Treatment options for pediatric craniopharyngioma

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ILLUSTRATIVE CASES

Case 1

A 13-year-old female with intermittent headaches evaluated by an ophthalmologist was noted to have a retinal abnormality, prompting a magnetic resonance imaging (MRI) scan and referral to the neurosurgery service. On initial exam, the patient was neurologically intact and without headache. Imaging revealed a complex heterogeneous cystic mass, arising from a suprasellar location, invading into the third ventricle, and closely apposed to the hypothalamus bilaterally. There was mild contrast enhancement peripherally and inferiorly. Of note, the initial MRI and clinical presentation [Figure 1] showed no hydrocephalus. Likewise, initial endocrine evaluation was normal. On follow-up imaging, however, the ventricular system was noted to be enlarging. After extensive discussion of the risks, benefits, and alternatives to surgery, a right frontal endoscopic transventricular resection was planned with a goal of gross total resection (GTR). Intraoperatively, the tumor was found to be densely adherent to the walls of the third ventricle. Approximately 50% of the tumor could be safely debulked. Postoperatively, she was noted to have hypopituitarism and required hormonal replacement with desmopressin, hydrocortisone, and levothyroxine. The patient was discharged in stable condition but returned soon after with symptoms and imaging consistent with a trapped right ventricle for which she underwent a septostomy and eventual ventriculoperitoneal shunt placement. She subsequently completed proton radiation for the residual tumor, which has remained stable over 4-year follow-up. After radiation, she developed hypothalamic obesity and suffered a gradual decline in her vision bilaterally. At last follow-up, she could count fingers on the right and could only detect motion on the left. Since completing her treatments, she has required 24-h care. The patient has had multiple emergency room visits and hospital admissions for sodium fluctuations. She has also suffered multiple bone fractures secondary to osteoporosis from chronic steroid use.

Case 2

A 13-year-old female presented with headache, fatigue, and nausea. On exam, she was neurologically intact though with severe headache. Imaging revealed a large, complex, heterogeneous cystic mass, arising from a suprasellar location, invading into the third ventricle, and closely apposed to the hypothalamus bilaterally. She had significant hydrocephalus resulting from obstruction of the third ventricle. An external ventricular drain was placed, followed by endoscopic fenestration of the cyst, biopsy of the mass, and placement of a ventriculoperitoneal shunt. Pathology from the biopsy confirmed the suspected diagnosis of craniopharyngioma. The following year, an Ommaya reservoir was placed into

Figure 1: Preoperative (left) and postoperative (right) T1-weighted magnetic resonance imaging with contrast images from the patient in Case 1. Coronal (top) and sagittal (bottom) images
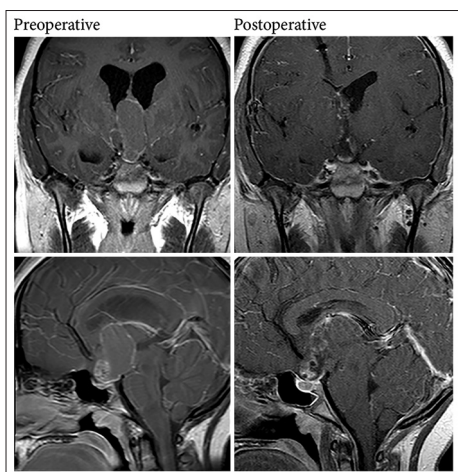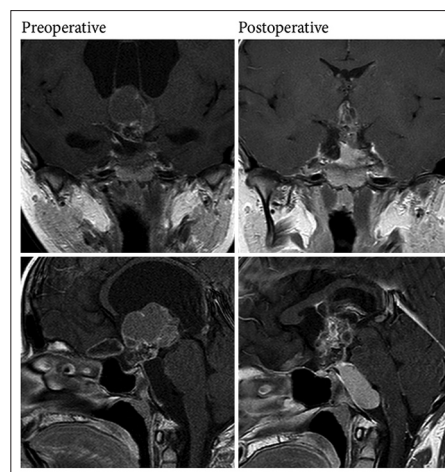

Figure 2: Preoperative (left) and postoperative (right) T1-weighted magnetic resonance imaging with contrast images from the patient in Case 2. Coronal (top) and sagittal (bottom) images

an enlarging suprasellar cyst for intermittent as-needed drainage of accumulating fluid. Postoperative imaging showed a decompressed suprasellar cyst; she continues with expectant management of an inferior prepontine cyst [Figure 2], which was clinically asymptomatic. Over the next 2 years, she developed mild hypopituitarism, requiring thyroid, steroid, and estrogen replacement, but she has had no issues with sodium balance. Neurologically, she remains intact and without visual decline. To date, the patient has not received any radiation treatment or chemotherapy infusions through the Ommaya. She continues with excellent academic performance and normal activities of daily living at 2-year follow-up.

EPIDEMIOLOGY AND CLINICAL PRESENTATION

Craniopharyngiomas are rare tumors, with an estimated incidence of 2–3/1 million. They are most common in children (age 5–15 years old) and older adults (60–70 years of age).[11,16,30] They are the most common nonglial tumor in the pediatric population, representing 6–9% of all brain tumors in this age range. No clear racial or gender predilection exists.[36]

These tumors are typically located in or above the sella turcica and produce symptoms by compression of adjacent neural structures. Slow growth and insidious onset of symptoms often delay arriving at a diagnosis. Potential symptoms are wide-ranging. They include visual deficits from compression of the optic apparatus, endocrine deficiencies, such as diabetes insipidus (DI) or pan-hypopituitarism from compression of the pituitary gland or stalk, hypothalamic compression and dysfunction resulting in abnormalities in sleep, appetite, or thermal regulation, or symptoms of hydrocephalus such as

headache or vomiting from obstruction of cerebral spinal fluid pathways.[12,25,35] At the time of diagnosis, 20–50% of children are noted to have hormonal insufficiencies, making endocrine testing mandatory.[36]

TUMOR BIOLOGY

Craniopharyngiomas occur in two histological subtypes: An adamantinomatous form that is the most common pediatric variant and a papillary form that is found almost exclusively in adults. The pediatric form is thought to arise from epithelial remnants of the craniophayngeal duct or Rathke's pouch, an embryologic structure that develops into the anterior pituitary. These remnants are thought to enlarge during the development of the pituitary gland and thus present early in life. Grossly, these tumors typically have both solid and cystic components and are often calcified on imaging. The cyst fluid is dark, oily, and rich in lipids with birefringent cholesterol crystals.[3,15,16,29] Papillary craniopharyngiomas, or adult craniopharyngiomas, on the other hand, are theorized to arise from metaplasia of existing squamous cell rests and thus present later in life.

Recent genetic analysis has also shown differences between these two subtypes. Mutations in B-catenin (CTNNB1), a downstream effector of the Wnt pathway that is, involved in cellular growth and development, has been described in 60–96% of adamantinomatous craniopharyngiomas.[4,5,22,33] By contrast, papillary craniopharyngiomas recently have been discovered to frequently harbor V600E mutations of the BRAF gene,[4] which is a key player in the mitogen-activated protein kinase pathway.

MEDICAL WORKUP AND MANAGEMENT

A complete workup for craniopharyngioma should include MRI with and without gadolinium contrast to

characterize the tumor and its relationship with critical nearby neural structures. As demonstrated in Case 1, these tumors may microscopically invade these structures even when this is not apparent on preoperative imaging. MR angiography can also be helpful in delineating the location of nearby vessels at the skull base. A noncontrasted computed tomography scan can also reveal complex calcifications and expansion of the sella, which is helpful in narrowing the differential. In addition, a workup for endocrinopathies should also be performed with measurements of growth hormone, thyroid stimulating hormone, follicular stimulating hormone/luteinizing hormone, prolactin, cortisol, and serum electrolytes. Any abnormalities ideally should be corrected before surgery is performed. Finally, formal visual acuity and visual field assessment are important to characterize any deficits that exist preoperatively.

TREATMENT AND OUTCOMES

Although histologically benign, these tumors frequently recur after treatment, and their close association with critical neurologic structures can lead to a much more malignant course. Surgical treatment options range from GTR to more conservative surgery (i.e., subtotal resection [STR] or biopsy only) followed by postoperative radiotherapy (RT), or other less invasive procedures such as endoscopic cyst fenestration or placement of an Ommaya reservoir into the tumor cyst for delivery of antineoplastic agents.[31] Nonsurgical options include stereotactic radiosurgery (SRS) or systemic chemotherapy. Over the past several decades, a paradigm shift has occurred in treatment from maximal resection to more scaled back interventions, in an attempt to balance tumor control and quality of life.

Historically, open cranial surgery with the goal of achieving GTR has been the treatment of choice, as it allows rapid decompression, provides a histological diagnosis, and is thought to minimize recurrence. The results of GTR have been influenced largely by surgeon experience, and the tendency of these tumors to invade nearby critical neuromuscular structures often leads to significant morbidity.[8,14] Multiple institutions have published their historical data in regard to this tumor, and we can extract from them several trends.[9,13,32,36,37] Reported reoccurrence rates after GTR range from 7% to 34%. Reported death rates were as high as 20%. Postoperative need for permanent hormone replacement was 80–86%, permanent DI from 75% to 90% and worsening of vision between 10% and 33%. Larger tumors and greater hypothalamic invasion were associated with worse outcomes. These results would lend to the conclusion that GTR is very often associated with a high surgical morbidity. Other factors that have also been shown to be associated with higher morbidity include

a diagnosis before the age of 10 and the presence of intracranial hypertension on initial presentation.[17]

The lack of acceptable outcomes with GTR has led to groups approaching these tumors with a more conservative surgical plan, including STR or biopsy, followed in some cases with RT.[6,21,24] Groups have found no significant difference in progression-free survival at 5 years between GTR and STR + RT;[8,18] however, STR without RT has significantly increased recurrence rates.[8] When looking at mean quality-adjusted life years (QALY) as the outcome at 5-year follow-up, biopsy + RT was associated with the most mean QALY (3.9, standard deviation [SD] 0.2), followed by endoscopic surgery (3.7, SD 0.2) and, more distantly, by STR + RT (2.9, SD 0.2) and GTR (2.7, SD 0.1).[3]

For the surgeon experienced in endoscopy, an endoscopic endonasal approach, as compared to an open approach, has been shown to provide higher rates for GTR (66–69% vs. 48%), with lower reoccurrence (18% vs. 28%), with lower rates of permanent DI (27–32% vs. 48%), and less visual deterioration (1.7% vs. 11%).[24] This surgical corridor largely avoids traversing critical neurovascular structures and allows for better visualization of the subchiasmatic space and intrasellar portions of the tumor, which is a commonly missed and a frequent cause of recurrence after open surgery.[14] However, this approach does not obviate the risks of stretch or manipulation injury due to tumor adherence to surrounding structures.

Perhaps the least invasive treatment option is the insertion of an Ommaya reservoir into the cystic aspect of the tumor followed by drainage with or without subsequent instillation of antineoplastic agents. Several reports have shown follow-up out to 7 years with good cyst size control and 43–73% of patients needing no additional treatment.[28,34] It is possible that a longer follow-up period would influence these results, but this may be a method that allows for delaying RT in young children. Historically, bleomycin was used for intracystic infusion, but concerns for central nervous system toxicity have led to the use of interferon-a (INFa) in its place.[7,34] In addition to intracystic chemotherapy, intracystic irradiation with yttrium-90 has also demonstrated long-term results in reducing the size of recurrent craniopharyngioma cysts when used as part of a multimodal treatment regimen though this treatment strategy has not been widely replicated or implemented.[20]

Radiation therapy, either as a first-line treatment or as an adjuvant to surgical resection, has become a frequent care option. SRS can deliver radiation with a steeper dose gradient between tumor and adjacent brain structures. It is believed to lead to lower rates of neurotoxic side effects in comparison to traditional fractionated RT. The potential side effects of radiation are similar

to that of open surgery and include the following: Panhypopituitarism, DI, hypothalamic dysfunction, vasculopathy, cognitive dysfunction, optic neuropathy, and secondary malignancies.[2,10,26] Published control rates for STR + SRS are good at 60–90%, depending on tumor type, with low rates of reported endocrine and visual deterioration in only 6% of patients using a lower marginal dose.[23,27] Because of high documented rates of optic neuropathy, SRS traditionally has been limited to smaller tumors (<3 cm) that were 3–5 mm away from the optic apparatus;[27] however, multisession SRS may allow for treatment of tumors closer to the chiasm.[1]

Finally, systemic chemotherapy treatment with INF-alpha-2b has been performed by the Pediatric Brain Tumor Consortium (PBTC-039) phase 2 trial in pediatric patients with recurrent craniopharyngioma. Three of the 12 patients tested experienced a response to the drug, and none developed any permanent side effects.[19] The same group recently published another study using the pegylated form of the drug in a cohort of five patients with recurrent disease in which four demonstrated response on imaging.[38]

CHOICE OF THERAPY

The treatment paradigm for craniopharyngioma has evolved over time, as our treatment options have expanded and our understanding of the long-term consequences of radical resection has grown. Originally, aggressive resection was the only hope of controlling this tumor; in spite of the often severe morbidity of such an approach, it remained the mainstay of treatment. But as the natural history of this tumor is recurrence, it may be considered a chronic disease, with the goal of maximizing control but minimizing patient morbidity. Our desire as surgeons to obtain tumor-free postoperative imaging may overlook the impact on our patient. Weighing risks, benefits, and alternatives to surgical goals and approaches are crucial in the treatment of this challenging tumor.

To date, no class I recommendations exist for the best treatment of these tumors. Management should be by a multidisciplinary team (neurosurgery, endocrinology, ophthalmology, psychology, oncology, and radiation oncology) and be individualized for each patient. There are some practical surgical considerations to keep in mind. In cases where total resection can be obtained without significant morbidity (i.e., cases where the tumor is not invading or adherent to the hypothalamus), GTR remains the treatment of choice. In cases where the tumor is small and the solid portions are primary intrasellar, without significant extension laterally in the suprasellar space or without encasement of vessels, an endoscopic approach may provide good outcomes. In

cases where the tumor is densely involved in critical structures and has a significant cystic component causing mass effect, an Ommaya placement with or without chemotherapy infusion may represent a less invasive way to decompress neural structures and control tumor progression. Finally, in cases of STR or recurrent disease, particularly with a favorable margin between the tumor and the optic chiasm, adjuvant RT or SRS is likely to improve progression-free survival. Promising treatments from PBTC trials may offer hope for future therapies with lower side effect profiles. Ultimately, this tumor remains one of the most difficult pediatric neurosurgical problems, and recommendations will continue to evolve.

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Conflicts of interest
There are no conflicts of interest.

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