



Case Report

Esthesioneuroblastoma with recurrent dural metastases: Long-term multimodality treatment and considerations

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ABSTRACT

Background: Esthesioneuroblastoma (ENB) is a rare malignant disease and treatment protocols have not been standardized, varying widely by disease course and institutional practices. Management typically includes wide local excision through open or endoscopic resection, followed by radiotherapy, chemotherapy, and stereotactic radiosurgery. Tumor control can differ on a case-by-case basis. Herein, the complex management of a rare case of recurrent disease with multiple dural metastases is presented.

Case Description: A 60-year-old patient was diagnosed with ENB after presenting with anosmia and epistaxis. The patient underwent combined endonasal and transfrontal sinus craniofacial resection, followed by proton beam radiation therapy and chemotherapy. Subsequently, he developed a total of 25 dural metastases that were controlled with repeated Gamma Knife Radiosurgery (GKRS). In spite of post-treatment course that was complicated by radiation necrosis and local vasculopathy, the patient made significant recovery to functional baseline.

Conclusion: The management of ENB entails multimodality and multidisciplinary care, which can help patients obtain disease control and long-term survival. Recurrent ENB dural metastases can behave as oligometastatic disease manageable with aggressive focal GKRS. As prognosis continues to improve, chronic treatment effects of radiation in such cases should be taken into consideration.

Keywords: Esthesioneuroblastoma, Gamma knife, Kadish, Radiotherapy, Recurrence

INTRODUCTION

First reported in 1924, esthesioneuroblastoma (ENB), also referred to as olfactory neuroblastoma, is a rare, malignant nasal tumor that arises from the olfactory neuroepithelium with an incidence of 0.4/1,000,000 individuals.^[15] No prospective and randomized clinical trials exist regarding the optimal treatment modalities. In the largest epidemiologic analysis to date of 311 patients from the surveillance, epidemiology, and end results tumor registry, the mean age was 53-years-old and overall 5- and 10-year survival rates were 62.1% and 45.6%, respectively.^[7] As expected, survival rates vary by local versus distant disease burden in accordance to the modified Kadish classification. Ten-year survival rates of patients with stage A or B disease, that is, confined to the nasal cavity or paranasal sinuses were 83.4% and

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49.0%, respectively. The patients with stage C disease extending to skull base, orbit, or cribriform plate have a rate of 38.6%. This is in comparison to stage D patients with lymph nodes and distant metastases, who experience 10-year survival rate of 13.3%.^[7]

The first report of endoscopically assisted resection with bi-coronal craniotomy was in 1997,^[19] and since then endoscopic craniofacial resection with craniotomy has shown promising results in terms of survival benefit.^[2] Evidence from single-institutional experiences supports wide excision through otolaryngologic or neurosurgical craniofacial resection followed by radiation therapy (RT).^[3,7] The role of chemotherapy as an adjuvant therapy remains unclear. Prognostic factors of improved survival include younger age and RT in the higher grade lesions.^[8]

While postoperative RT does independently predict better disease-specific survival,^[13] recurrences can occur and the knowledge on management of disease progression is underreported. Repeated radiation, in certain circumstances, can be associated with radiation necrosis and pseudoaneurysm formation.^[4,10] Herein, we report the complex course of a 60-year-old man with ENB who underwent resection, proton radiation, chemotherapy, and Gamma Knife Radiosurgery (GKRS) as multimodality management of recurrent metastases.

CASE REPORT

The patient was a 60-year-old right-handed man who initially presented with 5 months of progressive loss of sense of smell, right-sided epistaxis, and excessive tearing of the right eye. Magnetic resonance imaging showed evidence of Kadish C disease [Figure 1a and b]. Gross total resection of the tumor through a combined endoscopic endonasal and transfrontal sinus craniectomy was performed [Figure 1c and d]. A combination of pericranium flap, duraplasty, fat graft, and mesh cranioplasty was utilized for closure. A nasoseptal flap was elevated but was resected due to tumor involvement on biopsy. Pathology confirmed negative margins and Hyams Grade II. Traditionally, the modified Kadish system^[8] and Hyams histological grades are used for classification.^[16]

Following resection, the patient received fractionated proton beam radiotherapy at an outside institution and concomitant cisplatin. The patient experienced anosmia and a partial right sixth cranial nerve palsy. Five years later, the patient developed meningeal metastases. He received GKRS for a total of 12 dural-based metastases [Figure 2a and b]. This included a margin dose of 13 Gy to the foramen magnum tumor and 14 Gy to the remainder of lesion. Interval follow-up imaging after GKRS showing treatment response and decrease in tumor volume on sagittal [Figure 2c] and coronal [Figure 2d] sequences, which concurred with previous findings on prognostication for low-grade Hyams Grade I/II tumors.^[14]

Six months post-treatment, the patient returned with headache and personality changes. There were radiographic

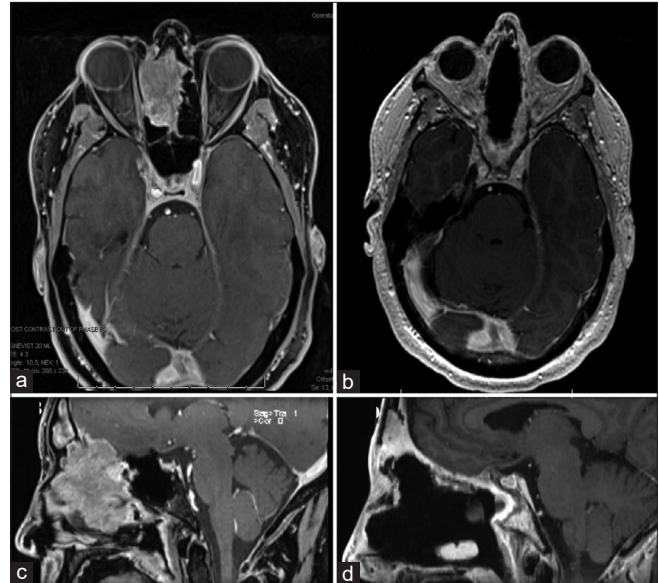


Figure 1: MRI of the skull base at the time of initial presentation: Preoperative axial sequence (a) and sagittal sequence (b) with contrast. Postoperative gross total resection with combined endoscopic endonasal and transfrontal sinus craniectomy on MRI axial (c), and sagittal (d) with contrast.

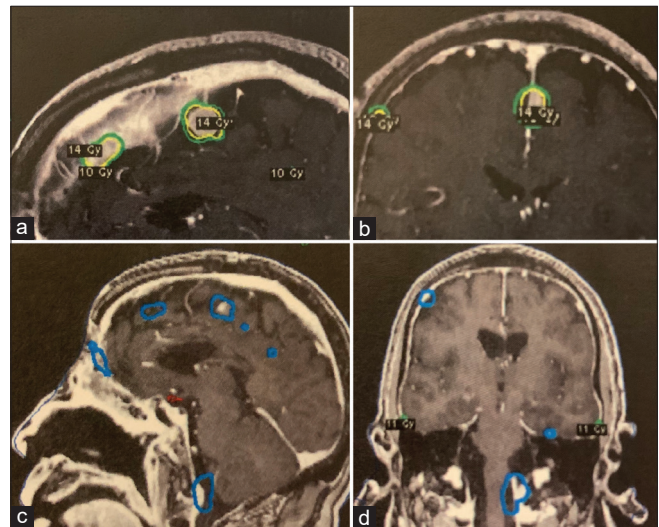


Figure 2: Brain fast spoiled gradient echo sequences with contrast depicting multiple meningeal metastases that are targeted during the second Gamma Knife Radiosurgery (GKRS) treatment, with the margin dose labeled in yellow on the sagittal (a) and coronal (b) planes on the day of GKRS. Interval follow-up imaging after GKRS showing treatment response and decrease in tumor volume on sagittal (c) and coronal (d) sequences.

findings of radiation necrosis and pericranium flap breakdown [Figure 3a and b]. Operative debridement was performed. During superficial debridement of the frontal lobes, brisk bleeding was encountered. The source was identified as a friable right pericallosal artery

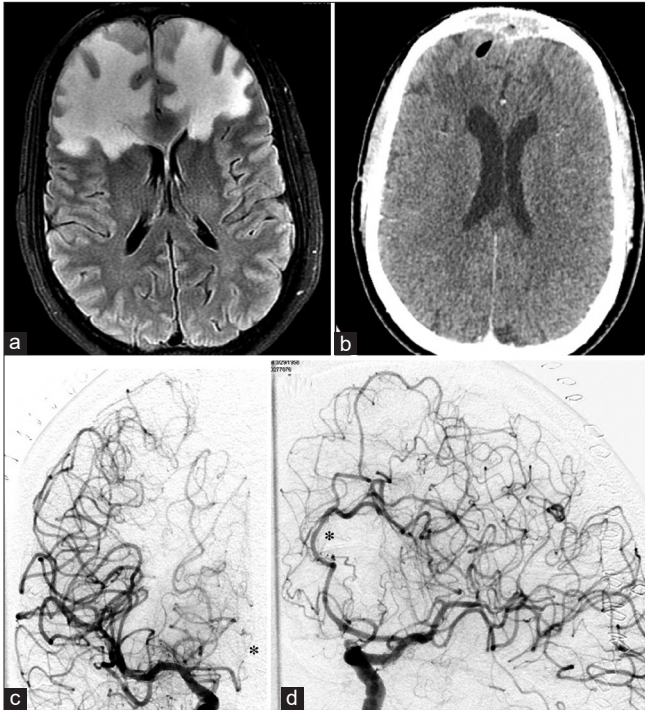


Figure 3: MRI brain FLAIR sequence demonstrating pericranium radiation necrosis of the frontal lobes (a), and CT head demonstrating flap compromise with intracerebral air (b). DSA performed postoperatively that demonstrates on the right coronal ICA injection an atretic ACA that fills sluggishly to the mid A2 segment where it abruptly stops (c). The left coronal ICA injection reveals irregularities in the distal branches of the A2 and A3 segments that are consistent with radiation changes (d).

pseudoaneurysm that ruptured. Given the caliber and quality of the vessel in the setting of multiple previous radiation treatments, it was controlled intraoperatively with sacrifice of the vessel, as seen on diagnostic angiogram (DSA) immediately postoperatively [Figure 3c]. There were also irregularities of the left distal branches of A2 and A3 segments likely consistent with postradiation changes DSA [Figure 3d].

For the reconstruction of the anterior cranial fossa, the plastic surgery team harvested vastus lateralis muscle free flap for anastomosis with superficial temporal artery. An external ventricular drain was placed. The vastus lateralis flap demonstrated good vascular supply and appeared healthy on follow-up endoscopy. The patient had postoperative left leg weakness that improved significantly with rehabilitation. Following debridement, the patient received two more treatments of GKRS for new dural metastases on surveillance imaging. The first treatment occurred 9 months later, to six tumors located in the left sigmoid, left tentorium, left lateral temporal, right lateral temporal, left parietal, and left posterior parietal. A margin dose of 14 Gy ranging in 50–80% isodose was given. Five months later, a new lesion

involving the left jugular tubercle was detected and GKRS was performed using a margin dose of 15 Gy. Aside from intermittent cognitive complaints, the patient remained functionally independent and active with no new metastases 24-months following the last treatment of GKRS.

DISCUSSION

ENB is a rare and slow-growing malignant neoplasm that comprises 2% of all sinonasal tract tumors. Nasal obstruction from the mass is the most common complaint from the patient. Other symptoms can be from the invasion of adjacent structures including the cribriform plate, orbit, eustachian tube, and frontal sinus. Early recognition is important to allow for the greatest potential for aggressive gross total resection in addition to adjuvant radiation for local control. Our patient had Kadish stage C progression with a histologically low-grade ENB. In a previous institutional report of 20 Kadish C patients, 45% of subjects had low-grade tumor and their 5-year disease-free survival was 75% following surgery with adjuvant therapy.^[9] Unlike high-grade tumors, the benefits of adjuvant radiation in low-grade tumors are not clearly established. Positron emission tomography evaluations were completed throughout the course of management, demonstrating radiotracer uptake to known dural based and calvarial metastases. There was no evidence of disease burden identified in other organ systems.

Radiotherapy or stereotactic radiosurgery (SRS) has been an integral modality of head and neck cancer therapy. While it is important to control recurrence as was the case in our patient, radiation is not without long-term effects. In surgical patients, adjuvant radiation can disrupt early inflammatory and proliferative wound healing stages, as well as the late remodeling phase important for tissue reconstitution. The effect of disorganized collagen deposition by fibroblasts in irradiated tissue can accumulate over the course of years, and dose-dependent gamma exposures in mice have been shown to possibly decrease collagen and vascular densities.^[6] For proton-beam therapy, energy deposition mostly occurs at the end of the particle path to in theory deliver lower integral radiation dosing to the surrounding tissues. With GKRS, treatment results are dependent on overall lesion dose, treatment volume, and location.^[5] In our patient, having received proton radiation and followed by need for multiple treatments with GKRS of skull base and dural metastases, likely put the patient at risk of compromised connective tissue integrity, incited chronic pro-inflammation in irradiated arteries, and decreased blood supply. The patient underwent fractionated proton beam and Linac-based RT at outside facility to bifrontal and skull base to a high dose of 74 Gy. Combined with multiple sessions of GKRS for metastases, these factors can contribute to radiation necrosis,

flap compromise, and vascular irregularities including local stenosis and pseudoaneurysm formation.^[1,12,17]

Combined surgery and radiation recently have become standards of practice in patients with this rare disease. Radiation options vary by institutional preference and the availability of in-hospital technology. In cases that require repeated treatment as well as eloquent regions, conformal SRS in single treatments can be performed with minimal toxicity to surrounding tissue. Reducing fall off dosage to surrounding tissue is critical. Given that the median survival is 7.2 years,^[18] whole brain RT can cause white matter injury and persistent radiation toxicity in these patients.

Radiation-induced vessel changes are an important consideration, especially in cases that need reoperation. Aneurysms and vasculopathy can occur within 10 years post-radiation, as was the case here in the setting of reirradiation. The pathogenesis is likely due to endothelial injury, with hemodynamic flow and structural weakness that lead to aneurysmal formation.^[13] A detailed review of 69 patients with intracranial aneurysms after RT -- none for ENB -- had 69% occurring in the anterior circulation, 27% posterior circulation, and 4% associated with arteriovenous malformations.^[11] Of these, 9% of cases were pseudoaneurysms. Notably, rupture risk is much greater than that of non-radiation-induced aneurysms, with 55% being discovered after rupture, of which 26% resulted in death.^[11] As seen in this patient, even small pseudoaneurysms are prone to rupture due to significant vessel structural weakening. Given the size, pathology, and intraoperative circumstances of the ruptured pseudoaneurysm, it was treated surgically with satisfactory outcome for the patient.

It is important to note the effectiveness of radiosurgery in management of the multiple metastases from ENB. There is not established chemotherapy protocol for recurrent disease leaving surgical resection (not feasible for multiple lesions in morbid locations) or radiation as options. Targeted radiosurgery would maximize tumor control and minimize secondary effects. The development of new dural metastases can be addressed with repeated GKRS. It appears that recurrent ENB dural metastases can behave as oligometastatic disease manageable with aggressive focal therapy.

CONCLUSION

As survival for patients with ENB improves through multimodality treatment, long-term treatment effects associated with recurrent disease have not been well reported in the literature. This is the first such report of a patient with extensive dural and skull base metastases for which targeted GKRS through single treatments were performed effectively for tumor control. Management relies on close radiographic

monitoring and repeated SRS. Chronic cerebrovascular changes in prior radiation fields should be identified early on.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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