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Case Report

Metastatic urinary bladder paraganglioma on Ga-68 DOTATATE PET/CT ☆,☆☆,★,★★

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ABSTRACT

Paragangliomas are extra-adrenal catecholamine-secreting neuroendocrine tumors that can present with adrenergic signs and symptoms. The urinary bladder is a rare location for a paraganglioma, and these tumors must be distinguished from other more common bladder neoplasms. In this case report, we discuss a 59 year-old woman who initially presented with tachycardia, palpitations, chest tightness, shortness of breath, and weight loss. Laboratory evaluation showed significantly elevated catecholamines in the plasma and urine. A CT (Computed Tomography) scan of the abdomen and pelvis revealed an enhancing mass arising from the urinary bladder and an enlarged right pelvic lymph node. A follow up Ga-68 DOTATATE PET/CT (Positron Emission Tomography and/or Computed Tomography) showed increased uptake in the primary bladder mass, right pelvic lymph node, numerous skeletal lesions, and pulmonary nodules, consistent with metastatic paraganglioma of the urinary bladder. This case report demonstrates the radiological findings of metastatic urinary bladder paraganglioma and highlights the importance of skull base to mid-thigh PET/CT using Ga-68 DOTATATE. It is crucial for the radiologist to be familiar with the characteristics of urinary bladder paragangliomas and identify these tumors on imaging to allow prompt initiation of surgical resection and/or systemic therapy.

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Introduction

Paragangliomas are extra-adrenal catecholamine-secreting neuroendocrine tumors derived from embryonic neural crest cells [1]. These rare tumors can present with adrenergic signs and symptoms such as headache, diaphoresis, palpitations, tremor, tachycardia, hypertension, and weight changes [2]. Urinary bladder is a rare location for a paraganglioma and these tumors must be distinguished from other more common bladder neoplasms [3]. Paragangliomas are usually initially discovered on routine imaging modalities such as CT, MRI (Magnetic Resonance Imaging), and ultrasound. Specific imaging techniques such as Ga-68 DOTATATE PET/CT can be subsequently used as confirmatory imaging [4]. The ability to recognize paragangliomas on imaging is crucial for prompt treatment with surgical resection and/or systemic therapy. With proper treatment, the prognosis of paraganglioma is rather favorable, especially if there are no metastases [5].

Case Report

Our patient is a 59 year-old African American woman who presented to the emergency department (ED) with tachycardia, palpitations, chest tightness, shortness of breath, and a 60-pound weight loss in the past year. After evaluation in the ED, she was admitted to the hospital with a primary diagnosis of acute exacerbation of chronic heart failure with reduced ejection fraction. The patient's condition stabilized, and she was discharged home in three days. On her second follow-up visit with a cardiologist three months later, she was found to have persistent hypertension, diaphoresis, and weight loss. Workup for possible pheochromocytoma revealed significantly increased norepinephrine (31,792 pg/mL, normal range: 80-520 pg/mL) and dopamine (544 pg/mL, normal range: 0-20 pg/mL) in the plasma and significantly increased normetanephrine (6,451 μg/d, normal range: 95-650 μg/d) and norepinephrine in the urine (12,649 μg/g creatinine, normal range: 0-400 μg/g creatinine). The patient was referred to endocrinology and CT of the abdomen and pelvis was performed to localize the tumor.

Computed tomography (CT) of the abdomen and pelvis with and without intravenous contrast revealed a 6.7 $\times$ 6.6 cm heterogeneously enhancing mass at the right infero-lateral aspect of the urinary bladder (Fig. 1A and B). There was an additional 2.5 $\times$ 3.0 cm right pelvic lymph node (Fig. 1C). The adrenal glands were grossly normal in appearance without any discrete mass lesion. Patient then underwent a skull base to mid-thigh PET/CT using Ga-68 DOTATATE. The mass in the urinary bladder along with the right pelvic lymph node showed intense uptake (Fig. 2). Numerous osseous lesions in the axial skeleton and nodules in both lungs showed focal uptake consistent with metastatic disease (Fig. 2). Pathology has not been confirmed yet, at the time of writing of this manuscript. The clinical presentation, laboratory results, CT findings, and Ga-68 DOTATATE uptake on PET/CT were consistent with a metastatic urinary bladder paraganglioma.

Discussion

Pheochromocytomas and paragangliomas are catecholamine-secreting neuroendocrine tumors derived from embryonic neural crest cells. Pheochromocytomas are located in the adrenal glands and paragangliomas are found in any extra-adrenal location [1]. Due to catecholamine secretion, patients with these tumors can present with a variety of signs and symptoms, including headache, diaphoresis, palpitations, anxiety, tremor, tachycardia, hypertension, and weight changes, though some may be asymptomatic [2]. Pheochromocytomas and paragangliomas are rare tumors with an approximate annual incidence rate of 0.8 per 100,000 person-years [6]. Most pheochromocytomas and paragangliomas occur sporadically, but they may be associated with genetic syndromes in up to 41% of cases. Commonly mutated genes include NF1 (Neurofibromatosis Type 1), VHL (von Hippel Lindau), RET (REarranged during Transfection), and SDH (Succinate Dehydrogenase) [7].

The most common extra-adrenal location for a paraganglioma is the abdomen, but they can be located in the pelvis, thorax, head, or neck [1]. The urinary bladder is a very uncommon location for a paraganglioma. A meta-analysis on urinary bladder paraganglioma conducted in 2013 found 80 suitable journal articles with 106 patients over a period from 1980 to 2012 [8]. Of those 106 patients with urinary bladder paraganglioma, only 10 had metastatic disease, which makes our case an extremely rare occurrence. A unique clinical presentation of urinary bladder paraganglioma is micturition syncope, which is syncope during or immediately after urination [9]. Painless gross hematuria is another common presentation [10].

Common imaging modalities used to visualize urinary bladder paragangliomas include CT, MRI, and ultrasound. Ultrasound examinations may show round, well-defined, hypoechoic mass with internal vascularity. A round mass with soft tissue or slightly lower density is the typical CT finding, along with avid contrast enhancement. MRI manifestations include high signal on T2 weighted image and low signal on T1 weighted image. They also show contrast enhancement and restricted diffusion on MRI. Other urinary bladder tumors such as urothelial cancer, leiomyoma, rhabdomyosarcoma, and lymphoma must be considered as differential diagnoses for suspected urinary bladder paraganglioma [11]. Nuclear medicine techniques such as I-123 or I-131 labeled MIBG, F-18 FDG PET/CT, and Ga-68 DOTATATE PET/CT are used in addition to traditional imaging modalities to further characterize paragangliomas [12].

A common characteristic of neuroendocrine tumors is overexpression of the somatostatin receptor on their cell surface. Ga-68 DOTATATE, a somatostatin analog radiopharmaceutical, binds to somatostatin receptors, allowing visualization of somatostatin receptor positive tumors on PET/CT. Ga-68 DOTATATE PET/CT is commonly used for imaging of pheochromocytomas and paragangliomas given their high specificity and relatively low cost [13]. A recent study found that Ga-68 DOTATATE PET/CT scans were positive in 19 of 22 patients with paragangliomas and the scan results impacted the treatment plan in 12 of 14 recurrent paragan-

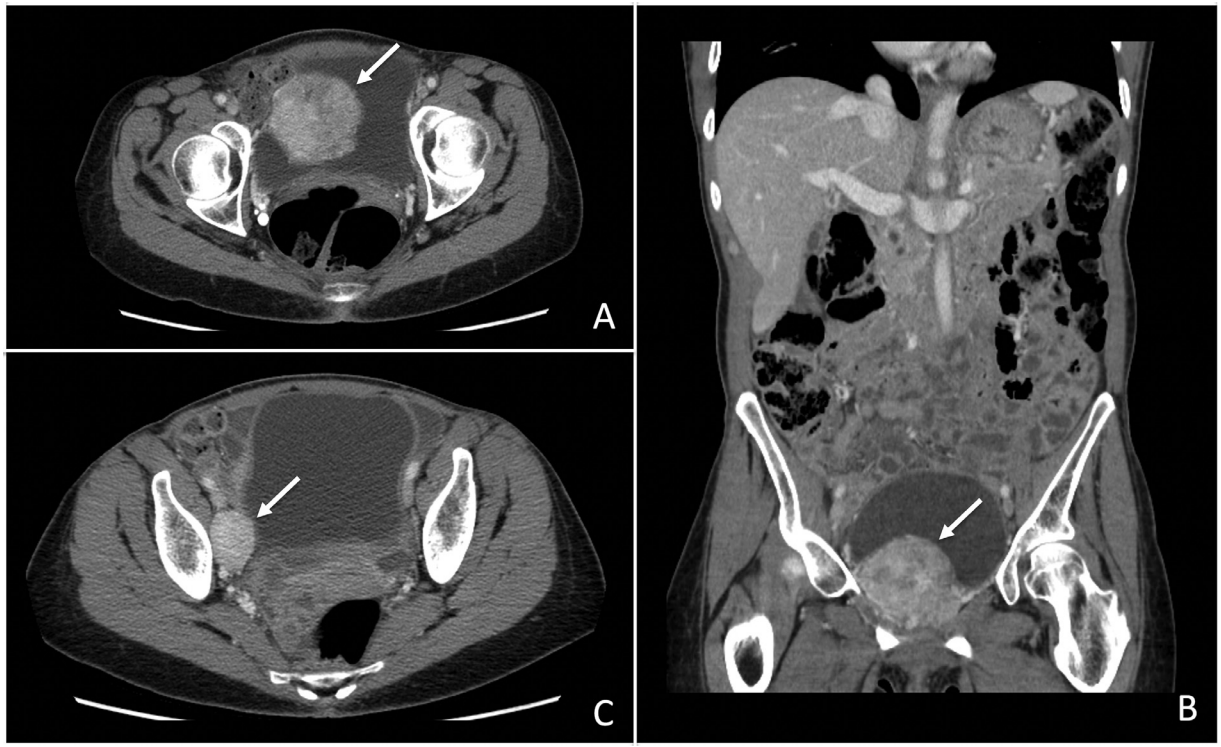

Fig. 1 – Multiple images from the CT of the abdomen and pelvis acquired after administration of intravenous contrast. A large (6.7 x 6.6 cm) heterogeneously enhancing mass is seen arising from the right infero-lateral wall of the urinary bladder and growing into the lumen (A), also shown on the coronal image (B) An enlarged (2.5 x 3.0 cm) and enhancing right pelvic lymph node is also seen (C) Adrenals bilaterally were normal (not shown).

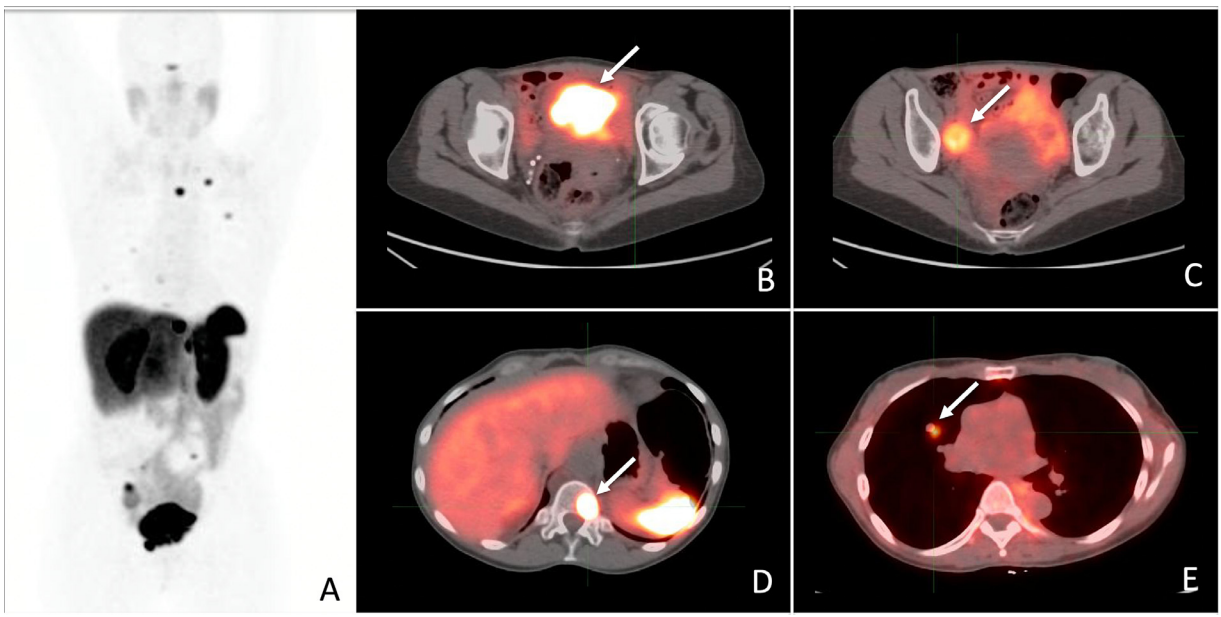

Fig. 2 – MIP (Maximum Intensity Projection) image (A) from the skull base to mid-thigh PET/CT acquired about 60 minutes after the intravenous administration of 5.4 mCi of Ga-68 DOTATATE shows multiple foci of increased uptake which correspond to the bladder mass, right pelvic lymph node, multiple bone lesions and bilateral lung nodules. Axial fused PET/CT images show intense uptake in the bladder mass (B) SUV 30.8, right pelvic lymph node (C) SUV 13.1, a bone metastasis in T-12 vertebral body (D) SUV 46.4, and a metastatic right upper lobe lung nodule (E) SUV 2.2.

glioma cases [4]. Another study demonstrated that Ga-68 DOTATATE PET/CT and I-131 MIBG SPECT/CT were equally more sensitive in evaluating pheochromocytomas or paragangliomas than F-18 FDG PET/CT (9 versus 8 tumors detected). Between Ga-68 DOTATATE PET/CT and I-131 MIBG SPECT/CT, the former was better able to identify other lesions associated with Multiple Endocrine Neoplasia (MEN) syndromes and yielded faster results with higher quality images [12]. Therefore, the authors concluded that Ga-68 DOTATATE PET/CT is superior to I-131 MIBG SPECT/CT or F-18 FDG PET/CT in the evaluation of pheochromocytomas and paragangliomas.

The prognosis for benign paraganglioma is highly favorable, with a 5 year survival rate of greater than 95% [5]. Prognosis for metastatic tumors is less promising, with an estimated 5 year mortality rate of 37% [14]. The mortality statistic for metastatic paraganglioma may not be highly accurate due to the rarity of the disease and lack of large volume research studies. The mainstay of treatment for urinary bladder paraganglioma is surgical resection, with common methods being transurethral resection, partial cystectomy, and radical cystectomy [3]. For localized tumors, surgical resection is an effective treatment. In a systematic review of 75 patients who had undergone surgery for urinary bladder paraganglioma, only 15 had tumor recurrence and 10 had metastasis at an average of 35 months follow up [8].

Treatment for metastatic tumor is less straightforward, with both surgical resection and systemic therapy typically being required. Our patient, who has metastasis to regional lymph nodes, bone, and lung, may benefit from resection of the primary urinary bladder tumor and affected lymph nodes and PRRT (Peptide Receptor Radionuclide Therapy) using high doses of Lu-177 DOTATATE. Lu-177 DOTATATE is a radiolabeled somatostatin analog that is used to treat patients with metastatic neuroendocrine tumors [15]. It efficacy for paragangliomas is currently being investigated through a clinical trial, and our patient is a potential candidate for enrollment [16]. Another possible systemic treatment for our patient is I-131 MIBG (Iobenguane I 131, available under the commercial name Azedra), a therapeutic agent that has been FDA approved for the treatment of metastatic pheochromocytoma or paraganglioma [17]. To be treated with Iobenguane I-131, the patient must first undergo MIBG scintigraphy to confirm that her tumor takes up MIBG.

Conclusion

Despite their rarity, it is important to recognize that urinary bladder paragangliomas do occur and may cause significant morbidity and mortality, especially if they are metastatic. It is crucial for the radiologist to be familiar with the characteristics of urinary bladder paragangliomas, identify these tumors on imaging, correlate them with clinical scenarios, and recommend further confirmatory imaging or procedures. This will allow prompt initiation of surgical resection and/or systemic therapy to relieve symptoms and prevent further growth and spread of the tumor.

Patient consent

A written informed consent was obtained from the patient for the publication of this case report.

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