Dramatic response to targeted therapy in an aggressive olfactory neuroblastoma: illustrative case

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BACKGROUND Olfactory neuroblastomas are rare sinonasal tumors that arise from the olfactory epithelium. The authors presented a case of an olfactory neuroblastoma with extensive cranial invasion that demonstrated dramatic response to sorafenib, a tyrosine kinase inhibitor.

OBSERVATIONS A 54-year-old man with history of prostate cancer and melanoma presented with left-sided proptosis and was found to have a 6.5-cm Kadish stage D olfactory neuroblastoma with cranial invasion that was refractory to chemotherapy and everolimus. However, it demonstrated dramatic response to sorafenib, causing extensive skull base defects that prompted operative repair. Genomic analysis of the tumor revealed mutations in *TSC1* and *SUFU*. The patient developed disease progression with liver metastases 35 months after starting sorafenib, prompting a change to lenvatinib. He experienced progression of his olfactory neuroblastoma 10 months following this change and died in hospice 1 month later.

LESSONS The authors reviewed the clinical presentation and management of a large olfactory neuroblastoma with dramatic response to sorafenib. They highlighted prior uses of targeted therapy in the management of refractory olfactory neuroblastoma within the context of current standard treatment regimens. Targeted therapies may play a vital role in the management of refractory olfactory neuroblastoma.

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Olfactory neuroblastoma (ONB) arises from the olfactory epithelium and comprises 3% to 5% of nasal cavity and paranasal sinus malignancies.[1] It presents most commonly in the second and sixth decades of life.[1,2] Kadish staging is a reliable predictor of overall survival and can be used to guide therapeutic management, while Hyams grading may predict survival in ONBs as well.[3–8] Olfactory neuroblastoma is commonly treated with a multimodal approach that includes resection, radiotherapy, and systemic chemotherapy.[4,5,9–11] Postoperative radiotherapy and chemotherapy improve prognosis, but extent of survival remains limited, especially for high-grade ONB.[7,11–13]

The rare nature of ONB has limited the feasibility of conducting prospective clinical trials to assess optimal therapeutic regimens, and no targeted therapies specific for ONB currently exist. To date, three reports have detailed positive response to targeted therapies in ONB. In one case, the receptor tyrosine kinase inhibitor sunitinib provided 15 months of stable radiological and clinical response in a stage B ONB.[14] In another, combinatorial sunitinib and cetuximab led to radiological resolution of a recurrent ONB containing mutations in *EGFR* and *RET* within 1 month.[15] In the last case, the antiangiogenic inhibitor of VEGF, bevacizumab, demonstrated long-term clinical response in a patient with refractory metastatic grade C ONB.[16]

In this report, we contribute to the literature on targeted therapy for ONB by presenting a 54-year-old man with a Hyams grade IVa, Kadish stage D ONB who displayed clinically significant tumor regression in response to adjuvant sorafenib.

Illustrative Case

A 54-year-old man with a history of prostate cancer and malignant melanoma presented with rhinorrhea as well as proptosis and tearing of the left eye. His prostate cancer had been treated with external beam radiotherapy and the melanoma with surgical excision. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a $3.7 \times 5.3 \times 6.5$-cm hypervascular, heterogeneously enhancing lesion centered in the nasal cavity with cervical and submandibular lymphadenopathy (Fig. 1A and B), characteristic of Kadish stage D. The mass demonstrated bilateral orbital, sphenoid sinus, and cranial invasion with dural enhancement. Endoscopic endonasal biopsy established the diagnosis of a Hyams grade IVa ONB.

Resection was believed to be unfavorable due to the tumor's size and stage; therefore, cisplatin and etoposide (1 dose per week at 75 mg/m^3, 3 doses per week at 100 mg/m^2) were initiated for 3 cycles (Fig. 2). After 3 months of stable radiological response, a drug holiday was initiated. Seven months after initiation of chemotherapy, interval radiological progression was observed, and everolimus (10 mg daily) treatment commenced for a 3-month course, followed by immediate initiation of the receptor tyrosine kinase inhibitor sorafenib (600 mg daily). One month later, the patient noted subjective improved left eye swelling. Two months after sorafenib was started, he experienced clear nasal drainage, prompting performance of CT, which revealed a reduction in tumor burden, causing extensive anterior skull base defects and consequent pneumocephalus (Fig. 1C and D). Persistent tumor remained within the left maxillary and ethmoid sinus with extension into the pterygopalatine fossa and bilateral frontal lobes.

Given concern for cerebrospinal fluid leak, repair of skull base defects was pursued, and aggressive tumor resection was considered simultaneously. Orbital exenteration was not considered because of bilateral involvement and the patient's stage. A bifrontal craniotomy and orbitotomy were performed for macroscopic resection of intracranial tumor as well as its extension into the sphenoid, bilateral ethmoid, and maxillary sinuses and the medial orbit. Reconstruction of the anterior skull base was achieved with abdominal fat graft, vascularized pericranial flap, and free temporalis fascia grafts. Postoperative MRI revealed resolution of pneumocephalus with gross-total resection of the tumor (Fig. 1E).

The resected ONB was profiled for 300 cancer-associated genes as previously described.[17] Genomic analysis revealed mutations in $SUFU^{R331W}$, which encodes suppressor of fused homolog (SUFU), and $TSC1^{G1035S}$, which encodes tuberous sclerosis 1 (TSC1), both of which contribute to the mammalian target of rapamycin (mTOR) cell survival signaling pathway. In addition, multiple low-level chromosomal gains and losses were observed across the genome.

Sorafenib (600 mg daily) was reinitiated after the operation. The patient continued to tolerate the treatment well with clinical and radiological stability until the development of liver metastases 35 months after he initially started sorafenib, prompting a change to lenvatinib (24 mg daily) although his intra- and extracranial disease burden remained stable at that time (Fig. 1F). He experienced progression of his primary disease 2 months later and, following that, ultimately transitioned to hospice and died 13 months later. In total, he survived for 50 months after the initiation of sorafenib.
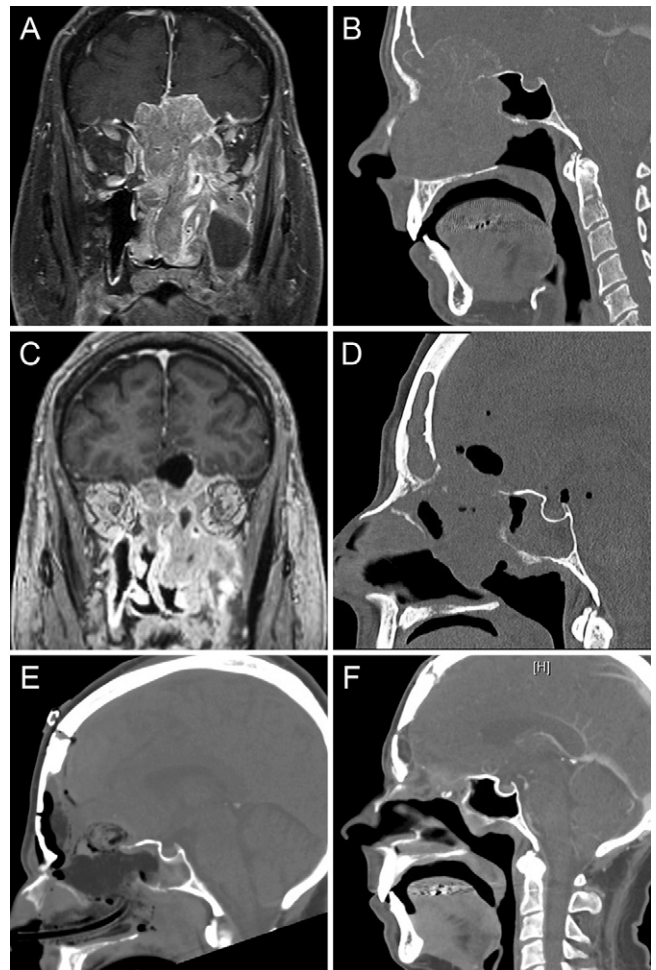

FIG. 1. Preoperative coronal contrast-enhanced T1-weighted MRI (**A**) and sagittal CT (**B**) revealed a soft tissue mass centered within the ethmoid and left maxillary sinuses with extension into the pterygopalatine fossa, foramen rotundum, ethmoid roof, and cribriform plate to the frontal lobe. Two months after initiation of sorafenib, MRI (**C**) and CT (**D**) revealed a significant reduction in tumor burden, causing extensive skull base defects and consequent pneumocephalus. A craniofacial approach was pursued for tumor resection and anterior skull base repair with durable results on CT immediately postoperatively (**E**) and at 34 months' follow-up (**F**).

Discussion

Observations

We report on a 54-year-old man who presented with a large, Kadish D ONB that demonstrated tumor regression following adjuvant sorafenib treatment. Although resection was not favored initially because of the extensive size and Kadish D stage, its response to sorafenib caused extensive skull base defects that prompted operative repair, with aggressive orbit-sparing tumor resection simultaneously.

The rare nature of ONB has rendered delineating optimal therapeutic regimens difficult. Olfactory neuroblastoma is most commonly classified by the Kadish staging system, in which group A tumors are confined to the nasal sinus, group B tumors extend from the
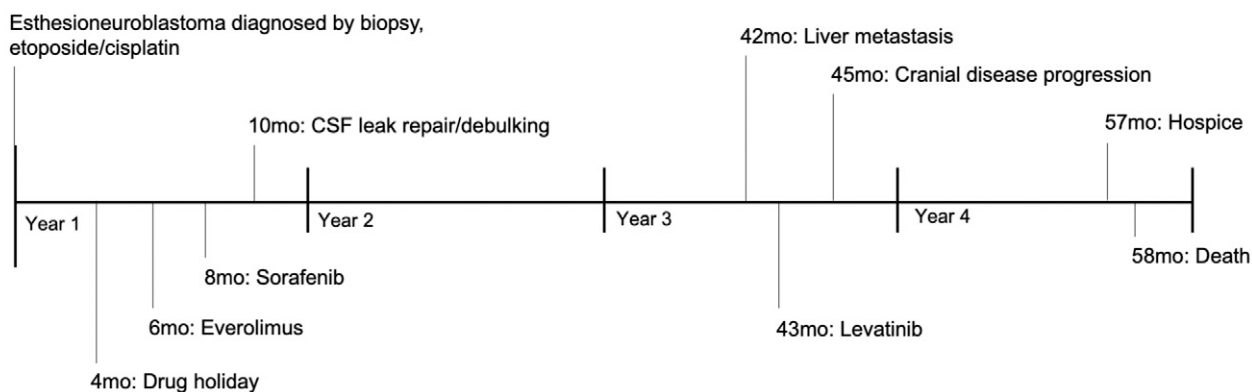
FIG. 2. Clinical course.

nasal cavity to the paranasal sinuses, and group C and D tumors extend beyond these structures.[8] Resection and postoperative radiotherapy have been the mainstays of treatment for Kadish A/B ONB, whereas Kadish C ONB generally entails adjuvant chemotherapy and Kadish D ONB prompts systemic chemotherapy and radiation.[4,5,9–11] A craniofacial approach was chosen in our case to allow maximal access for tumor debulking and repair of anterior skull base defects. Furthermore, negative surgical margins are associated with improved prognosis in ONBs, and this approach afforded the best opportunity to achieve this on initial resection.[18] Extended endoscopic approaches have also been reported as an alternative surgical option, with comparable outcomes to craniofacial procedures.[19–21] Chemotherapy is an effective neoadjuvant therapy and an effective postoperative adjuvant therapy in high-grade and high-stage ONBs.[5,10,22]

Targeted pharmacotherapies have been reported in managing high-grade or refractory ONB with clinical success, but guidelines on their usage have not been outlined.[14,15] Notably, one case of an ONB harboring mutations in *EGFR*, *RET*, *FGFR2*, and *KDR* demonstrated complete radiographic response and symptomatic improvement after receiving sunitinib, which inhibits multiple receptor tyrosine kinases, and cetuximab, which specifically inhibits EGFR.

While the underlying pathogenesis of ONBs remains unclear, recent discoveries about its molecular and genomic features may carry prognostic significance and hold therapeutic promise. For example, the apoptosis pathway member bcl-2 may contribute to angiogenesis in ONB and is associated with worse outcomes.[23,24] The tropomyosin receptor kinases Trk-A and Trk-B are also present in most ONBs and may serve as potential pharmacological targets.[25] *TP53* mutations have been associated with poor prognosis.[26] Certain mutations are associated with metastatic progression for ONB, indicating their potential as targets to prevent cancer evolution.[27] Sparse cytogenetic studies of ONB have revealed heterogeneous and complex changes, whose prognostic value remain to be validated.[26,28–30]

Lessons

Mutations in *SUFU* and *TSC1* have not been previously observed in ONB but may explain the positive response to the agents used in this case. Everolimus inhibits TSC1 and other components

of the mTOR pathway.[31] Sorafenib also demonstrates activity against tumors containing mutations of genes encoding proteins in the mTOR pathway.[32] Everolimus and sorafenib have synergistic effects in certain cancer models and primary cancers.[33–35] It is possible that the initiation of sorafenib immediately after discontinuation of everolimus accentuated the effect of sorafenib. Targeted inhibition of ONB in vitro is more effective when multiple signal transduction pathways are concurrently inhibited, even at lower doses, suggesting that treatment of refractory ONB may also benefit from combinatorial therapy.[36] Interestingly, ONBs with higher degrees of chromosomal instability may be associated with a more indolent clinical course.[26] The cytogenetic changes in this case align with prior abnormalities observed. Multiinstitutional collaborative studies will contribute to further understanding of ONB biology and aid the development of targeted treatments for this disease.

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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: all authors. Acquisition of data: Gupta, Bi, Annino. Analysis and interpretation of data: all authors. Drafting the article: Gupta, Bi. Critically revising the article: all authors. Reviewed submitted version of manuscript: Dunn, Gupta, Bi. Administrative/technical/material support: Dunn. Study supervision: Dunn, Bi.

Supplemental Information

Previous Presentations
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