^{177}Lu-DOTATATE PRRT in Recurrent Skull-Base Phosphaturic Mesenchymal Tumor Causing Osteomalacia: A Potential Application of PRRT Beyond Neuroendocrine Tumors

Sandip Basu and Preeti Fargose

Radiation Medicine Centre, Bhabha Atomic Research Centre, Parel, Mumbai, India

The potential of peptide receptor radionuclide therapy (PRRT) is described in a case of recurrent inoperable phosphaturic mesenchymal tumor causing osteomalacia in the left basiocciput, for which the patient had undergone surgery twice previously. After one cycle of PRRT, there was good symptomatic improvement, with a modest reduction in uptake on both ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT suggesting a favorable response. Hence, treatment with a second cycle was considered. Being somatostatin receptor–avid, this rare group of tumors when inoperable or recurrent may potentially be targeted with PRRT. Well-tolerated and noninvasive, PRRT could evolve as a promising targeted treatment approach in this clinical setting. In summary, tumor-induced osteomalacia with ^{68}Ga-DOTATATE–avid inoperable or recurrent tumor can be considered a potential clinical application for PRRT beyond neuroendocrine tumors.

Key Words: ^{177}Lu-DOTATATE PRRT; oncogenic osteomalacia; ^{68}Ga-DOTATATE PET/CT; tumor-induced osteomalacia

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Oncogenic osteomalacia is a relatively rare paraneoplastic syndrome with prominent musculoskeletal complaints (such as skeletal pain, fatigue, fracture, and muscle ache) that could make the patient wheel-chair–bound. The cause of oncogenic osteomalacia is usually benign mesenchymal or mixed connective tissue tumors (*1*) or, rarely, malignant mesenchymal tumors (*2*). Recently, *FGFR1* translocation has been described in a fraction of phosphaturic mesenchymal tumors of the head and neck (*1*). A substantial number of these tumors demonstrate somatostatin receptor expression, and ^{68}Ga-DOTATATE PET/CT has evolved as an important imaging modality to locate the causative tumors (*3*). The condition quickly corrects after complete resection of the tumor, with gradual normalization of skeletal abnormalities. When the tumor cannot be identified, supportive medical management with phosphorus and calcitriol is considered. Octreotide and cinacalcet, a calcimimetic that acts by allosteric activation of the calcium-sensing receptors, have also been found useful in patients with resistant hypophosphatemia (*4*).

The present report explores the potential application of ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) in a case of recurrent inoperable phosphaturic mesenchymal tumor of the skull base.

CASE REPORT

A 53-y-old woman diagnosed with vitamin D–resistant hypophosphatemic osteomalacia (presented 2 y previously with bilateral groin pain and difficulty walking and was evaluated with MRI, bone densitometry, and serum calcium and vitamin D profiles) was treated initially with vitamin D_3 supplements. On further investigation, her level of serum phosphorus was found to be low (1.5 mg/dL; reference range, 2.3–4.5 mg/dL) and her level of serum fibroblast growth factor 23 was high (725 reference units/mL; reference range, ≤180 reference units/mL), and she was started on phosphate supplements. Somatostatin receptor PET/CT and brain MRI showed a large, expansile osteolytic lesion breaching the cortex, with a 3.5 × 2.7 cm soft-tissue component involving the base of the skull and the left basiocciput (including the clivus and the occipital condyle), erosion of the mastoid and the petrous part of the adjacent temporal bone, and occlusion of the left jugular foramen. She underwent retromastoid craniotomy with excision of an extraaxial tumor. Histopathologic examination demonstrated a benign giant cell–rich lesion and was suggestive of a phosphaturic mesenchymal tumor (as differentiated from a brown tumor associated with hyperparathyroidism). In view of the recurrent symptoms, brain MRI was undertaken at the 4-mo follow-up after surgery and showed a 3.2 × 1.6 × 2.1 cm recurrent tumor of the left occipital skull base around the jugular foramen and involving the left arch of the atlas and the mastoid temporal bone. Craniotomy and repeated excision with occipitocranial fusion was performed, and the histopathologic findings were suggestive of recurrent or residual tumor consistent with the initial diagnosis. Enhanced

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For correspondence or reprints contact: Sandip Basu, Radiation Medicine Centre, Bhabha Atomic Research Centre, Tata Memorial Hospital Annexe, Jerbai Wadia Rd., Parel, Mumbai, Maharashtra, India, 400012.
E-mail: drsanb@yahoo.com
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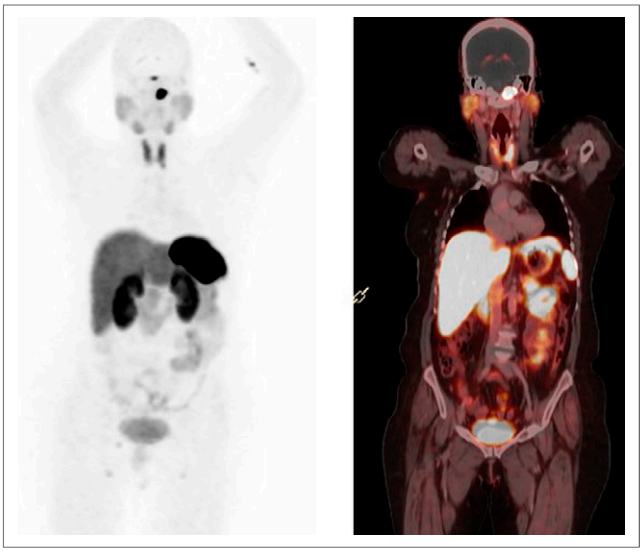

FIGURE 1. ^{68}Ga-DOTATATE PET/CT scan (maximum-intensity projection and fused coronal view) demonstrating enhancing soft-tissue lesion (2.3 × 1.9 × 2.1 cm) in left basiocciput and left occipital condyle involving left jugular foramen.

CT at 3 mo after the second surgery showed a residual enhancing 1.8 × 2.2 × 1.6 cm lesion in and around the left hypoglossal canal. The serum phosphorus levels were consistently low, and the patient was started on phosphorus supplements. ^{68}Ga-DOTATATE PET/CT 6 mo after the enhanced CT scan (9 mo after the second surgery) demonstrated growth of the lesion (2.3 × 1.9 × 2.1 cm), which was seen in the region of the left jugular foramen and involving the left hypoglossal canal (Fig. 1). The patient had persistent but a somewhat improved level of pain while walking, and the phosphorus supplements were able to maintain the serum phosphorus level at the low-normal level (2.6 mg/dL).

In view of the two previous skull-base surgeries, persistence of symptoms, and recurrence of the lesion at the same site, alternative therapeutic approaches were sought. Because the tumor was ^{68}Ga-DOTATATE–avid (Krenning score, IV), PRRT with ^{177}Lu-DOTATATE therapy was considered in a multidisciplinary meeting. The patient was administered 5,661 MBq of ^{177}Lu-DOTATATE according to the standard treatment protocol. Three months after the first cycle, she reported good symptomatic improvement (>25% compared with baseline), and SUV was seen to be reduced on both ^{68}Ga-DOTATATE PET (from 33.85 g/mL to 23.93 g/mL, a 29.6% reduction) (Figs. 2 and 3) and ^{18}F-FDG PET/CT (from 16.98 g/mL to 12.88 g/mL, a 24.15% reduction) (Fig. 4).

DISCUSSION

Tumor-induced osteomalacia is an uncommon paraneoplastic condition typically characterized by phosphaturia, hypophosphatemia, and osteomalacia. The cause is enhanced tumor production of fibroblast growth factor 23, which inhibits phosphate reabsorption in the proximal convoluted tubule (by reducing expression of *NPT2,* a sodium-phosphate cotransporter in the proximal convoluted tubule (*5*)) and reduces renal calcitriol production (by inhibiting 1-α-hydroxylase, thus suppressing its activation of vitamin D and preventing calcium absorption (*6*)). Encoded by the *FGF23* gene located on chromosome 12, loss of *FGF23* activity can cause hyperphosphatemia

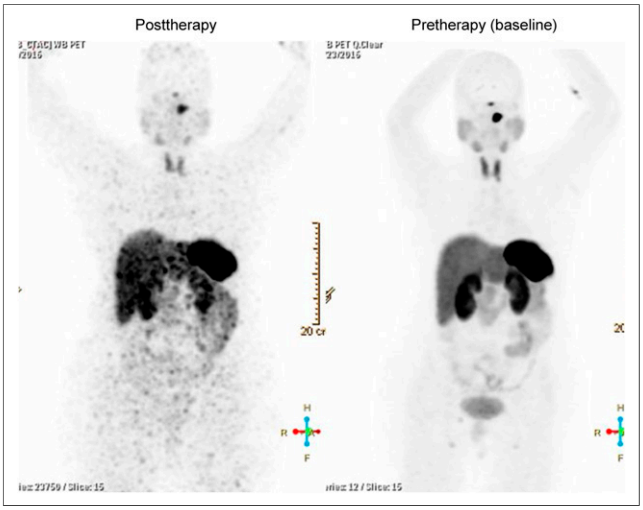

FIGURE 2. ^{68}Ga-DOTATATE PET scan (before and 3 mo after first cycle of ^{177}Lu-DOTATATE PRRT) demonstrating modest decrease in uptake.

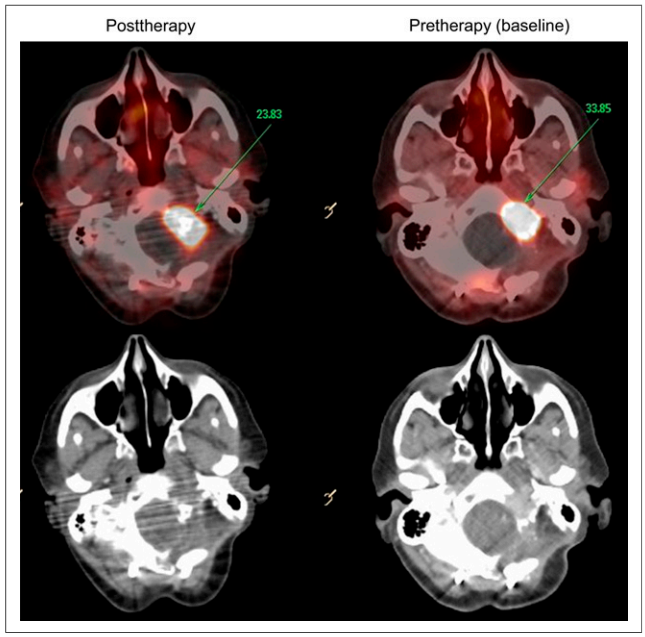

FIGURE 3. ^{68}Ga-DOTATATE PET/CT scan (before and 3 mo after first cycle of ^{177}Lu-DOTATATE PRRT) demonstrating modest decrease in uptake.

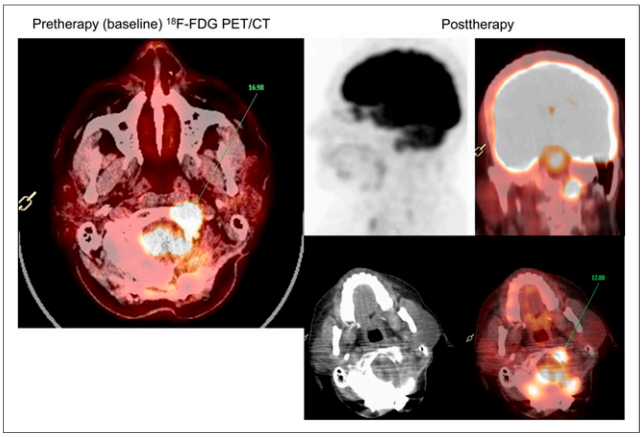

FIGURE 4. ^{18}F-FDG PET/CT scan (before and 3 mo after first cycle of ^{177}Lu-DOTATATE PRRT) showing reduction of tracer uptake from 16.98 to 12.88 (24.15% reduction).

and calcinosis whereas enhanced levels of fibroblast growth factor 23 (e.g., by phosphaturic mesenchymal tumor) or enhanced *FGF23* activity (mutation in autosomal dominant hypophosphatemic rickets) causes rickets and osteomalacia (*2*).

PRRT with ^{177}Lu-DOTATATE can potentially be used in cases of inoperable or recurrent phosphaturic tumor after documentation of high somatostatin receptor expression in the causative tumor (i.e., Krenning score III/IV uptake on ^{68}Ga-DOTATATE PET/CT). This treatment approach could be more efficacious than the present medical management options, with a convenient administration schedule of every 3 mo and good tolerability.

CONCLUSION

To the best of our knowledge, ours is the first report of the use of ^{177}Lu-DOTATATE PRRT in an inoperable recurrent phosphaturic mesenchymal tumor. Further investigation of this use might establish the effectiveness of PRRT as a targeted therapy for resistant oncogenic osteomalacia in patients with inoperable or recurrent tumors.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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