Growth hormone–secreting macroadenoma of the pituitary gland successfully treated with the radiolabeled somatostatin analog ^{90}Y -DOTATATE: case report

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Pituitary tumors causing acromegaly are usually macroadenomas at the time of diagnosis, and they can grow aggressively, infiltrating surrounding tissues. Difficulty in achieving complete tumor removal at surgery can lead toward a strong tendency for recurrence, making it necessary to consider a means of treatment other than those currently used such as somatostatin analogs (SSAs), growth hormone (GH) receptor antagonist, surgical removal, and radiotherapy. The purpose of this paper is to describe a patient diagnosed with an aggressive, giant GH-secreting tumor refractory to medical therapy but ultimately treated with the radiolabeled somatostatin analog ^{90}Y -DOTATATE.

A 26-year-old male with an invasive macroadenoma of the pituitary gland ($5.6 \times 2.5 \times 3.6$ cm) and biochemically confirmed acromegaly underwent 2 partial tumor resections: the first used the transsphenoidal approach and the second used the transcranial method. The patient received SSAs pre- and postoperatively. Because of the progression in pituitary tumor size, he underwent classic irradiation of the tumor (50 Gy). One and a half years later, the patient presented with clinically and biochemically active disease, and the tumor size was still 52 mm in diameter (height). Two neurosurgeons disqualified him from further surgical procedures. After confirming the presence of somatostatin receptors in the pituitary tumor by using ^{68}Ga -DOTATATE PET/CT, we treated the patient 4 times with an SSA bound with ^{90}Y -DOTATATE. After this treatment, the patient attained partial biochemical remission and a reduction in the tumor mass for the first time.

Treatment with an SSA bound with ^{90}Y -DOTATATE may be a promising option for some aggressive GH-secreting pituitary adenomas when other methods have failed.

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PITUITARY adenomas are mostly benign, slow-growing tumors within the sella turcica. Invasive somatotrophic pituitary adenomas, without features of growth hormone (GH) overproduction, are marked with dural invasion and may be characterized by lateral extension into 1 or both cavernous sinuses. Suprasellar extension results in compression of the optic chiasm or third ventricle. In these cases, current treatment with “cold” (unlabeled) somatostatin analogs (SSAs) such as octreotide or lanreotide, dopamine agonists, pegvisomant combined with surgery, and radiation has been proven to be ineffective.¹¹

Like octreotide, DOTATATE binds to somatostatin

receptors (SSTRs) that are highly expressed in most neuroendocrine tumors; therefore, the radiolabeled SSA ^{90}Y -DOTATATE is used as treatment for neuroendocrine tumors with very good efficacy.¹⁸ The first attempt at ^{90}Y -DOTATATE administration in inoperable pituitary tumors was reported by Kaminski's team with promising results.⁷ After drug administration, these authors observed partial biochemical remission and clinical improvement in 4 patients treated with SSA coupled with the β -emitter ^{90}Y .

This paper presents new possibilities in the treatment of invasive, potentially fatal pituitary macroadenomas refractory to medical therapy.

ABBREVIATIONS ACTH = adrenocorticotrophic hormone; GH = growth hormone; SSA = somatostatin analog; SSTR = somatostatin receptor.

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Case Report

History and Examination

A 26-year-old man with acromegaly was admitted to the Department of Endocrinology, Metabolism and Internal Medicine for evaluation and treatment. A diagnosis had been made when he was 23 years of age because of visual disturbances in the left eye and severe headaches. At that time, he presented with all the classic clinical features of active acromegaly including headaches, joint pain, excessive perspiration as well as acral enlargement and facial dysmorphism. In addition, he developed signs of hypopituitarism. Laboratory tests confirmed GH hypersecretion and hypopituitarism requiring levothyroxine, hydrocortisone, and testosterone replacements. At the time of diagnosis, MRI of the head showed an invasive pituitary macroadenoma 5.6 (height) $\times$ 2.5 (anteroposterior diameter) $\times$ 3.6 (width) cm with infiltration of both cavernous sinuses, intrasellar and extrasellar extension, compression of the optic chiasm, and pushing up into the third ventricle (Fig. 1).

Initial Treatment

The patient underwent transsphenoidal partial resection of the pituitary tumor mass. Histopathological examination confirmed the diagnosis of pituitary adenoma with positive immunohistochemical staining for GH markers.

He received both pre- and postoperative long-acting SSA. Initially, he was treated with octreotide (30 mg intramuscularly) every 28 days, then with lanreotide (120 mg subcutaneously) for the same duration. However, during treatment with “cold” SSA, the patient did not attain biochemical remission.

Postoperatively, the visual field defects ameliorated, and the patient required continual hormone replacement therapy. Six months later, he noticed a decrease in his visual field, and an increase in tumor size was observed on MRI.

Subsequent Treatments

One year after the operation the tumor increased in size and still extended up into the optic chiasm and third ventricle, although without any signs or symptoms of chiasmatic compression. Therefore, the patient received a 50-Gy course of intensity-modulated radiation delivered to the pituitary tumor mass over 6 weeks.

FIG. 1. Presurgical sagittal (left) and coronal (right) T1-weighted MR images. Intra- and extrasellar size of macroadenoma: height 56 mm, length 25 mm, width 36 mm.

One and a half years after irradiation, the patient still presented with clinically and biochemically active disease, and the pituitary tumor mass measurements on MRI were as follows: intrasellar part: 2.2 (height) $\times$ 2.6 (anteroposterior diameter) $\times$ 2.7 (width) cm and suprasellar part: 3.3 $\times$ 1.6 $\times$ 1.4 cm (Fig. 2 left). The patient underwent ^{68}Ga -DOTATATE PET/CT scanning, and the presence of SSTR expression in the pituitary tumor was confirmed. Because of the tumor size and persistent disease activity, we decided to treat the patient with the radiolabeled SSA ^{90}Y -DOTATATE. Before administration of the ^{90}Y -DOTATATE, basal hormone studies showed values still indicative of active disease (Fig. 3). The patient was treated with a total dose of 400 mCi of ^{90}Y -DOTATATE (100 mCi administered every 3 months). The treatment led to regression in the tumor size over 12 months to 1.8 $\times$ 2.3 $\times$ 2.7 cm for the intrasellar part and 2.8 $\times$ 1.0 $\times$ 1.0 cm for the suprasellar part (Fig. 2 right). Moreover, the young man had attained for the first time partial biochemical remission.

Discussion

The primary goal in the management of acromegaly is to reverse the effects of GH hypersecretion and to decrease the tumor size as much as possible.^{2,4} According to current guidelines on GH-secreting pituitary tumor treatment, surgery is the primary option when an experienced surgeon is available and the tumor is resectable, especially for small well-circumscribed adenomas. Somatostatin analogs are commonly introduced prior to surgery.¹⁴ They may be considered for first-line therapy for patients with invasive tumors who are unlikely to attain surgical remission and who do not require surgical debulking to treat mass effect symptoms such as visual field deficits. Moreover, if the operation does not lead to biochemical control of the disease, SSA treatment should be continued.^{5,13}

In our patient, medical monotherapy with long-lasting octreotide or lanreotide did not result in an improvement in disease control, nor did it influence the tumor size. It was considered to be part of a combination therapy consisting of SSA and cabergoline or pegvisomant; however,

FIG. 2. Left: Pretreatment sagittal T1-weighted MR image. Intrasellar size of adenoma: height 22 mm, length 26 mm, width 27 mm. Suprasellar size: 33 mm, 16 mm, 14 mm. Right: Posttreatment MR image revealed shrinkage in tumor size. Intrasellar size: 18 mm, 23 mm, 27 mm. Suprasellar size: 28 mm, 10 mm, 10 mm.

FIG. 3. Graph shows the decrease in insulin-like growth factor (IGF)–1 concentration during therapy with ^{90}Y -DOTATATE. Arrows indicate the administration of each dose of ^{90}Y -DOTATATE.

the patient did not agree to the cabergoline because of its high cost.¹⁷ Moreover, current data show that pegvisomant therapy may lead to GH-producing pituitary tumor growth.^{3,12} We did not qualify the patient for pegvisomant treatment because this medication has been shown to cause a further increase in tumor size. Therefore, therapy with pegvisomant in our patient with the giant pituitary adenoma could bring a significant risk of tumor progression resulting in the deterioration of his clinical status, especially visual field problems. Nonetheless, according to the ACROSTUDY, pegvisomant is currently available as a third-line therapy.⁶

No data are yet available to indicate whether the size of a GH-producing tumor is modified by treatment with SSA coupled with ^{90}Y -DOTATATE. Somatostatin receptor expression can be evaluated using immunohistochemistry or receptor scintigraphy.⁸ In our case, to assess the expression of SSTR we used ^{68}Ga -DOTATATE PET/CT and $^{99\text{m}}\text{Tc}$ -HYNIC-TOC receptor scintigraphy. In such studies, a pituitary adenoma is highlighted as the focus of increased tracer accumulation. It shows high expression of SSTR Types 2 and 4. This is the basic aspect of eligibility for treatment with “hot” (labeled) SSA (for example, ^{90}Y -DOTATATE).

Somatostatin receptor expression in neuroendocrine tumors using ^{68}Ga -DOTATATE PET/CT was carefully studied.¹⁰ Sansovini et al. found that treatment with the radiolabeled SSA ^{177}Lu -DOTATATE for advanced pancreatic neuroendocrine tumors was effective.¹⁵ Sowa-Staszczak et al. showed that ^{90}Y -DOTATATE therapy for neuroendocrine tumors resulted in symptomatic relief and tumor mass reduction.¹⁶

Therapy with ^{90}Y -DOTATATE or ^{177}Lu -DOTATATE exhibited an antiproliferative effect and reduced hormone secretion. The standard treatment for neuroendocrine tumors consists of 2 cycles of ^{90}Y -DOTATATE (100 mCi/m² body surface every 6–12 weeks) or 3–5 cycles of ^{177}Lu -DOTATATE (150–200 mCi every 6–12 weeks).¹⁹ Tissues exposed to radiation during treatment include the bone marrow and kidneys. During the course of therapy, a mixture of amino acids (lysine and arginine) is given to protect the renal tubules. In addition, cell blood count should

be determined postadministration. This therapy is highly effective and safe.⁹

The present case features the first patient in whom therapy with “hot” SSA influences pituitary tumor size. During treatment, the tumor mass decreased in size, especially within the suprasellar part. Moreover, serum concentrations of insulin-like growth factor (IGF)–1 and GH decreased but did not fall within the normal range according to the current guidelines. The patient improved symptomatically, and the therapy was well tolerated with transient adverse effects including anemia and leucopenia.

To our knowledge, this is the second report of an acromegalic patient treated with SSA coupled with ^{90}Y -DOTATATE. The study concerning radiolabeled SSA therapy for pituitary tumors was performed by Kaminski and coauthors at the Military Institute of Health Services in Warsaw, Poland.⁷ The researchers evaluated the response of functional pituitary tumors to SSA coupled with the β -emitter ^{90}Y . They described a decrease of adrenocorticotrophic hormone (ACTH) in patients with Nelson’s syndrome (ACTH-secreting pituitary tumors treated with bilateral adrenalectomy) and a GH decrease in acromegalic patients. Moreover, clinical improvement was attained in all cases. These authors did not evaluate pituitary tumor size, nor did they mention it in the abstract.

Tumor aggressiveness in the patient in our case may reflect a subgroup of patients in whom close follow-up of tumor size is mandatory with any treatment. New pharmacological approaches in the treatment of aggressive pituitary tumors should be considered.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Waligórska-Stachura, Gut, Liebert. Acquisition of data: Waligórska-Stachura, Gut, Sawicka-Gutaj, Gryczyńska, Blanco-Gangoo. Analysis and interpretation of data: Waligórska-Stachura, Gut, Sawicka-Gutaj, Gryczyńska, Baszko-Błaszyk. Drafting the article: Waligórska-Stachura, Sawicka-Gutaj. Critically revising the article: Liebert, Gryczyńska, Ruchała. Reviewed submitted version of manuscript: Sawicka-Gutaj, Baszko-Błaszyk, Ruchała. Approved the final version of the manuscript on behalf of all authors: Waligórska-Stachura. Study supervision: Liebert, Gryczyńska, Ruchała.

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