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Case Report

Treatment of an Aggressive Gonadotroph Pituitary Neuroendocrine Tumor With ^{177}Lutetium DOTATATE Radionuclide Therapy

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Abstract

Aggressive pituitary neuroendocrine tumors (PitNETs) present significant morbidity, and multimodal therapies including surgery, radiotherapy, and medications are frequently required. Chemotherapy, particularly temozolomide, is often pursued for tumors that progress despite these treatments. Although peptide receptor radionuclide therapy (PRRT) using radiolabeled somatostatin analogs is approved for the treatment of well-differentiated gastrointestinal neuroendocrine tumors, its use in aggressive PitNETs is limited. We describe the case of a 65-year-old man who presented with vision changes and hypopituitarism at age 33 secondary to a nonfunctioning gonadotroph PitNET. His initial treatment included a craniotomy followed by radiation therapy. With tumor regrowth, he required transsphenoidal surgeries at age 44 and age 52. At age 56, further tumor regrowth and a positive octreotide scan prompted treatment with long-acting octreotide for 1 year. Given absent tumor response, 12 cycles (4 treatment cycles and 8 maintenance cycles) of PRRT with ^{177}Lutetium-DOTATATE were pursued. This resulted in partial response with significant tumor shrinkage. Notably, there was no tumor regrowth 40 months after treatment discontinuation. This is only the second report on the effectiveness of PRRT in patients with aggressive gonadotroph PitNETs. We also provide an overview of PRRT for PitNETs and describe clinical outcomes previously reported in the literature.

Key Words: peptide receptor radionuclide therapy, PRRT, pituitary neuroendocrine tumor, PitNET, gonadotroph adenoma

Introduction

Clinically relevant pituitary neuroendocrine tumors (PitNETs) are common (prevalence around 1 in 1000), and most can be initially managed with surgery; however, up to 50% of nonfunctioning tumors may show regrowth after 10 years (1-4). Metastatic PitNETs (pituitary carcinomas) and aggressive PitNETs are less frequent with estimated incidences of 0.1% and 0.5%, respectively (4); often these PitNETs cannot be managed solely with surgery (2). The 2018 European Society of Endocrinology Clinical Practice Guidelines define an aggressive pituitary tumor as one that demonstrates radiologic invasion or has ongoing growth despite conventional treatments, which entail surgery, radiotherapy, or medical therapy (eg, dopamine agonists or somatostatin analogs) (1, 5). Markers that predict tumor refractoriness to conventional treatment include a Ki-67 proliferation index >3%, increased number of mitoses, and degree of p53 expression (6).

Additional treatment options for aggressive PitNETs include temozolomide alone or in combination with radiotherapy (Stupp protocol) or capecitabine, and recently, immune-checkpoint inhibitors (1, 2, 5). Other than immune-checkpoint inhibitors, the use of mechanistic target of rapamycin inhibitors, epidermal growth factor inhibitors, cyclin-dependant kinase inhibitors, and bevacizumab in the treatment of aggressive PitNETs remains limited (1, 2, 5).

An option that appears promising in selected patients with aggressive PitNETs is peptide receptor radionuclide therapy (PRRT) (5, 7). PRRT is a form of radiopharmaceutical therapy, where peptides (small proteins) are labeled with a radiation-emitting isotope (7). The peptides used are analogues of somatostatin and they target somatostatin receptors present in pituitary tumor cells, mainly type 2 (SSTR2) (7). These peptides can be labeled with either therapeutic isotopes such as Lutetium (^{177}Lu) or Yttrium (^{90}Y), or diagnostic isotopes such as Gallium (^{68}Ga) (7). The compound radiopeptide binds with high affinity to the desired receptor delivering a targeted form of radiation therapy (7).

While PPRT has been established for gastrointestinal (GI) or pancreatic neuroendocrine tumors (NETs), there have been only case reports or small case series describing PRRT use for PitNETs, metastatic PitNETs, or even GI/pancreatic NETs that have metastasized to the pituitary, with varying degrees of success (6-20).

Herein, we describe the case of a 65-year-old man with a nonfunctioning aggressive gonadotroph PitNET and subsequent use of PRRT resulting in partial tumor response. Our case adds to the literature on the use of PRRT in PitNETs, in particular for aggressive gonadotroph PitNETs.

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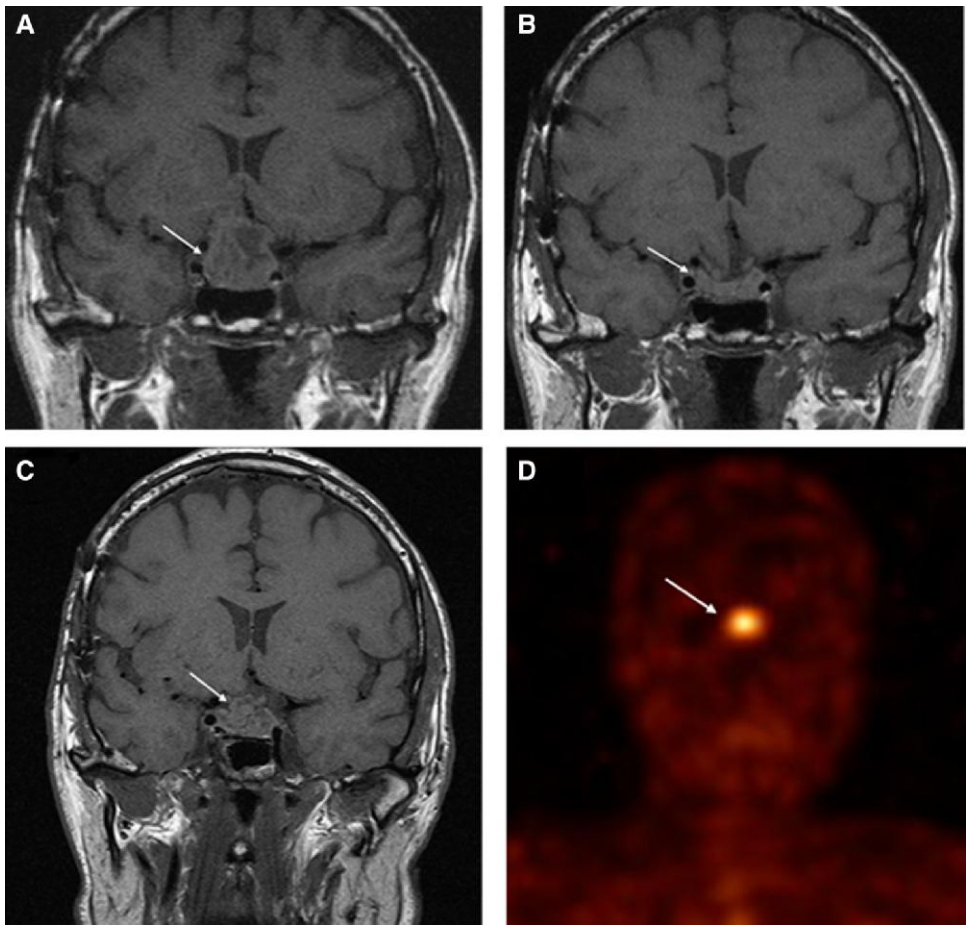

Figure 1. (A) Coronal MR T1 image of sella showing tumor progression at age 44. Sellar lesion (arrow) measures 24 × 25 × 21 mm. (B) MR sella following transsphenoidal surgery showing tumor debulking. (C) MR sella showing further tumor progression at age 56 with right optic nerve abutment and left optic nerve elevation. (D) Octreotide scan demonstrating increased uptake in sella.

Abbreviation: MR, magnetic resonance.

Case Presentation

Our patient initially presented in 1991 (age 33) with vision loss, fatigue, and temperature intolerance. He was diagnosed with hypopituitarism and commenced hormone replacement therapy (cortisone acetate, levothyroxine, and intramuscular testosterone). Visual field testing confirmed bitemporal hemianopsia. A computerized tomography scan of the sella revealed a 30 × 23 mm sellar lesion with suprasellar extension and optic chiasm compression. He underwent right frontoparietal craniotomy followed by external beam radiotherapy in 3 fields (4000 Centigray to 90%) at age 34 for residual tumor.

His tumor progressed at age 44 with magnetic resonance imaging (MRI) of the sella revealing a 24 × 25 × 21 mm sellar lesion (Fig. 1A and 1B) that was managed with transsphenoidal resection. This was repeated at age 52 due to tumor regrowth causing right optic nerve elevation on repeat MRI. Pathology from the last 2 surgeries revealed a PitNET with focal positivity for FSH consistent with a silent gonadotroph tumor. Additional immunohistochemistry completed recently showed tumor cells positive for steroidogenic factor 1 and GATA binding protein 3, confirming gonadotroph lineage. The MIB-1/Ki-67 proliferative index was low (0 to <3%) with rare p53-immunoreactive nuclei.

He had tumor regrowth at age 56, with MRI revealing right optic nerve abutment and left optic nerve elevation (Fig. 1C). He was reluctant to pursue repeat surgery with noncurative intent. With a positive octreotide scan (Fig. 1D), somatostatin analogue therapy was commenced (octreotide long-acting repeatable 20 mg intramuscular every 4 weeks). Although this led to a reduction in chromogranin A from 1200 µg/L (normal <94 µg/L) to 70 µg/L, repeat MRI 1 year later did not show tumor shrinkage (Fig. 2A).

Diagnostic Assessment

Our patient would not consider additional radiotherapy. Temozolomide probably would have been tried had it been readily available for the management of aggressive PitNETs at our cancer clinic. A partial tumor response of another patient with a sellar neurocytoma and a positive octreotide scan prompted a referral for PRRT (7). Our patient's pretreatment Indium-111 octreotide scan showed focal and moderate uptake in the sellar mass (Fig. 2B).

Treatment

Access of treatment for our patient was through a clinical trial (NCT01876771). By protocol, he received 4 induction treatments of ^{177}Lutetium-DOTATATE every 10 weeks plus 8 maintenance treatments every 6 months [cumulative dose

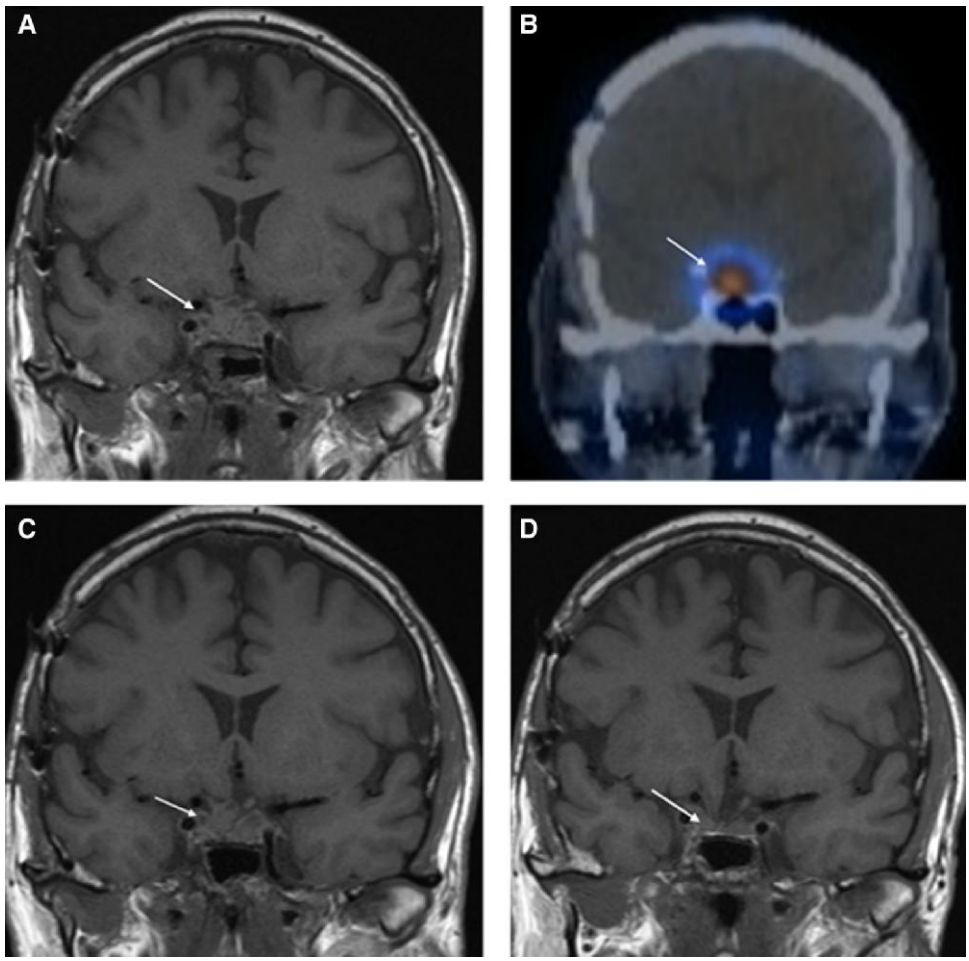

Figure 2. (A) Coronal MR T1 image of sella after 1 year of octreotide long-acting repeatable 20 mg intramuscular every 4 weeks showing persistent sellar lesion (arrow). (B) Indium-111 octreotide single photon emission computed tomography demonstrating moderate uptake in the sellar lesion. (C) MR sella after 4 treatment cycles of ^{177}Lu-DOTATATE showing no significant tumor shrinkage. (D) MR sella after 8 maintenance cycles of ^{177}Lu-DOTATATE showing partial tumor response.

Abbreviation: MR, magnetic resonance.

46.13 Gigabecquerel (GBq)]. An amino acid solution was administered for nephroprotection with each PPRT cycle.

Outcome and Follow-up

PRRT had no significant effect on the tumor size after the 4 treatment cycles (Fig. 2C). However, there was partial tumor shrinkage after the 8 maintenance cycles (Fig. 2D). In addition to MRI, response was also assessed by posttherapy scan using the gamma emission of the therapeutic dose.

Other than nausea, fatigue, thrombocytopenia, and creatinine elevation (all transient and grade 1), the patient tolerated the treatment well. At his most recent follow-up, 40 months after PRRT discontinuation, his sellar MRI showed a stable lesion. A recent Gallium-68 DOTATATE scan showed an octreotide avid and stable sellar lesion. His recent visual field assessment showed mild upper bitemporal constriction that has been stable after his initial craniotomy.

Discussion

Surgery, radiotherapy, and medications (dopamine agonists or somatostatin analogues) remain well-established first-line therapies for the management of PitNETs (1-3). As outlined by the 2018 European Society of Endocrinology Clinical Practice Guidelines, temozolomide (± radiotherapy) should be pursued for aggressive pituitary tumors refractory to standard management (1). For tumors that require further intervention, the guidelines do not provide specific recommendations (1). Although immune-checkpoint inhibitors have recently emerged as a therapeutic modality, PRRT may also represent an alternate treatment option (2).

Table 1 provides a summary of the 27 cases of PRRT use for pituitary masses that have been reported in the literature, as well as our patient (6-20). However, 2 cases have virtually no clinical information (15), and 3 additional case reports used PRRT primarily for treatment of GI/pancreatic NETs (13, 19, 20). Among the remaining 22 cases, PRRT has varying rates of response, with 8 cases demonstrating a decrease in tumor size (partial response), 4 cases showing tumor size stabilization (stable disease), and 10 cases with tumor progression (progressive disease). The success rate (partial response + stable disease) of PRRT of 54.5% (12/22) is higher than the 33% reported in a previous case series and slightly higher than the rate in a recent review of 47% (2, 11). This is likely because 2 additional cases (1 by Lin et al and our

Table 1. Summary of published cases (in chronological order) of PRRT for pituitary masses

Age/Sex	Ref	Tumor subtype	Initial tumor size or volume	Treatments before PRRT	PRRT agent	Cycles	Total dose	Outcome of PRRT and treatments after PRRT	Ki-67	p53
69F	(20)	Metastasis (ileal NET)	NR	TSS SSA	^{90}Y-DOTATATE ^{177}Lu-DOTATATE	4	10.94 GBq	Tumor shrinkage after 2 cycles (Excluded)	10%	NR
71F	(13)	NR (treatment for pancreatic NET)	22 × 17 × 11 mm	None	^{177}Lu-DOTATATE	1	5.55 GBq	PRRT ongoing, so outcome unknown (Excluded)	NR	NR
58F (42, age at dx)	(12)	PRL	61.1 cm^3	TSS RT DA × 2	^{111}In-DTPA-octreotide	5	29 GBq[a]	Tumor volume 15.3 cm^3 (75% reduction), stable 2 years later (PR, 24 m)	NR	NR
16F	(17)	ACTH, PC	25 × 20 mm	TSS × 8 RT 90 Gy Bilateral Adx SRT 24 Gy/2#	^{90}Y-DOTATOC	2	14.8 GBq	Died due to high intracranial pressure 1 year later (PD)	5%–25%	80–100%
55M	(9)	NF	NR	TSS SRT 50 Gy	^{177}Lu-DOTATOC	3 2 1	22.2 GBq NR NR	Stable disease for 9 years, 2 additional cycles reported 10 years and 1 cycle 15 years later (SD,180 m)	11.6%	NR
63M	(14)	NF-PC	NR	TSS × 2 RT	^{177}Lu-DOTATATE	4	29.57 GBq	Radiologically stable for 40 months (SD, 40 m)	3%	Normal
42F	(14)	GH/PRL	NR	TSS × 5 RT 50.4 Gy/28# SSA DA Carmustine implant TMZ × 2 SRT	^{177}Lu-DOTATATE	2	15.3 GBq	Accelerated PRRT given brainstem compression but deterioration resulting in death within 1 year (PD)	6% → 22%	Overexpression
32M	(14)	Silent ACTH	NR	TSS × 3 TCS × 1 RT 50.4 Gy/28# TMZ × 7	^{177}Lu-DOTATATE	1	NR	Increase in pain shortly after PRRT resulting in hospitalization. Received PCV with progression after 2 cycles. Had further surgery and radiation (45Gy/25#). Died 4 months later (PD)	Very high	Very high
68M	(18)	Gonadotroph-PC	NR	TSS RT Spinal surgery	^{177}Lu-DOTATATE	3	22.2 GBq	Progression-free survival for 4 years (SD, 48 m)	Low	NR
46M	(6)	GH-PC	NR	TSS × 6 SSA Pegvisomant RT TMZ × 2	^{90}Y-DOTATATE	NR	NR	Progressive growth. Died 8 months after TMZ stopped (PD)	60%	< 10%
23M	(6)	PRL	NR	TSS × 4 DA SSA TMZ × 4	^{68}Ga-DOTATATE	NR	NR	Died 8 months after TMZ stopped (PD)	41%	> 10%

(*continued*)

Table 1. Continued

Age/Sex	Ref	Tumor subtype	Initial tumor size or volume	Treatments before PRRT	PRRT agent	Cycles	Total dose	Outcome of PRRT and treatments after PRRT	Ki-67	p53
59M	(6)	NF	NR	TSS × 3 SSA TMZ × 6	^{177}Lu-DOTATATE	NR	NR	Died 5 months after TMZ stopped (PD)	10%	Few
26M	(10)	GH	56 × 25 × 36 mm	TSS and TCS SSA RT	^{90}Y-DOTATATE	4	14.8 GBq	Biochemical and radiologic improvement. Tumor volume reduction 28% (intrasellar component) and 62% (suprasellar component) (PR, 12 m)	NR	NR
NR	(15)	NR	NR	NR	DOTATOC	NR	NR	PRRT ongoing (Excluded)	NR	NR
NR	(15)	NR	NR	NR	DOTATOC	NR	NR	PRRT ongoing (Excluded)	NR	NR
42F	(11)	PRL	63 mL	DA TSS RT	^{111}In-DTPA-octreotide	5	37 GBq	Tumor shrinkage over 8 years of follow-up to 15.3 cm^3 (95.1% reduction) (PR, 96 m)	NR	NR
54M	(11)	PRL	20.2 mL	TSS × 3 DA Hypofractionated SRT	^{177}Lu-DOTATOC	2	12.6 GBq	Increase in tumor size (414%) resulting in discontinuation of PRRT. TMZ and CYC given without benefit. Visual impairment, gait difficulties, temporo-spatial disturbance (PD)	NR	NR
53F	(11)	NF	7.7 mL	TSS × 5 RT TMZ	^{177}Lu-DOTATOC	5	29.8 GBq	Increase in tumor size (183%), loss of vision in left eye (PD)	NR	NR
35M	(19)	GH	19 mm	SS × 2 SSA × 2 y DA × 2 y	^{177}Lu-DOTATATE	6	NR	PRRT for a GI NET with liver metastasis, good response; no mention of pituitary response (Excluded)	4–8%	NR
48M	(16)	GH	38 × 27 × 31 mm	TSS Medical therapy (NR)	^{177}Lu-DOTATATE	3	22.2 GBq	Biochemical and radiologic improvement for 1 year before presenting with apoplexy needing surgery (PR, 12 m)	NR	NR
45F	(8)	ACTH-PC	NR	TSS × 4 Fractionated SRT SSA Ketoconazole DA CAPTEM × 5 Bilateral Adx CE × 2 RT Ipi/Nivo × 13 SRT 25.09 Gy/5# SO SRT 21 Gy × 2	^{177}Lu-DOTATATE	4	28.07 GBq	Biochemical response (ACTH reduction). Nivolumab resumed after PRRT. Decrease in tumor size (61% reduction) after 6 months of PRRT (PR, 6 m)	NR	NR

(*continued*)

Table 1. Continued

Age/Sex	Ref	Tumor subtype	Initial tumor size or volume	Treatments before PRRT	PRRT agent	Cycles	Total dose	Outcome of PRRT and treatments after PRRT	Ki-67	p53
NR	(7)	NF, ?ACTH	NR	Sx, NR TMZ	^{90}Y-DOTATOC	2	NR	Stable disease 12 months (SD, 12 m)	4% (mitotic count 2)	NR
NR	(7)	TSH	NR	Sx, NR TMZ	^{177}Lu-DOTATATE	2	NR	PD (PD)	60%	NR
NR	(7)	NF	NR	Sx NR TMZ	^{177}Lu-DOTATATE	4	NR	PR > 26 months (PR, 26 m)	NR	NR
NR	(7)	Silent GH/ ACTH	NR	Sx NR TMZ × 2	^{177}Lu-DOTATATE	4	NR	PR 8 months (PR, 8 m)	10% (mitotic count 10)	NR
NR	(7)	PRL	NR	Sx NR TMZ Bevacizumab	^{177}Lu-DOTATATE	1	NR	PD (PD)	25% (mitotic count 13)	NR
NR	(7)	PRL	NR	Sx NR TMZ × 2	^{90}Y-DOTATOC	2	NR	PR (PD)	30% (mitotic count 20)	NR
56M (33, age at dx)	Current	Gonadotroph	33 × 23 mm	TCS RT TTS × 2 SSA	^{177}Lu-DOTATATE	4 8	20.56 GBq 25.57 GBq	PR > 100 months (PR, 100 m)	<3%	NR

Abbreviations: Adx, adrenalectomy; CAPTEM, capecitabine + temozolomide; CE, carboplatin + etoposide; CYC, cyclophosphamide; DA, dopamine agonist; F, female; #, fractions; GBq, Gigabecquerel; GI, gastrointestinal; Ipi/Nivo, Ipilimumab + Nivolumab; M, male; NET, neuroendocrine tumor; NF, nonfunctioning; NR, not reported; PC, pituitary carcinoma; PCV, procarbazine hydrochloride, lomustine, and vincristine sulfate; PD, progressive disease; PR, partial response; PRL, prolactin; PRRT, peptide receptor radionuclide therapy; Ref, reference; RT, radiation therapy (reported in Gray over fractions); SO, salpingo-oophorectomy; SSA, somatostatin analogue; SRT, stereotactic radiation; TMZ, temozolomide; TSS, transsphenoidal surgery

[a]Dose of fifth PRRT cycle not reported.

current case) both increase the success rate (8). In patients with partial response or stable disease after treatment with PRRT, the reported duration of progression-free survival ranged from 6 to 180 months, with a median and mean duration of 25 months and 47 months, respectively. In the responders, the cumulative dose of treatment was 27.97 GBq. As reported previously, a lower Ki-67 index was associated with better outcomes (7).

The use of PRRT in the treatment of pituitary lesions was first reported in 2008 when an ileal NET that had metastasized to the pituitary was managed with ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE (20). Treatment for a de novo pituitary mass with PRRT was first pursued in 2012 when Baldari and colleagues administered ^{111}In-DTPA-ocreotide for the treatment of a giant prolactinoma refractory to transsphenoidal surgery, radiation therapy, and dopamine agonists (12). Another study in 2012 used ^{177}Lu-DOTATATE in a patient with multiple endocrine neoplasia type 1 with simultaneous pancreatic and pituitary NETs (13). Since 2014, PRRT has mainly been used after temozolomide has failed, as outlined by a case series of 3 patients (14). To date, PRRT has been used (1) for aggressive functioning and nonfunctioning PitNETs (including metastatic PitNETs), (2) for multiple endocrine neoplasia type 1 with pituitary and extra-pituitary tumors, and (3) synergistically with immune-checkpoint inhibitors (6-20). Notably, most cases of PRRT use entailed functioning PitNETs compared to nonfunctioning PitNETs (13/22 vs 9/22; see Table 1). Adverse outcomes from PRRT include cytopenia, renal injury, liver injury, and the long-term risk of myelodysplastic syndrome and leukemia (21).

Our patient received PRRT given a positive octreotide scan and his decision against pursuing a fourth surgery with noncurative intent. Our patient had a partial response to PRRT with tumor shrinkage, and his disease has remained radiologically stable without progression or change in visual field deficit; currently it has been 40 months since the end of treatment and nearly 101 months since the first treatment. As per our PRRT protocol, our patient had 12 treatments with a cumulative dose of 46.13 GBq of ^{177}Lutetium-DOTATATE, which is higher than the average dose of 25.96 GBq reported in the literature but similar to the cumulative dose of salvage PRRT for NETs (22). Although there was no change in the tumor size with the initial 4 treatment cycles (total dose 20.6 GBq), partial response was achieved with additional maintenance treatments (total dose 25.6 GBq). Currently, there is no consensus on the optimal dose or duration of PRRT for treatment of aggressive PitNETs.

A pituitary tumor of gonadotroph lineage was confirmed in our patient via positive immunohistochemistry for steroidogenic factor 1 and GATA binding protein 3. This represents the second patient with an aggressive gonadotroph PitNET treated with PRRT, with the other patient presenting with a gonadotroph pituitary carcinoma (18); however, 5 additional patients with nonfunctioning PitNETs have received PRRT (6, 7, 9, 11, 14). The previous patient with gonadotroph carcinoma had a progression-free survival of 4 years with PRRT (18). Unlike other pituitary tumors, gonadotroph PitNETs represent a unique treatment challenge because there is a paucity of treatment options beyond surgery and radiotherapy (23). Somatostatin analogues and high-dose cabergoline have limited efficacy, and even temozolomide seems to be less efficacious (23). A previous case-control study of patients with nonfunctioning PitNETs demonstrated no tumor shrinkage with octreotide long-acting repeatable in all 26 patients with tumor size increase in 5 of 26 patients (19%) (24).

Our patient's Ki-67 proliferation index was low (0 to <3%) even though he had a clinically aggressive PitNET. In general, aggressive PitNETs are presumed to have a Ki-67 index >10%, with even higher Ki-67 indices in metastatic PitNETs (2). However, a low Ki-67 index does not necessarily preclude aggressive PitNET behavior or metastatic potential (2). A limitation of our study is that we cannot exclude a higher Ki-67 index in surgical samples from other time points or other areas of the tumor because Ki-67 indices can fluctuate as much as 5% to 25% (17). This case of a patient with a low Ki-67 index and durable response to PRRT aligns with the association of low Ki-67 indices with better outcomes as described in the literature (2).

Learning Points

- Aggressive PitNETs often require additional treatment beyond conventional multimodal therapies (surgery, radiation, and medications) such as temozolomide.
- PRRT represents a potential tool for the management of aggressive PitNETs, particularly when there is regrowth despite conventional therapy.
- Further information is needed to establish PRRT dosing and understand factors that predict responsiveness and the sequence of use in relation to other treatments for PitNETs.

Contributors

All authors made individual contributions to authorship. C.G. and C.C were involved in the draft of the manuscript. C.C. was involved in the diagnosis and endocrinologic management of the patient, while S.K. was involved in the management of PRRT. All authors reviewed and approved the final draft.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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