Pituitary Adenoma and Secondary Radiation-Induced Meningioma in an Adult Patient

RONALD R. HAGGETT, RN, MNSc, ACNP-BC, OCN®

From the University of Arkansas for Medical Sciences, Little Rock, Arkansas

Author's disclosures of potential conflicts of interest are found at the end of this article.

Correspondence to: Ronald R. Haggett, RN, MNSc, ACNP-BC, OCN®, University of Arkansas for Medical Sciences, Department of Hematology/Oncology, 4301 West Markham Street, Little Rock, AR 72205.
E-mail: haggettronaldr@uams.edu

Weighing in at 500 to 900 mg, the pituitary gland lies at the base of the skull within the sphenoid bone, bordered by the cavernous sinus and the optic chiasm (Figure 1). It is attached to the lower surface of the hypothalamus by the infundibular stalk and receives its blood supply via hypothalamic-portal circulation. Its main function is the secretion of hormones responsible for the regulation of several of the body's processes, including growth, metabolism, and reproduction.

The annual incidence of pituitary adenomas in the United States is 0.2 to 2.8 cases per 100,000, accounting for 10% to 20% of all intracranial tumors (Monson, 2000; Wrensch, Minn, Chew, Bondy, & Berger, 2002). Pituitary tumors are grossly classified as those that secrete excessive amounts of pituitary hormones (hormone-active) and those that do not (hormone-inactive or nonfunctional). Pituitary adenomas that do not secrete

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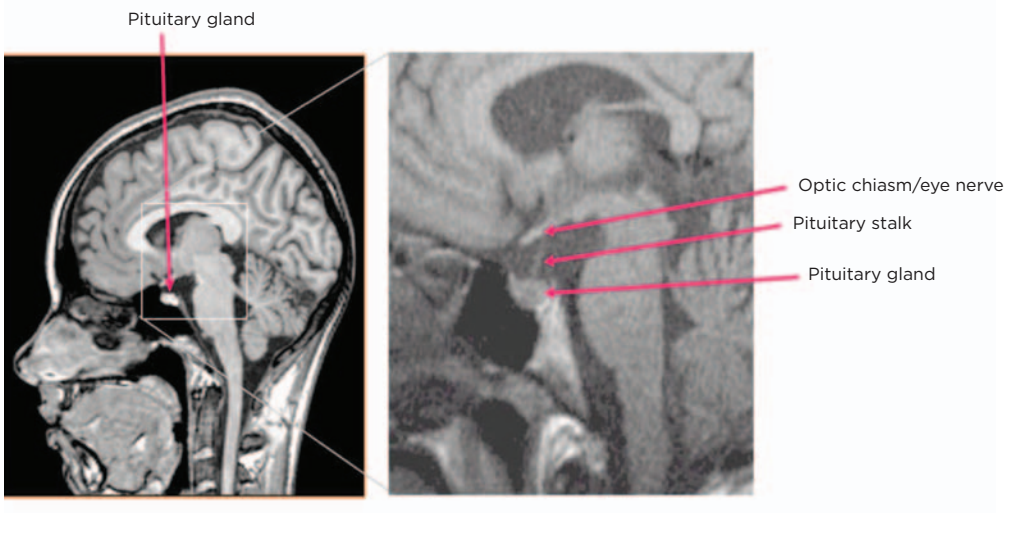

Figure 1. MRI of normal pituitary gland and surrounding structures. Image used with permission from University of Arkansas for Medical Sciences, Little Rock, Arkansas.

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Case Study

The patient, D.P., was a Caucasian male who was diagnosed in 1989 with a null-cell or nonfunctioning pituitary adenoma at age 29. His only symptoms at that time were visual field changes and fatigue. He was seen by an ophthalmologist for his complaints of loss of acuity and diplopia. A subsequent MRI of the brain revealed a pituitary mass involving the optic chiasm. He was treated with surgical ablation through the trans-sphenoidal approach followed by adjuvant stereotactic radiosurgery. Postsurgically, he received 43 Gy of radiation with a tumor margin dose of 20 Gy. Due to his treatment, the patient became dependent on hormonal replacement; testosterone (200 mg IM every 3 weeks), thyroid (levothyroxine 125 µg daily), and hydrocortisone (20 mg in the morning and afternoon and 10 mg at bedtime) were necessary. His hormone levels were monitored by his primary care physician, who adjusted dosages as needed.

D.P. was followed closely without evidence of recurrence until 1994, when he was found to have developed an enhancing mass in the middle and infratemporal cranial fossa. A complete resection was performed; the pathology was positive for radiation-induced meningioma with bone involvement.

Further resection for recurrent tumor was performed in 1998 and 2000. Following the resection in 2000, D.P. had right-sided weakness and eventual hemiplegia. Additionally, he had a complete absence of third and sixth nerve function and complete blindness in his left eye (Figure 2). In 2004, he experienced a recurrence, now with a left-sided middle fossa and intraorbital meningioma and involvement of the ocular contents.

In April 2008 (Figure 3), D.P. was found to have a massive recurrence of his tumor that involved the paranasal sinuses, bone, and soft tissues as well as the peripapillary choroid intraocularly and the epibulbar long and short posterior ciliary arteries and nerves. Resection was done, including complete enucleation of the left eye. Additional reconstruction of the skull was performed during a 20-hour surgical procedure (Figure 4).

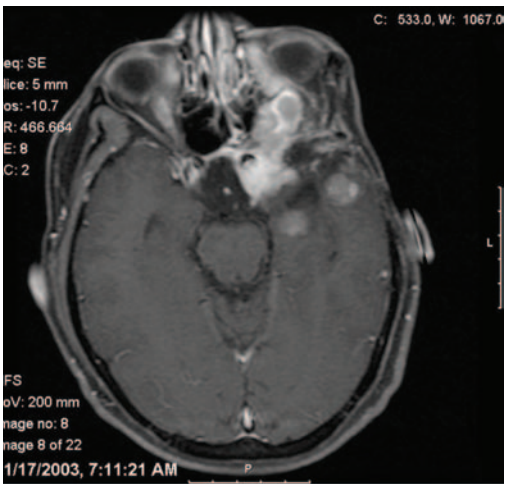

Figure 2. Noted is extension of the cavernous sinus mass into the medial left orbit through the superior orbital fissure. There was also extension of the cavernous sinus mass below the skull base by direct involvement of the floor of the middle cranial fossa and through the foramen ovale with extension of the enhancing tumor into the left infratemporal fossa. There is a separate nodule located immediately above the left petrous apex abutting the petrous ridge and the origin of the left tentorium. Image used with permission from University of Arkansas for Medical Sciences, Little Rock, Arkansas.

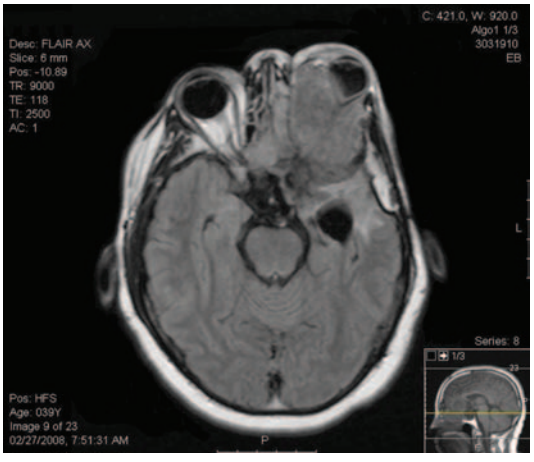

Figure 3. The homogeneously enhancing extra-axial mass arising from the left cavernous sinus region extending into the left orbit is again noted. It measures ~ 8 x 5 cm in the anteroposterior and transverse dimensions. Significant proptosis is noted. Involvement of the left infraorbital nerve and encasement of the left internal carotid artery are also noted. Image used with permission from University of Arkansas for Medical Sciences, Little Rock, Arkansas.

MEDICAL TREATMENT RECORD

In November 2003, D.P. began palliative treatment with chemotherapy. (See Table 1 for a summary of D.P.'s medical treatment throughout his disease course.) He was initially treated with interferon-alpha, 1 million units SC daily, augmented with tamoxifen 10 mg twice daily (Sioka & Kyritsis, 2009; Rockhill, Mrugala, & Chamberlain, 2007). He tolerated the treatment with few problems. This regimen was stopped in August 2004, when his disease was found to have progressed. Incomplete surgical resection was performed, and D.P. was started on targeted therapy with gefitinib (Iressa) 250 mg daily (Norden, Drappatz, & Wen, 2007). This was continued until April 2005, when he was again found to have disease progression on MRI. Rather than repeat resection at this time, the patient chose to change medical treatment in the hopes of stopping or shrinking his tumor.

In July 2005, D.P.'s treatment was changed to single-agent bevacizumab (Avastin) 10 mg/kg IV every 14 days (Norden et al., 2007). Initially, a reduction in tumor size was noted, but after 2 months, the agent was discontinued due to tumor growth. During treatment with bevacizumab, the patient experienced hypertension and required treatment with triamterene/hydrochlorothiazide (37.5 mg/25 mg) daily. Upon discontinuing the bevacizumab, the treatment was changed to hydroxyurea 500 mg orally twice daily (Newton, 2007). D.P. was able to tolerate this treatment with few side effects or complications. He continued this drug with relative stability of his tu-

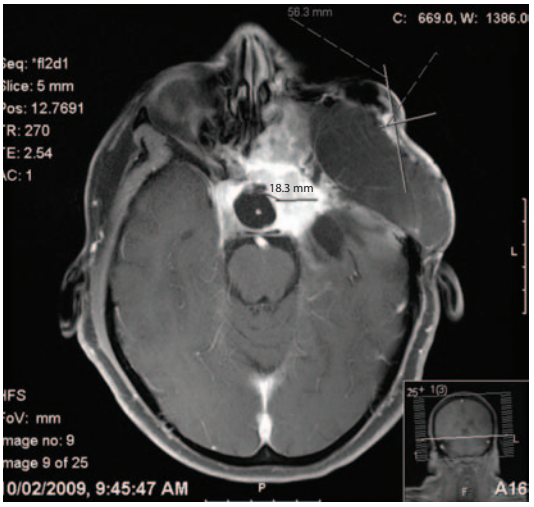

Figure 4. There has been resection of the orbit with frontoparietal craniotomy. Postsurgical changes are seen in the infratemporal fossa and middle cranial fossa. There has been fatty graft placement in the region of the surgical bed. Image used with permission from University of Arkansas for Medical Sciences, Little Rock, Arkansas.

Table 1. Patient With Pituitary Adenoma and Radiation-Induced Meningioma: Chemotherapy Treatment Summary

Start date	Treatment	Dose	End date	Total length
November 2003	Interferon-α plus tamoxifen	1 million units 10 mg bid	August 2004	9 mo
September 2004	Gefitinib	250 mg daily	April 2005	8 mo
July 2005	Bevacizumab	10 mg/kg IV every 14 days	September 2005	2 mo
October 2005	Hydroxyurea	500 mg bid	December 2006	14 mo
January 2006	Sorafenib	400 mg bid to 200 mg every other day	July 2007	7 mo
August 2007	Sunitinib	50 mg daily	March 2008	8 mo
December 2008	Bevacizumab plus liposomal doxorubicin monthly	15 mg/kg 30 mg/m^2	March 2010	24 mo

mor until December 2006, at which time he had further progression on MRI so he was referred back to neurosurgery.

After consulting with the neurosurgery team, D.P. again decided to try changing his medical treatment rather than opt for a repeat resection. He was started on sorafenib (Nexavar) 400 mg twice daily (Newton, 2007). He was unable to tolerate the full dose due to grade 3 diarrhea, palmar-plantar erythrodysesthesia, and grade 2 neutropenia. The dose was lowered to 200 mg twice daily, which was further reduced after 2 weeks to an every-other-day schedule due to continuing problems. Eventually, D.P. was taken off sorafenib due to the toxicities described above. In July 2007, he was started on sunitinib (Sutent; Newton, 2007) and experienced fewer side effects. He was maintained on a dose of 50 mg daily until March 2008, at which time his tumor had progressed to a substantial size, requiring repeat resection.

Following the April 2008 resection, D.P. again started on bevacizumab with the addition of liposomal doxorubicin (Doxil; Travitzky, Libson, Nemirovsky, Hadas, & Gabizon, 2003). Due to logistic constraints, past history with hypertension, and dosing schedules, it was decided to treat the patient with monthly, rather than the customary twice monthly, bevacizumab, and monthly liposomal doxorubicin. The bevacizumab was dosed at 15 mg/kg IV, followed by the liposomal doxorubicin at 30 mg/m^2 IV. He was maintained on this regimen with stable tumor size for 24 months, with no apparent adverse effects.

In January 2011, D.P. was seen in the hospital for weakness, fatigue, and neurologic changes. An MRI revealed a thromboembolic event in his brain, possibly associated with the use of bevacizumab. At that time, bevacizumab was stopped and the patient was discharged home on hospice. He expired 2 days after returning home, at the age of 42.

hormones account for about 30% of all pituitary tumors (Milker-Zabel, Debus, Thilmann, Schlegel, & Wannenmacher, 2001). Problems with inactive pituitary adenomas are typically related to tumor enlargement, which exerts pressure on surrounding brain structures. Common presenting symptoms include visual changes due to compression of the optic nerve, which causes chronic headache, bitemporal hemianopsia, acuity loss, and diplopia. Large pituitary tumors can also compress the normal pituitary gland with consequential pituitary failure. Compression or distortion of the pituitary stalk or gland may result in hormone insufficiencies, giving rise to symptoms such as decreased libido, impotence, fatigue, and weakness.

Hormone-producing pituitary adenomas, the most common type, manufacture an active hormone in excessive amounts. The most common involvement is with the anterior portion of the pituitary (adenohypophysis), which is responsible for synthesis and secretion of several important hormones. Adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), growth hormone-releasing hormone (GHRH), prolactin (PRL), and gonadotropic hormones constitute the most common imbalances seen at diagnosis. Of these, about 25% of tumors produce PRL, 20% produce GHRH, 10% produce ACTH, and approximately 1% account for thyrotropic symptoms (Laurent, Webb, Jane, & Laws, 2005).

Patients present with symptoms related to the hormonal imbalance that are detectable with simple blood tests. Individuals with ACTH-producing tumors will usually present with symptoms of Cushing's disease resulting in a broad face with acne (Cushing facies), fatty deposits over the back of the neck (buffalo hump), stretch marks on the abdomen, arms, or legs, easy bruising, increased hair growth, diabetes mellitus, muscle loss, fatigue, depression, and possibly psychosis. Those with TSH-producing tumors may experience thyrotoxicosis, with symptoms such as heat intolerance, sweating, tachycardia, fine tremor, and weight loss. Patients with PRL-secreting tumors will often relate a history of galactorrhea, amenorrhea, and infertility in women and hypogonadism or impotence in men. In GHRH-secreting tumors,

the clinician is likely to see gigantism in children, or acromegaly in adults, which is accompanied by enlargement of hands, feet, and facial features, hypertension, and heart disease. Large hormone-producing pituitary tumors can also cause problems related to compression of brain structures similar to those of the non–hormone-secreting tumors.

Surgery

Regardless of the type, recurrence of these tumors can happen, with microsurgery alone providing only about 50% to 80% long-term control (Laws, Ebersold, & Piepgras, 1982). Surgery has the advantage of rapidly lowering hormone levels as well as relieving pressure on surrounding structures. For small tumors, the cure rate is greater than 50%. Tumors larger than 1 cm can recur and may require additional treatment, usually with ionizing radiation.

Radiation

Adjuvant treatment with radiation can be used to inhibit recurrence or as treatment for known residual disease (incomplete resection; Sheehan et al., 2005). Available options are either whole-brain radiation or stereotactic radiosurgery. In 1951, Lars Leksell published his technique of "closed skull destruction of an intracranial target using ionizing radiation," today known as stereotactic radiosurgery, or gamma knife (GK; Leksell, 1951). He performed his first procedure with GK in 1968 to treat a patient with pituitary adenoma. Today the goal of GK surgery is to reduce tumor size, inactivate tumor cells to prevent growth, and normalize hormone overproduction. This is an important modality in the treatment regimen; response rates with a weighted average of 96% control of tumor size and from 83% to 100% tumor control rates are reported in the literature (Sheehan et al., 2005).

SECONDARY MALIGNANT MENINGIOMAS

Treatment with ionizing radiation for pituitary adenomas, as well as for vestibular schwannomas, hemangioblastomas, tinea capitis, and dental x-rays, can result in secondary central nervous system neoplasms (Umansky, Shoshan, Rosenthal, Fraifeld, & Spektor, 2008). Radiation-induced meningiomas (RIMs) are the most common neoplasms associated with exposure to higher doses of ionizing radiation. For classification, Harrison, Wolfe, Lau, Mitnick, and Sachdev (1991) grouped RIMs into three categories: those due to high-dose (over 20 Gy), intermediate-dose (10–20 Gy), and low-dose (10 Gy) radiation. Radiation-induced meningiomas are defined according to the following criteria: (a) The tumors must occur within the initial field of radiation, (b) the lesion must differ histologically from the original tumor, and (c) there must be a delay of several years from the time of treatment to the appearance of the new tumor. The incidence of RIMs has not been established, as most reports are of individual cases (Gittoes, 2005; Erfurth, Bülow, Mikoczy, Svahn-Tapper, & Hagmar, 2001).

The World Health Organization (WHO) classification system for meningiomas has proven useful in further identifying these tumors. The system of classification proposed by the WHO in 1993 was revised in 1997 and in 2000, and is based on cytologic features of anaplasia rather than purely histopathologic descriptions (Perry, Louis, Scheithauer, Budka, & von Diemling, 2007). The term malignant is generally applied to WHO grade IV tumors. Radiation-induced meningiomas are more atypical (grade IV) and have a much poorer clinical outcome (Shoshan, et al., 2000).

Discussion

Advanced practitioners (APs) can be instrumental in the management of these highly complex cases by becoming familiar with their natural history, current treatment recommendations, and associated side effects. Patients who were diagnosed with both secreting and nonsecreting pituitary adenomas may now be on replacement hormones after partial resection of the pituitary gland itself. Interval checkups with hormone levels to ensure proper replacement dosing is important to ensure reduction of further complications (e.g., Cushing's syndrome, adrenal insufficiency and crisis [ACTH], decreased muscle mass, impotence [GHRH], and hypo- and hypertension [TSH]).

Surgery remains the primary treatment option for most patients with RIMs. However, there is currently no agreed-upon medical treatment algorithm and results vary. Chemotherapy is an option but generally provides only temporary regression or stability of tumor growth; it is

considered palliative in outcome. Because of the blood-brain barrier, cytotoxic treatment at levels high enough to successfully treat the tumor often results in damage to normal, healthy tissues, resulting in delay or cessation of treatments. Fever, hair loss, nausea and vomiting, compromised immune status, and fatigue are common side effects associated with traditional chemotherapy, which can make treatments limiting.

Targeted therapies may play a role in increasing overall survival in these patients. Overexpression (also known as upregulation) of epidermal growth factor receptor (EGFR) has been found on many cancer cell types. These mutations can lead to constant activation and uncontrolled cell proliferation, which results in tumor formation or progression. Epidermal growth factor receptor exists on the cell surface and is activated by the binding of its specific ligands. As a result, much research is being done to identify specific molecules to bind with these ligands to inhibit intracellular phosphorylation and dimerization, which results in the uncontrolled growth of abnormal cells (Yan & Beckman, 2005). Some monoclonal antibodies and tyrosine kinase inhibitors have already been identified as molecules capable of blocking the epigenetic pathways in some cancers and are in common use. Application to intracranial tumors is natural, as these lesions have also been shown to overexpress EGFR (Norden, Drappatz, & Wen, 2007). As these drugs are not cytotoxic by definition, many patients are able to tolerate treatment for longer periods and with fewer adverse effects on healthy tissues. Rash, fatigue, palmar-plantar erythrodysesthesia, thrombosis, hemorrhaging, and diarrhea can be limiting complications associated with the use of EGFR therapies.

Conclusions

Although the treatment of pituitary adenomas is well described in the literature, the management of malignant meningiomas is evolving. Recurrence rates for RIMs, despite treatment, remain very high—as much as 78% in 5 years. Information on recurrence and overall survival rates is limited due to the small numbers of patients available; at least one study has reported an overall survival rate of 0% at 10 years (Harrison et al., 1991). At this time, a collaborative effort among the patient, surgeon, oncologist, and AP can help guide the best individual course for patients with primary and recurrent intracranial neoplasms. Information regarding the use of newer, targeted therapies as adjuvant treatment from larger cohort studies could help guide the clinician when making treatment recommendations.

DISCLOSURE

The author has no conflicts of interest to disclose.

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