False Positive of $^{68}$Ga-DOTATATE PET-CT in a Paraganglioma

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Abstract: Background: Functional imaging with $^{68}$Ga-DOTATATE PET-CT is widely employed to detect both primary and metastatic pheochromocytomas and paragangliomas (PGL), but its results may be occasionally misleading as in the case here reported.

Case Presentation: We report here a 75-year-old woman with an interaortocaval PGL that was diagnosed after a hypertensive crisis occurring during the resection of a kidney tumor. $^{68}$Ga-DOTATATE PET-CT disclosed pathologic uptake in the abdomen and at the iliac crest. After the resection of the abdominal tumor, with the histological confirmation of PGL, arterial blood pressure and metanephrine levels were normalized. Genetic testing was negative. Thereafter, the bone lesion increased in size and became painful, requiring multiple medications. A selective biopsy disclosed a metastatic lesion arising from the renal tumor.

Conclusion: The false-positive result of $^{68}$Ga-DOTATATE PET-CT is discussed.

Keywords: Paraganglioma, pheochromocytoma, imaging, Ga-DOTA-peptides, bone metastasis, differential diagnosis.

1. INTRODUCTION

Pheochromocytomas (PCC) and paragangliomas (PGL) are rare tumors (annual incidence 0.1 to 0.6 per 100,000 population) arising from chromaffin-producing cells in the adrenal gland or in extra-adrenal sites (sympathetic paravertebral ganglia of thorax, abdomen, and pelvis or parasympathetic ganglia in the neck and at the skull base), respectively [1].

PCCs and PGLs of sympathetic chains usually cause symptoms due to catecholamine over-secretion [1].

PCCs/PGLs are characterized by a high frequency of hereditary forms (overall 35%) with a propensity for multifocal disease. Most PGLs are benign; malignant disease is defined by the presence of tumor deposits in lymph nodes and other regions in which chromaffin cells are normally absent (i.e., liver, lung, bone). Owing to the well-known heterogeneous clinical pattern of these tumors, prompt characterization of the disease is critical in order to select the best therapeutic approach and proper follow-up.

After the biochemical diagnosis of PCC/PGL is established, first-line imaging studies are computed tomography (CT) or magnetic resonance imaging (MRI) [1]. Radionuclide imaging modalities are complementary to CT and/or MRI to provide functional characteristics of the tumor [1, 2].

This was historically performed with $^{123}$I-metaiodobenzylguanidine ($^{123}$I-MIBG) scintigraphy, but a leading role has recently gained attention by fusion imaging techniques, such as positron emission tomography (PET)-CT, mostly with radiotracers mapping somatostatin receptors (SSTR). In this context, an alternative option is $^{18}$F-desoxyphenylalanine (DOPA)-PET, which provides excellent sensitivity for chromaffin cells and is a useful diagnostic tool in the detection of extra-adrenal PGL [2]. Whenever facing the clinical suspicion of PCC/PGL, it would be a serious mistake to attempt a cytologic examination, potentially causing a fatal hypertensive crisis.

We describe here a patient affected by PGL where functional imaging was misleading.

2. CASE REPORT

A 75-year-old woman with long-lasting arterial hypertension, on chronic treatment with valsartan and hydrochlorothiazide, underwent abdominal surgery in July 2017 for the selective resection of a recently found 20-mm left kidney tumor. During surgery, an interaortocaval lesion was detected, but it could not be removed due to a severe hypertensive crisis occurring during surgical manipulation. Histologic examination of the kidney mass showed a clear cell renal carcinoma, stage pT1b.

Family history was remarkable for an adrenal cortical carcinoma causing the death of a 78-year-old sister.

After surgery, hormonal workup revealed increased excretion of urinary metanephrines and normetanephrines, 441

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μg/24 h (normal range – nr – 74-297 μg/24 h), and 525 μg/24 h (nr 105-354 μg/24 h), respectively. Serum calcium was normal, and calcitonin was undetectable. Abdominal CT and MRI showed a 28 x 21 mm solid ovoid contrast-enhancing lesion below the left renal vein, suggestive for PGL. In addition, a 35-mm osteolytic lesion was disclosed at the left iliac crest (Fig. 1).

**Fig. (1).** Multidetector spiral CT scan. In the left panel, 28 x 21-mm enhancing ovoid mass between the aorta and inferior vena cava, below the left renal vein. In the right panel, 45-mm solid pathologic tissue at the left sacral wing, interrupting both the anterior and posterior cortical profile. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

**68**Ga-DOTATATE PET-CT induced an avid uptake of radiotracer in both lesions (Fig. 2).

**Fig. (2).** **68**Ga-DOTATATE PET/TC showing the two lesions. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

The working diagnosis was thus PGL with bone metastasis. After pre-operative selective adrenergic blockade with doxazosin and a DDR pacemaker implantation due to bundle branch block, the interaortocaval lesion was uneventfully resected.

After surgery, blood pressure was lowered further in a few days, allowing the tapering of anti-hypertensive medications, and the patient was discharged home in good clinical conditions. Both metanephrines and normetanephrines were normalized in a short time.

The histopathologic examination revealed a sympathetic PGL, without neither vascular invasion, nor necrosis or mitosis; Ki67 was <5%. Immunohistochemistry was positive for chromogranin A, synaptophysin, S100 protein, neuron-specific enolase and negative for cytokeratins AE1-AE3 and glial fibrillary acidic protein.

After informed consent, genetic analysis was performed, using targeted next-generation sequencing (NGS) technology according to the Consensus Statement on NGS-based diagnostic testing of hereditary PGL and the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines for the interpretation of sequence variants [3, 4]. No variants of clear pathogenic significance were highlighted.

After three months, while on persisting well-being, the urologist consultant suggested only yearly follow-up for blood pressure control. In the following months, the patient complained of low back pain requiring escalating analgesic treatment. Whole body CT disclosed increased size (up to 50 mm) of the osteolytic lesion that was partially protruding into the spinal canal. Bone scintigraphy with **99**Tc-MDP revealed increased uptake at the left iliac crest, consistent with the osteolytic lesion. Metanephrines and normetanephrines were still within the normal range. At bone biopsy, immunohistochemistry was positive for CK7+, PAX2+, PAX-8 and negative for CK20, CD10 and racemase, thus pointing to the kidney as the primary lesion. The lesion was labeled as unresectable. An oncologist consultant recommended adjuvant treatment with sunitinib, a tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor approved for metastatic renal cell carcinoma, antiresorptive therapy with zoledronic acid, and external-beam radiotherapy. Low back pain improved dramatically in a short time after these treatments.

**3. DISCUSSION**

The challenge in this elderly woman was the characterization of a bone lesion after the previous resection of two different neoplasms, a kidney tumor, considered in remission, and a PGL.

Pretreatment imaging is crucial for providing an accurate staging of PGL, regardless of size and/or hereditary syndromes, with the identification of metastatic lesions [1, 2]. Morphological imaging with CT and MRI provides excellent anatomical detail and high sensitivity but lacks specificity. To overcome these drawbacks, the specificity of functional imaging provides an important contribution. The major advantage of radionuclide imaging is to provide high visual contrast between tumor and healthy tissue due to the affinity of tumor cell receptors for specific tracers. Thus, nuclear imaging allows the detection of functional tumor tissues that could be potentially missed by morphological imaging. This was historically performed in PCC/PGL with **123**I-MIBG scintigraphy. This technique, however, suffers from poor
sensitivity due to limited spatial resolution, difficulty in detection of small tumors (<1.5–2.0 cm), or of large tumors with extensive necrosis/hemorrhage, lack of tracer uptake in some tumors, and interference with certain medications, all potentially leading to false-negative results. The addition of single photon emission computed tomography (SPECT) improves the sensitivity, but the spatial resolution is still low (<1.5 cm) and the detection of small lesions is often difficult [2].

PCC and PGL widely express SSTRs, particularly subtypes 2, 3 and 5 [5]. SSTRs can be imaged in vivo by pentetreotide scintigraphy and, more recently, by PET using DOTA-coupled SSTR agonists labeled with ⁶⁸Ga [2]. All radiolabeled DOTA-peptides can target SSTR2 effectively. Unlike MIBG, radiolabeled SST analogs are not specific for extra-adrenal PGL, but offer high sensitivity due to SSTR binding, particularly in subtypes 2, 3 and 5. Compared to planar scintigraphy and SPECT MIBG imaging, the advantages of using ⁶⁸Ga-DOTATATE PET/CT are the optimal tumor-to-background ratio, thus providing a better quality of the images and better visualization of the lesion. Furthermore, results are available within hours in comparison to days.

It was reported that ⁶⁸Ga-DOTATATE had better sensitivity than ¹²³I-MIBG in all anatomical areas, in particular for bone lesions [6], most likely due to their smaller size. A metaanalysis [7] of 17 studies (including 629 patients) compared ⁶⁸Ga-SST analogs and ¹⁸F-FDG in the diagnosis of metastatic PCCs/PGLs, showing that the pooled sensitivity was 85% (confidence interval - CI - 95%, 78-91) for FDG and 95% (CI 95%, 92-97) for ⁶⁸Ga, whereas the corresponding figures for specificity were 55% (CI 95%, 37-73) and 87% (CI 95%, 63-96).

⁶⁸Ga-SST PET/CT has also been demonstrated to provide relevant prognostic information: since the intensity of uptake is an indirect measure of tumor differentiation, with higher uptake correlating with a better prognosis [8].

It is worthwhile considering that in addition to neuroendocrine tumors arising from the gastrointestinal tract, pancreas, bronchi, and endocrine organs, many other tumors, such as meningiomas [9], breast cancers [10], prostate cancers [11], small cell lung cancers [12] and lymphomas [13], or inflammatory processes, such as radiation pneumonitis, gastritis, sequelae of recent surgeries, reactive lymphadenopathy, granulomatous lesions, and fibrous dysplasia of bone (e.g., McCune-Albright syndrome, oncogenic osteomalacia) [2, 14, 15], may show a false positivity of SST-based imaging. ¹⁸F-DOPA PET imaging should be more specific, but it is not widely available [16]. We can speculate that when the clinical context is equivocal, the use of ¹⁸F-DOPA PET-CT might avoid the false-positive results. Due to its reported 100% specificity [17], the diagnosis of PGL is ruled out if the mass is unable to concentrate this radiotracer.

Falsely positive radiolabeled DOTA peptides uptake has been already described in a few reports in patients with non-neuroendocrine tumors, such as metastases from renal cell carcinoma, similar to our patient. Kanthan et al. [18] reported thyroid and pancreatic localization in a 66-year-old woman. Vamadevan et al. reported a pancreatic metastasis in a 64-year-old man [19] and a year later, a thigh metastasis in the same patient [20].

CONCLUSION

Functional imaging plays a chief role in the characterization of a neoplastic mass, but its results must always be considered in the whole clinical context. Despite its high sensitivity and specificity, false-positive results due to other pathologic states may potentially induce erroneous clinical choices.

LIST OF ABBREVIATIONS

- CD10 = Neprilysin
- CI = Confidence Interval
- CK = Cytokeratin
- CT = Computerized Tomography
- DOPA = Desoxyphenylalanine
- DOTATATE = 1,4,7,10 Tetraazacyclododecane-1,4,7,10-Tetraacetic Acid Tyrosine-3-Octreotate
- FDG = Fluorodesoxyglucose
- MDP = Methylene Diphosphonate
- MIBG = Metaiodobenzylguanidine
- MRI = Magnetic Resonance Imaging
- NGS = Next-Generation Sequencing
- nr = Normal Range
- PAX = Paired Box Transcription Factor
- PCC = Pheochromocytoma
- PET = Positron Emission Tomography
- PGL = Paraganglioma
- SPECT = Single Photon Emission Computed Tomography
- SSTR = Somatostatin Receptors

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

A written informed consent was obtained from the patient prior to the publication of the study.

STANDARDS OF REPORTING

CARE guidelines and methodology were followed to conduct the study.
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The authors declare no conflict of interest, financial or otherwise.

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