products. Tumors associated with significant amounts of epinephrine are sympathetic in origin; whereas, dopamine is the main product of parasympathetic PGLs. The 2 types occur with similar frequency; however, this distinction is important to make because parasympathetic PGLs are more often familial and less likely to be malignant [3].

In general, PGLs are more often asymptomatic than PCCs. Very often, the location of the PGL is related to its presentation, due to a mass effect. For example, parasympathetic PGLs, which are usually found in the head and neck produce palpable neck masses, tinnitus, and cranial nerve palsies; whereas, PCCs and sympathetic PGLs, which can be located anywhere along the sympathetic chain from the base of the neck to the bladder and prostate, are typically seen with the classic pentad associated with hypersecretion of catecholamines (headaches, palpitations, diaphoresis, pallor, orthostasis) [2].

Diagnosis of PCC and PGL relies on biochemical evidence of excess catecholamine production. Typically, urine and/or plasma metanephrines are evaluated for this purpose. Metanephrines are the metabolites of catecholamines. This is used because, although, the release of catecholamines

fluctuates, their metabolism is relatively constant [4]. Norepinephrine and vanillylmandelic acid levels are also assessed.

Because PCCs and sympathetic PGLs are nearly identical biochemically and functionally, it can be difficult to differentiate the two [2]. However, it is important to make the distinction because of the implications for associated neoplasms, risk for malignancy, and genetic testing. Thus, once the diagnosis has been confirmed biochemically, appropriate imaging should be evaluated to locate the tumor. As stated earlier, PCCs are a disease of the adrenal medulla, and sympathetic PGLs can occur anywhere along the sympathetic chain. 98% of which are found below the diaphragm [5]. One such location below the diaphragm is the organ of Zuckerkandl, which is a mass of chromaffin cells that span from the superior mesenteric artery or renal arteries to aortic bifurcation.

CT or MRI of the abdomen and pelvis are usually performed first. Overall, there is great variability seen on imaging secondary to the presence of tissue necrosis, cystic degeneration, and hemorrhage. On unenhanced CT, the mass may range from low density to soft-tissue attenuation. In addition, approximately two-thirds of PCC are solid; whereas, the rest are noted to be complex or cystic. Contrast-enhanced CT may further reveal either a homogenous mass or variable enhancement depending on the previously mentioned factors [6].

On T2-weighted MRI, PCCs classically present as a “light-bulb” hyperintense lesion, which is comparable with the signal of cerebrospinal fluid. This is due to increased water content as a result of necrosis and cystic degeneration. The appearances on T1-weighted images are also variable. They are usually isointense to muscle and hypointense to the liver; however, there may also be heterogeneous in signal intensity. Typically, avid gadolinium enhancement is seen, but, just like the other findings, this is dependent on the presence of cystic-necrotic areas. A characteristic “salt and pepper” pattern also is commonly seen representing enhancing parenchyma and flow void of vessels [6].

Given the nonspecific imaging appearances, functional imaging using I-131 or I-123 radiolabeled meta-iodobenzylguanidine (MIBG) and more recently, F-fluorodopamine and F-fluorodopa positron emission tomography (PET) have been used to detect metastatic PCCs and PGLs with substantial sensitivity and specificity [7]. In addition, it is important to note that MIBG is a norepinephrine analogue; thus, making it particularly useful for extra-adrenal PGL detection [6]. PGLs can also show activity on Indium 111 octreotide scans.

Furthermore, Gallium 68 (Ga) 1, 4, 7, 10-tetraazacyclododecane—1, 4, 7, 10-tetraacetic acid (DOTA)—octreotate (Ga-DOTATATE) PET/CT is quickly becoming the functional modality of choice for the detection and characterization of multiple neuroendocrine tumors, including PCCs and PGLs. This is due to the improved spatial resolution, lesion detectability, and quantification abilities of this study compared with others [8]. The abilities of Ga-DOTATATE PET/CT and FDG PET/CT are complimentary in tumor characterization. Thus, together, these modalities are able to demonstrate well and poorly differentiated phenotypes, which, in

turn, provide valuable information regarding tumor characterization, prognostication. Moreover, this information is helpful in guiding biopsies and selecting therapies for individual patients [9].

Ga-DOTATATE PET/CT is also preferred in terms of convenience and risk to the patient. For one, Ga-DOTATATE PET can be completed in less than 2 hours. In contrast, octreoscan or MIBG studies may require 2 days. Lastly, patients are exposed to less radiation using Ga-DOTATATE PET [8].

Most PGLs appear to be sporadic; however, about 10% of tumors are associated with hereditary syndromes, mainly multiple endocrine neoplasia type 2, von Hippel Lindau disease, and neurofibromatosis type 1 [7]. In addition, familial tumors are more frequently bilateral or extra-adrenal. As a result, genetic testing should be performed for at-risk family members, as it may affect medical management [2].

Most PCCs and PGLs are benign. Malignancy is defined as the presence of distant metastases, which occurs in 5%-13% of PCCs, 15%-23% of sympathetic PGLs, and 2%-20% of parasympathetic PGLs [7]. Malignant tumors present similarly to benign tumors. Metastases typically involve local lymph nodes, bone (50% of malignant cases), liver (50%), and lung (30%). Several imaging modalities have been used for diagnosis and staging of these tumors. As previously mentioned, this is best detected via MIBG and F-fluorodopamine PET [6].

The treatment of choice for PCCs and sympathetic PGLs is surgical resection. Preferably, this is performed laparoscopy; however, if the tumor is greater than 6 cm or there is a higher risk of malignancy, an exploratory laparotomy is performed. Before the operation, patients are pretreated with alpha-blockers, doxazosin, and phenoxybenzamine to minimize surgical complications and reduce mortality to less than 3% [2]. Some patients may require the addition of a beta-blocker for further control of tachyarrhythmias or angina. An isotonic saline infusion is also given the day before surgery to compensate for volume depletion, which is typically seen in this population. The main concern intraoperatively is catecholamine release secondary to tumor manipulation. This can potentially lead to a hypertensive episode. Postoperatively, blood pressure should be monitored, as the alpha-blockade is now unopposed [2]. It is recommended that plasma and/or urine metanephrines be rechecked 2-4 weeks postoperatively. A normal level indicates successful resection of the tumor. Regarding malignant disease, chemotherapy has been used for metastatic disease with only a partial and mainly palliative effect [7].

Summary points

- PCCs and PGLs present with a wide variety of clinical presentations and characteristic imaging findings.
- Diagnosis is made via plasma and/or urine metanephrine levels. Imaging is then used to localize the mass.
- Management consists of providing an alpha-blocker (doxazosin or phenoxybenzamine) followed by surgical resection of the mass.
- Complications of improper diagnosis and treatment include hypertensive crises, heart attacks, strokes, and death.

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