Case Report

Peptide receptor radionuclide therapy with lutetium-177 DOTATATE in a case of recurrent extradrenal retroperitoneal malignant paraganglioma with nodal and bone metastasis

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ABSTRACT

Extra-adrenal retroperitoneal paragangliomas (PGLs) are rare tumors causing considerable difficulty in both, diagnosis and treatment. They can be unicentric or multicentric, tend to be locally invasive and therefore have a high incidence of local recurrence. PGLs shows somatostatin receptor positivity, which can be imaged with technetium-99m (Tc-99m)-hydrazinonicotinyl-Tyr3-octreotide (HYNIC-TOC) and can be treated with lutetium-177 (Lu-177) DOTATATE. We present a case of recurrent unresectable retroperitoneal PGL with nodal and bone metastases in a 27-year-old male, 6 months postsurgery detected with Tc-99m-HYNIC-TOC and was administered with peptide receptor radionuclide therapy using Lu-177 DOTATATE.

Key words: Lutetium-177 DOTATATE, recurrence, retroperitoneal paraganglioma, technitium-99m-hydrazinonicotinyl-tyr3-octreotide

INTRODUCTION

Extra-adrenal retroperitoneal paragangliomas (PGLs) arise from dispersed paraganglia that tend to be symmetrically distributed in close relation to the aorta and sympathetic nervous system. The prognosis of PGLs can be very difficult to predict. They have high rate of recurrence after surgery.[1] Lutetium-177 (Lu-177) DOTATATE is used as treatment modality for most of the neuroendocrine tumors expressing somatostatin receptors (SSTRs). Although PRRNT is not approved in many countries, including the United States, it is feasible to refer patients to sites in Asia and Europe where they can receive this therapy under local regulations.

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Clinical trials with these agents are getting under way in the United States. The 177Lu-DOTATATE study is an international phase 3 multicenter trial for patients with midgut neuroendocrine tumors and metastases; patients are randomized to 177Lu-DOTATATE in four doses administered every 4 week with time to progression and overall survival as endpoints. This trial is expected to open in 13 centers in the United States and should provide sufficient safety and efficacy data to lead to Food and Drug Administration approval.[2] Our case describes the use of technetium-99m ethylenediamine-N, N′-diacetic acid-hydrazinonicotinyl-Tyr3-octreotide (HYNIC-TOC) in imaging the SSTR positivity of recurrent deposits, lymph nodes in the retroperitoneum and bone metastasis. He underwent treatment with peptide receptor radionuclide therapy (PRRT) using Lu-177 DOTATATE.

CASE REPORT

A 25-year-old male patient presented with abdominal pain underwent computed tomography (CT) of the abdomen that revealed retroperitoneal mass lesion on the left

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side [Figure 1]. His 24 h urinary Vanillyl mandelic acid was 3 mg/24 h (normal range <8 mg/24 h) and serum cortisol at 8 am was 26 μg/dl (normal range 7-25 μg/dl). He underwent mass removal along with left adrenalectomy, splenectomy and distal pancreactectomy. Histopathological examination confirmed extraadrenal PGLs with lymphovascular and capsular invasion spleen and pancreas were not involved by tumor. Immunohistochemistry revealed chromogranin positive and S-100 negativity in sustentacular cells that predict malignant behavior. Ki-67 proliferative index was 8%. Postoperative I-131 MIBG scintigraphy revealed no residual disease and no other sites of metastasis [Figure 2]. After 6 months, he presented with pain in the left lumbar region and His follow-up CT abdomen revealed left subdiaphragmatic deposits, left crural deposit indenting fundus of the stomach and left paraaortic lymph nodes and left ilium lytic lesion. Whole body planar scintigraphy was done after intravenous injection of 20 mCi (740 Mbq) of Tc-99m-HYNIC-TOC [Figure 3] that showed intense uptake in the subdiaphragmatic and crural deposits and left ilium, minimal tracer uptake noted in left pararaortic node. F-18 fluorodeoxyglucose/positron emission tomography/CT (FDG PET/CT) [Figure 4] revealed low-grade uptake in the deposits and bone lesion, but intense tracer uptake in the paraortic lymph node suggesting dedifferentiated tumor. He was treated with PRRT after 1 month using 140 mCi (5180 MBq) of Lu-177 DOTATATE [Figure 5]. He had symptomatic relief of bone pain in the left ilium at 6 months and follow-up Tc-99m-HYNIC-TOC study shows complete resolution of uptake in the left ilium and reduction in tumor deposits in the abdomen [Figure 6]. He was advised to take a second dose of Lu-177 DOTATATE.

DISCUSSION

Extra-adrenal PGLs of retroperitoneum are neoplasias of the chromaffin cells that are located in the para-aortic sympathetic chain and the aortic bifurcation.[3] They often manifest themselves by symptoms of episodic freeing of catecholamines, such as high blood pressure, migraines, sweating and palpitations. It is reported silent extra-adrenal PGL of retroperitoneum is probably due to mutations of the gene for succinate dehydrogenase-B.[4] Extra-adrenal retroperitoneal PGLs have a more aggressive course than their adrenal counterparts, which are called pheochromocytomas. The prognosis of PGLs can be very difficult to predict. However, their anatomical location may influence their biological behavior: carotid body PGLs have a relatively low rate of malignant behavior while retroperitoneal PGLs tend to have a higher incidence of malignant transformation. Approximately, 20-42% of PGLs metastasize, compared with only 2-10% of adrenal pheochromocytomas. Dissemination occurs both lymphatically and hematogenously, with the most common sites of metastasis being the regional lymph nodes, bone, liver, and lung.[2,4] The tumors usually appear as rounded or oval masses with a similar density to the liver on unenhanced CT. Larger lesions may show

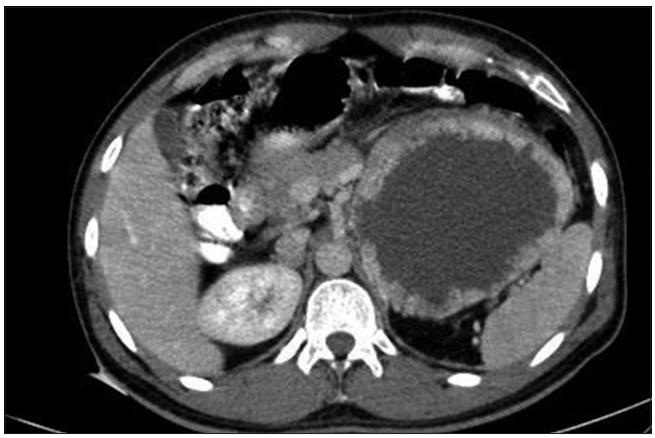

Figure 1: Preoperative axial computed tomography scan showing large retroperitoneal mass lesion on left side with central areas of necrosis

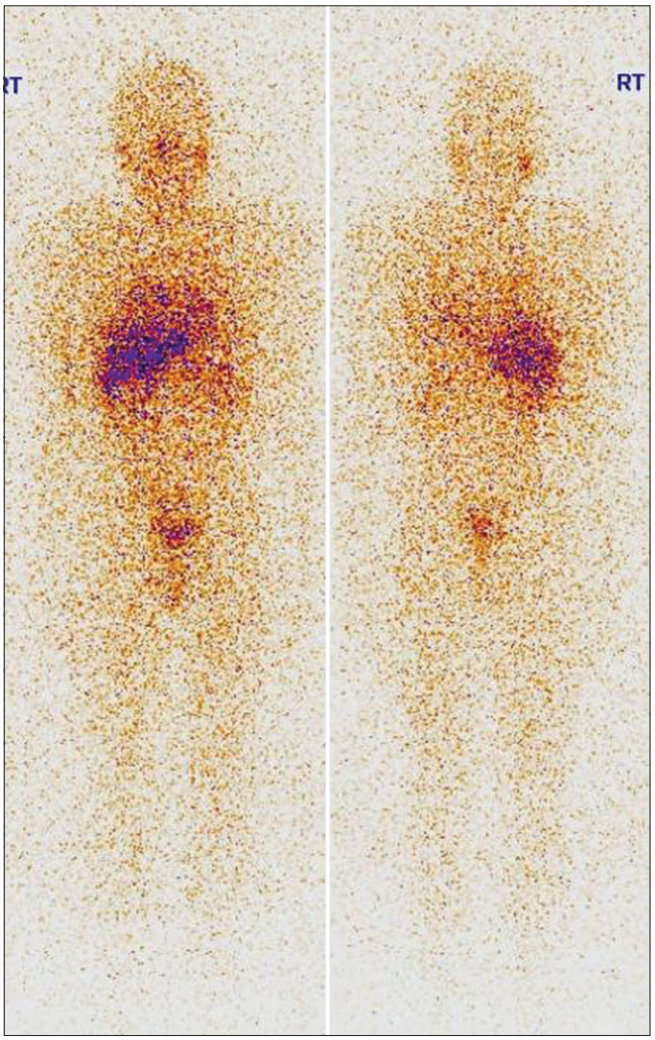

Figure 2: I-131 MIBG scintigraphy showing no residual disease in the retroperitoneum. Physiological uptake is noted in salivary glands, liver and bladder

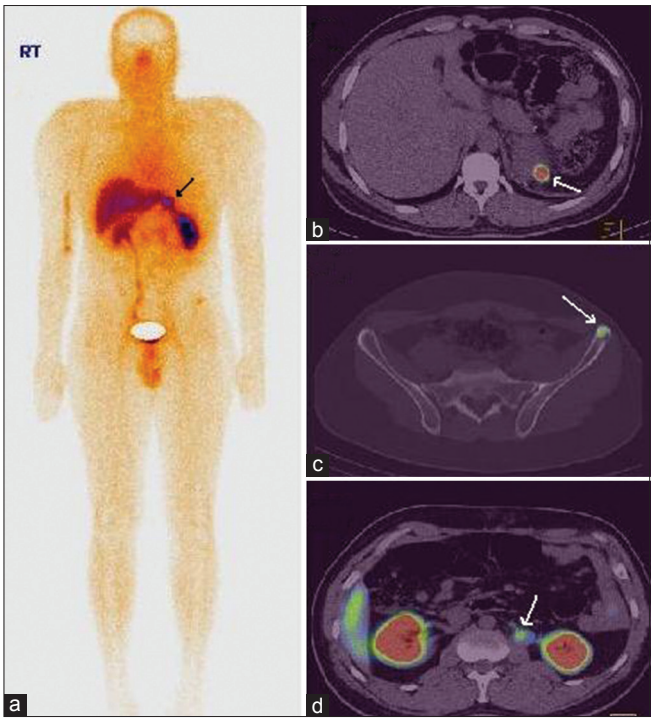

Figure 3: Whole body technitium-99m hydrazinonicotinyl-Tyr3-octreotide (a) and single photon emission computed tomography/computed tomography showing intense uptake in the deposits (b), left ilium (c) and mild uptake in the paraaortic lymph nodes (d) (arrows)

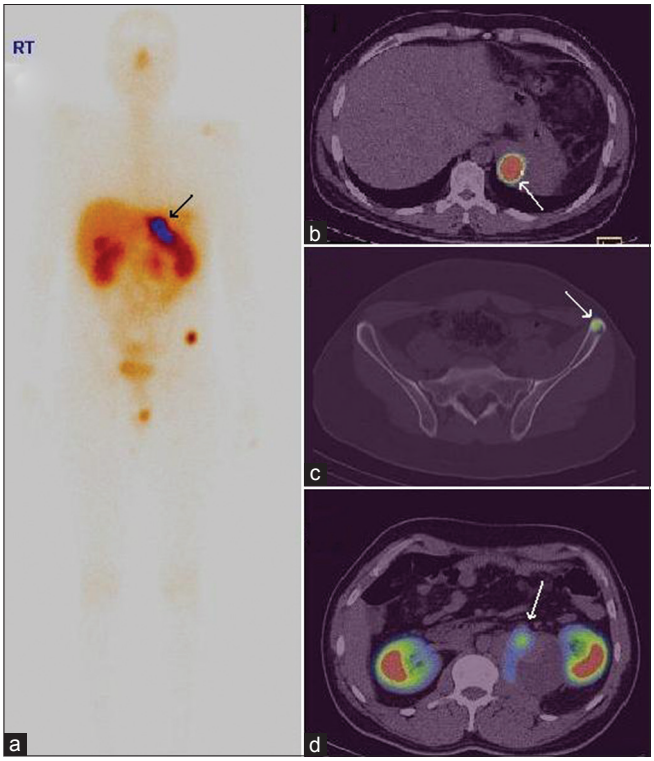

Figure 5: Whole body lutetium-177 DOTATATE (a) and single photon emission computed tomography/computed tomography images showing intense uptake in the deposits (b) and left ilium (c), mild uptake in the paraaortic lymph nodes (d)

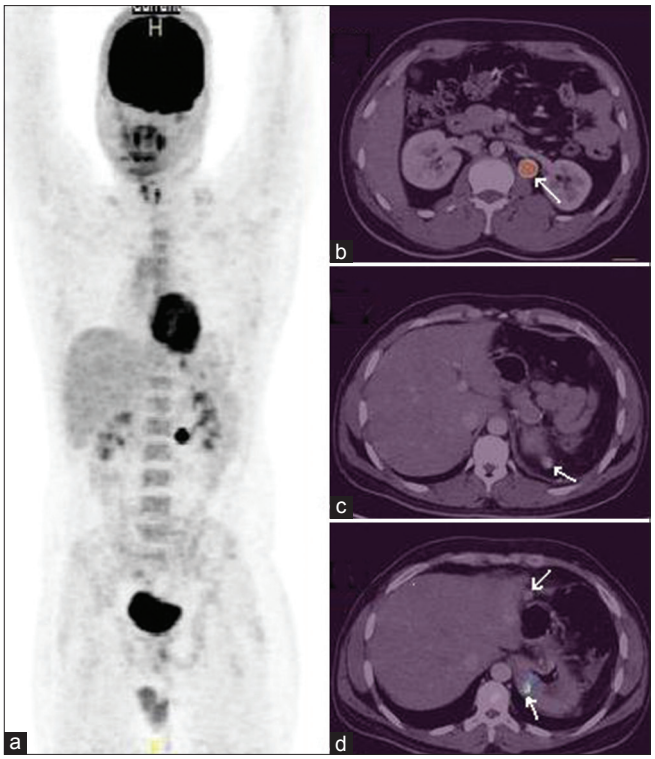

Figure 4: Whole body fluorodeoxyglucose-positron emission tomography (PET)/computed tomography (CT) maximum intensity projection image (a), Fused PET/CT showing intense tracer uptake in the pararaortic lymph nodes (b), but mild grade uptake in the deposits (c and d) (arrows)

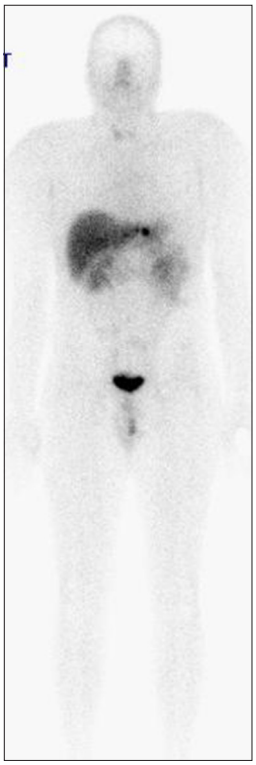

Figure 6: Follow up Whole body technitium-99m hydrazinonicotinyl-Tyr3-octreotide showing intense uptake in the deposits with decrease in deposits and interval resolution of uptake in left ilium

a cystic component due to central necrosis or hemorrhage. Calcification is present in some cases.[5] Diagnosis of malignant PGLs is based on evidence of extensive local invasion, or more reliably on documentation of metastasis

to one or more sites where nonchromaffin tissue is not normally present.[6] These may indicate the disease has a tendency to relapse.

Overexpression of SSTRs is noted in these tumors and this pathophysiology is exploited in radioimmunoscintigraphy (RIS). SSTR imaging in PGLs is indicated for the detection of the primary, staging, monitoring response to therapeutic somatostatin and treatment planning for SSTR directed radionuclide therapy.[7] All the subtypes of SSTR expressed by PGLs have affinity for the native peptide but vary in their affinity for the somatostatin analogs; hence, the sensitivity of the study depends on the density of the SSTR in the tumor and the type of analog used in the study. The disadvantages of long half-life, physiological uptake in abdominal organs, and higher energy of in-111 warranted research in use of a Tc-99m labeled agent for RIS, which is better-suited for single photon emission computed tomography imaging. Tc-99m labeled TOC has been identified as a suitable tracer, which uses HYNIC as a complexing ligand.[8]

Change in biology of the tumors is a known phenomenon and is attributed to either a change in the tumor receptor density or expression of a new receptor. Delineating this receptor changes assists in prognosticating the disease and alter management.[9] Patients on followup with clinical or biochemical suspicion of a recurrence evaluated with RIS with poor to absent SSTR expression raise the probability of altering receptor status. Neuroendocrine tumors will have well-differentiated pathology and does not express glucose transporter (GLUT) receptors and hence an F-18 FDG PET/CT study is not utilized in the work up. Dedifferentiating tumors show an increase in the GLUT receptor expression with a decline in the SSTR density; hence, F-18 FDG PET/CT study would be efficacious in locating sites of tumor spread.[10] Targeted internal radiotherapy in the form of PRRT with Lu-177 DOTATATE offers a good chance of resolution of these recurrent tumors in surgically unresectable cases. DOTATATE is the abbreviated form of [DOTA0, Tyr3, Thr8]-octreotide. DOTA stands for the bifunctional chelating molecule 1,4,7,10-tetraazacyclo-dodecane-1,4,7,10-tetraacetic acid, and Tyr3-octreotide is the modified octreotide. Zovata *et al*. studied four patients with hereditary nonmetastatic PGLs syndrome type 1, with progressive disease, in whom surgical excision was not possible.[11] They were treated with Lu-177 DOTATATE (3-5 cycles) and all had a partial response or stable disease to the treatment. Their conclusion was that a good alternative treatment when surgical or radiation therapy are contraindicated could be radiometabolic therapy with Lu-177 DOTATATE. Gupta *et al*.[12] treated a patient with recurrent carotid body PGLs with spinal metastases with Lu-177 DOTATATE, and total dose of 750 mCi (27 GBq) cumulative activity was administered in five cycles at an interval of 12 weeks. significant response at the primary site and complete disappearance of nodal and T7 vertebral metastases were noted. Our patient HYNIC-TOC images demonstrate intense positivity in the sub diaphragmatic deposits and bone lesion showing good differentiation while lymph nodes showed a mild positivity. F-18 FDG PET-CT showed low-grade uptake in deposits and bone lesions, but nodes were showing high-grade positivity. Lu-177 DOTATATE showed good uptake in the deposits indicating there will be good response while nodes showed a mild positivity indicating there will be a minimal response to PRRT. This case illustrates the importance of Lu-177 DOTATATE therapy in surgically unresectable, recurrent PGLs with nodal metastases.

REFERENCES

1. Whalen RK, Althausen AF, Daniels GH. Extra-adrenal pheochromocytoma. J Urol 1992;147:1-10.
2. Delbeke D, Graham MM. Addendum to the editorial "Joint guidance on peptide receptor radionuclide therapy in neuroendocrine tumors". J Nucl Med 2013;54:1170.
3. Yamaguchi T, Tada M, Takahashi H, Kagawa R, Takeda R, Sakata S, *et al*. An incidentally discovered small and asymptomatic para-aortic paraganglioma. Eur Surg Res 2008;40:14-8.
4. Timmers HJ, Pacak K, Huynh TT, Abu-Asab M, Tsokos M, Merino MJ, *et al*. Biochemically silent abdominal paragangliomas in patients with mutations in the succinate dehydrogenase subunit B gene. J Clin Endocrinol Metab 2008;93:4826-32.
5. Rufini V, Calcagni ML, Baum RP. Imaging of neuroendocrine tumors. Semin Nucl Med 2006;36:228-47.
6. Lack EE, Lloyd RV, Carney JA, Woodruff JW, Association of Directors of Anatomic and Surgical Pathology. Recommendations for the reporting of extra-adrenal paragangliomas. The Association of Directors of Anatomic and Surgical Pathology. Hum Pathol 2003;34:112-3.
7. Balon HR, Brown TL, Goldsmith SJ, Silberstein EB, Krenning EP, Lang O, *et al*. The SNM practice guideline for somatostatin receptor scintigraphy 2.0. J Nucl Med Technol 2011;39:317-24.
8. Kamaleshwaran KK, Subramanian PV, Natarajan S, Mohanan V, Shinto AS. Bone metastasis from a neuroendocrine tumor detected by 99m-technetium-hydrazinonicotinyl-Tyr3-octreotide single-photon emission computed tomography/computed tomography. Indian J Nucl Med 2013;28:187-8.
9. Garin E, Le Jeune F, Devillers A, Cuggia M, de Lajarte-Thirouard AS, Bouriel C, *et al*. Predictive value of 18F-FDG PET and somatostatin receptor scintigraphy in patients with metastatic endocrine tumors. J Nucl Med 2009;50:858-64.
10. Shah S, Purandare N, Agrawal A, Rangarajan V. A pictoral review on somatostatin receptor scintigraphy in neuroendocrine tumors: The role of multimodality imaging with SRS and GLUT receptor imaging with FDG PET-CT. Indian J Radiol Imaging 2012;22:267-75.
11. Zovato S, Kumanova A, Demattè S, Sansovini M, Bodei L, Di Sarra D, *et al*. Peptide receptor radionuclide therapy (PRRT) with 177Lu-DOTATATE in individuals with neck or mediastinal paraganglioma (PGL). Horm Metab Res 2012;44:411-4.
12. Gupta SK, Singla S, Karunanithi S, Damle N, Bal C. Peptide receptor radionuclide therapy with (177) Lu DOTATATE in a case of recurrent carotid body paraganglioma with spinal metastases. Clin Nucl Med 2014;39:440-1.

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