CASE REPORT

Somatostatin Therapy for Glomus Tumors: A Report of Two Cases

M. A. Rafferty, M.D.,[1] R. M. Walsh, M.D.,[1] and M. A. Walsh, M.D.[1]

ABSTRACT

Glomus tumors of the head and neck are benign vascular lesions that often provide dilemmas in management. The presence of somatostatin receptors on the tumor cell surface has facilitated an additional imaging technique in the form of radiolabeled octreotide scanning. The use of the somatostatin analogue, octreotide, also provides a therapeutic option for inoperable or recurrent tumors. We present two patients, one with a surgically inaccessible tumor that recurred after primary radiotherapy and one who underwent incomplete resection because of the tumor's proximity to the internal carotid artery. Neither tumor has shown further growth 5 and 3 years after treatment with octreotide, respectively.

KEYWORDS: Glomus tumors, somatostatin receptor scintigraphy, octreotide

Paragangliomas of the head and neck are neuroendocrine tumors of the autonomic nervous system that arise from chemoreceptor tissue at various sites in the skull base and neck. Although generally considered to be benign, slow-growing tumors, they can be locally invasive and cause bone destruction and cranial nerve dysfunction. Approximately 5 to 10% of these tumors can be malignant, with the potential for metastasis.[1,2] Bilateral lesions or multicentric involvement may occur in 10% of cases. At least 10% of paragangliomas are familial, with an increased likelihood for multicentricity.[3]

Histologically, these tumors possess a high concentration of somatostatin hormone-binding sites on their cell surface.[4] Somatostatin is composed of a heterogeneous group of 14 to 28 amino acids, which have diverse physiological actions including neuropeptide and hormonal actions. Receptors for the compound have been demonstrated in the central and peripheral nervous system, salivary glands, gastrointestinal tract, pancreas, and adrenal glands. Numerous pathological tumors possess receptors, such as acromegalic adenomas, meningiomas, breast tumors, paragangliomas, and the amine-secreting tumors referred to as APUDomas (i.e., amine precursor uptake and decarboxylation) or neurocrinopathies.[4]

The primary function of somatostatin is to inhibit the secretion of several hormones, including growth hormone and insulin. Complex interac-

Skull Base, volume 12, number 2, 2002. Address for correspondence and reprint requests: Michael Walsh, M.D., Department of Otolaryngology, R.C.S.I. Education and Research Centre, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland. E-mail: mwalsh@rcsi.ie. [1]Department of Otolaryngology/Head and Neck Surgery, Beaumont Hospital, Dublin, Ireland. 1531-5010,p;2002,12,02, 053,058,ftx,en;sbs00262x.

tions with numerous gastrointestinal hormones have also been observed.[5] Several in vivo and in vitro studies have shown that somatostatin and its analogues have properties that inhibit tumor growth.[6–8] These properties include direct or indirect inhibition of cellular growth factors (i.e., IGF-1) and direct in vitro inhibition of angiogenesis. Certain analogues have direct antimitotic effects, acting via receptors on the tumor cell surface.[8–10] Another postulated mechanism is enhancement of the action of natural killer cells that have been demonstrated in humans.[4] Such a change in immunological activity might contribute to the tumor growth-inhibitory effects of these compounds. Over time, however, the inhibitory action on tumor growth seems to diminish. This loss of efficacy is due to desensitization of the suppressive effects of somatostatin analogues on the release of growth hormone (GH), insulin, and other tumor growth factors (such as IGF-1), and to the down regulation of somatostatin receptors on these tumors.[5]

Somatostatin and its analogues have been reported to be successful in both imaging and treating paragangliomas of the head and neck. In particular, improvement in symptomatology and stabilization of tumor growth over a 36-month follow-up has been reported.[11] We report two further cases that demonstrate the successful use of a somatostatin analogue (octreotide) in the management of two tumors that failed to respond to surgery and radiotherapy.

ILLUSTRATIVE CASES

Case 1

A 24-year-old male presented with a 2-month history of right-sided pulsatile tinnitus and hearing loss. The patient had no other contributory medical history nor any family history of paragangliomas. Otoscopy was normal and facial nerve examination showed a House-Brackmann grade II lower motor neuron paresis. Lower cranial nerve weakness was present in cranial nerves IX, X, XI, and XII. Audiometry revealed complete hearing loss in the right ear.

Computed tomography (CT) showed destruction of the petrous temporal bone with involvement of the foramen magnum and extension into the parapharyngeal space. Magnetic resonance imaging (MRI) revealed a 5- to 6-cm enhancing mass that extended into the cerebellopontine angle and displaced the brain stem. A signal void confirmed that the internal carotid artery was patent. Four-vessel angiography showed an extensive vascular tumor compressing the internal carotid artery. The tumor was supplied by branches of the right external carotid artery, dural branches from the cavernous portion of both internal carotid arteries, and muscular branches from both vertebral arteries. The diagnosis was consistent with a glomus tumor, Fisch grade Di 3. The tumor was deemed inoperable because of its location and size. The patient underwent a 5-week course of external beam radiation (50 Gy in 25 fractions).

Follow-up MRI at 10 months showed that the size of the tumor had increased. Brain stem compression and displacement persisted. An octreotide radioisotope study confirmed increased uptake consistent with residual tumor (Fig. 1) but showed no evidence of any other systemic paragangliomas. The patient began octreotide treatment, initially given as a 200-micrograms subcutaneous injection three times a day. Later deep muscular injection (20 milligrams) was given once every 3 months. The long-acting preparation is considered preferable and was used as soon as it became commercially available. The patient has now been followed for 5 years and the residual tumor has shown no significant increase.

CASE 2

A 54-year-old woman presented with a history of hearing loss and pulsatile tinnitus for 2 months. She had no family history for paragangliomas. She

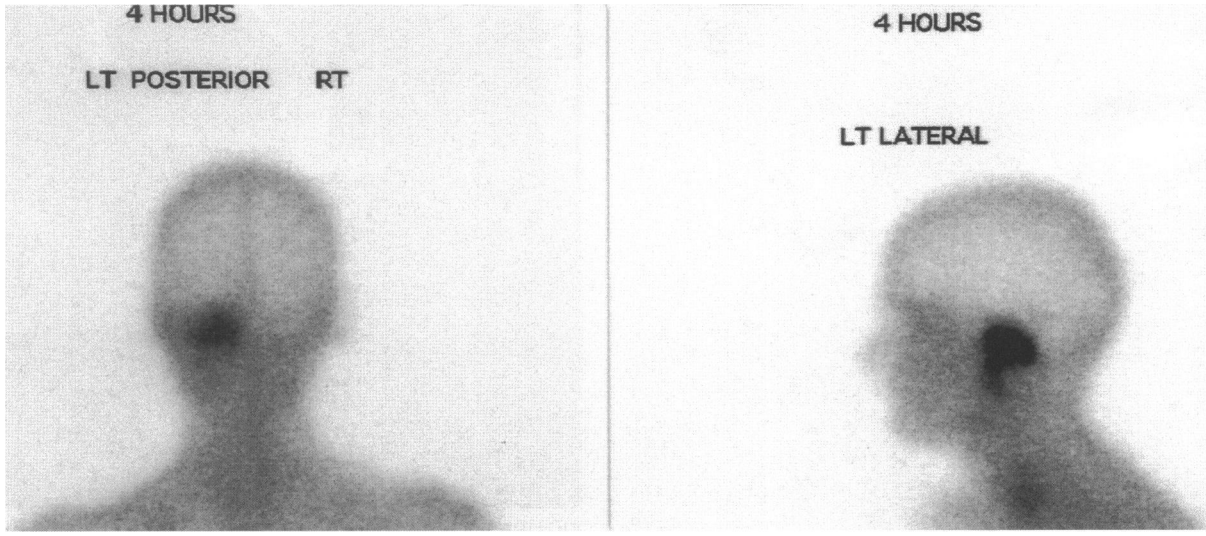

FIGURE 1 An octreotide radioisotope study confirmed increased uptake consistent with residual tumor following radiotherapy.

had a classical right-sided "setting sun" sign on otoscopy. Her facial nerve function was normal, but her lower cranial nerve examination revealed a hypoglossal nerve palsy. MRI showed a Fisch grade Di 2 tumor in the cerebellopontine angle (Fig. 2). Angiography demonstrated filling from the ipsilateral internal and external carotid arteries (Fig. 3).

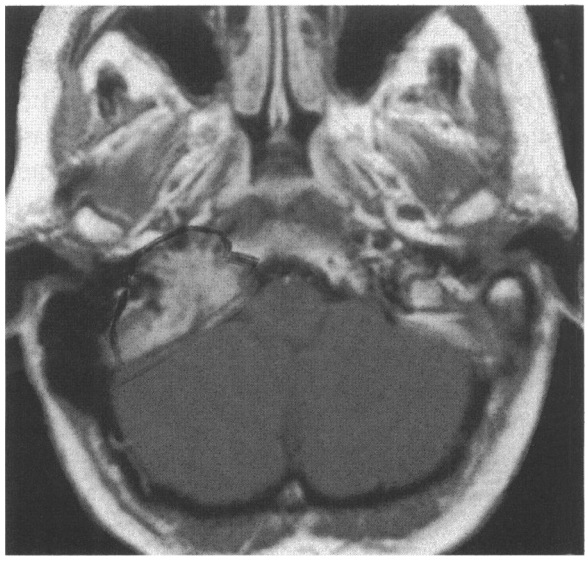

FIGURE 2 MRI demonstrating the tumor in the cerebellopontine angle.

The patient underwent preoperative embolization of the ascending pharyngeal and occipital feeding branches followed by a surgical excision undertaken via an infratemporal fossa approach. The resection was incomplete because excessive bleeding was encountered during the procedure. Postoperative angiography showed residual tumor. She underwent a second procedure 2 weeks later to remove the residual tumor from the cerebellopontine angle. Postoperatively, she had a House-Brackmann grade IV lower motor neuron paresis of her facial nerve. At a 9-month follow-up examination, this deficit had improved to a House-Brackmann grade III. The hypoglossal nerve palsy was well compensated.

A 6-month follow-up MRI showed residual or recurrent tumor in the cerebellopontine angle, parapharyngeal space, and around the internal carotid artery (Fig. 4). An octreotide radioisotope study showed increased uptake in the region of the residual tumor, but there was no evidence of any other systemic paraganglioma. The patient began octreotide treatment, initially given as a 200-micrograms subcutaneous injection three times a day. Like the other patient, a 20-milligram deep muscular injection was administered once every 3

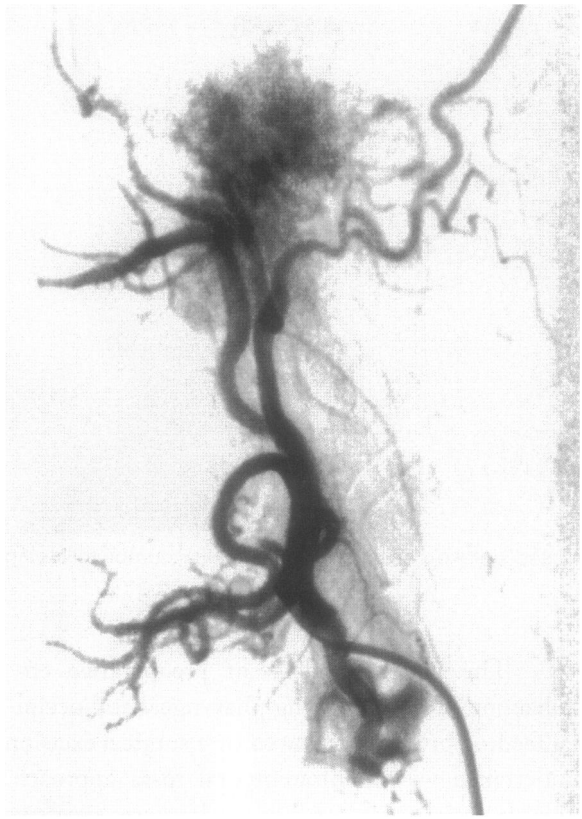

FIGURE 3 Angiography demonstrating filling of the tumor by the ipsilateral internal and external carotid arteries.

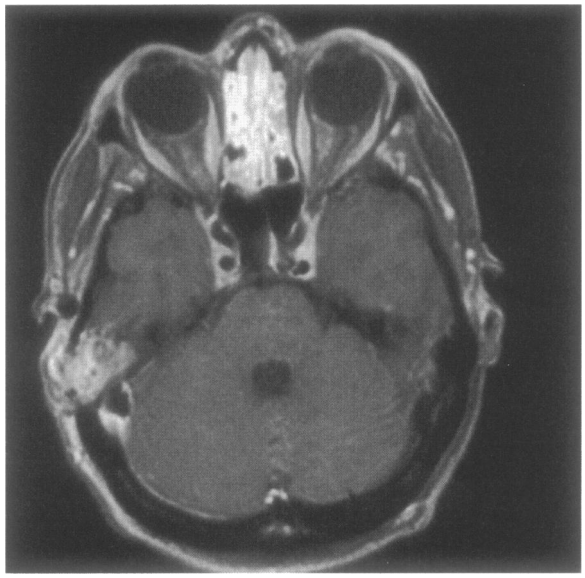

FIGURE 4 MRI demonstrating residual or recurrent tumor after surgical resection.

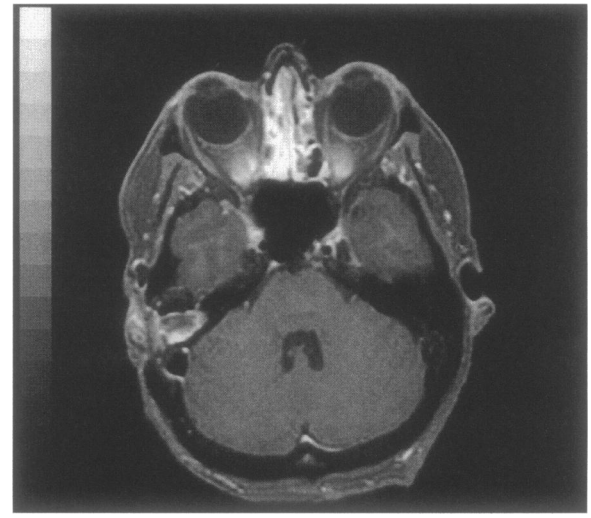

FIGURE 5 MRI demonstrating no increase in the size of the tumor after 36 months on somatostatin therapy.

months. There has been no further increase in the size of the tumor on MRI or octreotide scanning 36 months after somatostatin therapy (Fig. 5).

DISCUSSION

Glomus tumors of the head and neck are neoplasms that are often difficult to manage. Primary diagnosis can be problematic because histological confirmation of these highly vascular tumors, which are often located in highly inaccessible areas of the skull base, is both technically difficult and can be further complicated by hemorrhage. Consequently, physical examination, CT, MRI, and angiography are the main methods of diagnosing and staging these tumors. Angiography also helps to determine the vascularity of a tumor and can be combined with preoperative embolization to reduce the bleeding encountered perioperatively. These imaging modalities are used primarily to define the anatomical region. It is often impractical, for economic or radiation dosage reasons, to use them to look for synchronous tumors or metastases. Recently, it has been shown that the use of radiolabeled octreotide scans can overcome some of the failings of conventional imaging with an ac-

curacy rate of 90%, a sensitivity rate of 94%, and specificity of 75%.[12] This option not only improves the clinician's diagnostic ability but also offers a useful method of long-term follow up for such tumors.

Surgical resection is the primary treatment option for glomus tumors of the head and neck in many neuro-otology units. Unfortunately, due to the indolent nature of presenting symptoms, these tumors often become symptomatic at an advanced stage, making surgical excision technically difficult and increasing the likelihood of cranial nerve and cerebral complications. Nonetheless, in experienced hands, total surgical excision has been reported in 82% of a large series of patients with advanced glomus tumors.[13] Of those patients in whom total excision was possible, 98% attained a disease-free survival.[13]

The role of radiotherapy in the management of these tumors is controversial. The absence of a histological diagnosis, the risk of side effects from radiation, and the potential for delayed iatrogenic malignancies are all issues that must be considered. There is some discussion about the optimum dose, but many radiotherapists have shown good results and an acceptable side-effect profile with doses of 40 to 50 Gy using conventional fractionation.[14] Despite the controversy over which treatment modality is superior, both individual tumor and patient factors must be considered in each case.

Paragangliomas contain somatostatin receptors, and the inhibitory effects of somatostatin on tumor growth have previously been documented.[5,8] Somatostatin has a biological half-life of 2 to 3 minutes, which limits its clinical use. The synthesis of a more potent analogue (octrotide) with a half-life of 90 to 100 minutes enabled the development of a therapeutic modality using these anti-proliferative properties.[15] The main initial side effects of treatment are fatty stools and diarrhea, but patients tend to tolerate these inconveniences with slow and incremental increases in dosage. Other problems include the necessity to self-administer this treatment subcutaneously three times daily and the high cost of the drug.[11] However, in our experience, the depot form of octreotide has improved the convenience of the treatment for patients. Kau and Arnold used the somatostatin analogue octreotide and observed no tumor growth during therapy. In some cases, the size of the tumors even decreased.[11]

The possibility of delivering a therapeutic dose of radiation to receptor-bearing tumors by administering specific radiolabeled somatostatin analogues also exists.[16,17]

In our first patient, the tumor was deemed inoperable and the patient continued to be symptomatic after completing radiation therapy. This poor response, combined with evidence of a slight increase in size of the tumor on MRI scan and considerable brainstem compression, led us to offer somatostatin therapy. The patient has remained stable for 5 years since the introduction of therapy, and serial MRI has shown no increase in the size of the tumor over this period.

The second patient was offered somatostatin therapy because of extensive residual glomus tumor. At the patient's 3-year follow-up examination, the tumor showed no increase in size on serial imaging. There is no evidence of either an increase or decrease in the uptake of octreotide on sequential scintigraphy, and the patient is symptomatically stable. Hence, long-term use of somatostatin therapy may have controlled the tumor.

To our knowledge, this is only the second report of somatostatin receptor scintigraphy and therapy for glomus tumors of the head and neck. The optimal duration of treatment is unclear; however, this therapy appears to be a safe and promising adjunctive treatment for these tumors. These two cases suggest that somatostatin therapy should be considered as a further treatment option in the management of patients with recurrent or inoperable glomus tumors of the head and neck.

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Commentary

The article by Rafferty et al. explores a new modality of treatment for paragangliomas. The use of somatostatin or somatostatin analogues may provide an additional therapeutic option for patients with these tumors. This option would be especially useful in patients similar to those reported by the authors who had unresectable or incompletely resected tumors or for patients who decline or cannot undergo surgery. Although only a few cases have been reported where this treatment modality has been used, the results have been encouraging. Larger controlled series of patients are needed to confirm the efficacy of this treatment, to determine if the results can be maintained over time, and to identify any side effects from long-term use of somatostatin analogues. In addition, its use as an adjuvant therapy with radiation or surgery must be investigated. The use of somatostatin for the treatment of paragangliomas, although still experimental, demonstrates the results that can be achieved from the application of basic scientific research to clinical problems.

Mark Gustafson, M.D.[1]
Myles L. Pensak, M.D., F.A.C.S.[1]

Skull Base, volume 12, number 2, 2002. [1]Department of Otolaryngology, University of Cincinnati, Cincinnati, Ohio. 1531-5010,p;2002, 12,02,058,058,ftx,en;sbs00263x.