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Navigating the Complexity of Olfactory Neuroblastoma: A Case Report and Review of the Literature

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Abstract **Case Report**

This comprehensive case report presents a 65-year-old male with olfactory neuroblastoma, notable for its rarity and diagnostic challenges. The patient's clinical history includes significant smoking, alcohol consumption, and comorbidities. The initial presentation involved nasal obstruction, pain, and recurrent epistaxis, leading to a detailed imaging assessment revealing an extensive and infiltrative tumor. The biopsy confirmed grade II olfactory neuroblastoma. A thorough multidisciplinary discussion guided the treatment strategy, involving neoadjuvant chemotherapy with CISPLATIN and ETOPOSIDE. Remarkably, the patient exhibited a 30% reduction in tumor volume after three cycles, setting the stage for surgical intervention. The subsequent surgical excision revealed a high-grade tumor invading multiple structures, emphasizing the aggressive nature of olfactory neuroblastoma. Postoperative radiotherapy, intended for the positive margins and involved lymph nodes, was implemented, accompanied by manageable toxicities. The case highlights the intricate decision-making process in managing olfactory neuroblastoma, considering tumor extent, grade, and therapeutic response. In conclusion, this case underscores the need for a personalized and multidisciplinary approach to olfactory neuroblastoma, integrating chemotherapy, surgery, and radiotherapy. Despite the absence of established guidelines, the case offers insights into therapeutic decision-making, emphasizing the importance of ongoing clinical and imaging monitoring for optimal long-term outcomes.

Keywords: Olfactory Neuroblastoma, Esthesioneuroblastoma, Sinonasal tumor, Management Strategies, Surgery, Radiotherapy.

INTRODUCTION

Olfactory neuroblastoma, a rare malignancy originating from the olfactory epithelium, presents diagnostic and therapeutic challenges. With a prevalence of just two percent among sinonasal tumors, this neuroectodermal tumor tends to affect individuals aged 30 to 70 years, displaying a slight male predominance. The clinical spectrum includes symptoms like nasal obstruction, epistaxis, and pain, making early diagnosis crucial. This article explores the multifaceted landscape of olfactory neuroblastoma, delving into its diagnostic methods, staging complexities, and the evolving therapeutic approaches that shape its management. Furthermore, it emphasizes the uncertainties surrounding chemotherapy guidelines and underscores the imperative need for extended post-treatment monitoring to promptly detect and address potential recurrences, contributing to improved long-term outcomes.

CASE REPORT

We report the case of a 65-year-old, male patient with a documented medical history of arterial hypertension, type 2 diabetes, and a history of adenoid vegetation removal four years ago. He is a confirmed active smoker with an 80-pack-year and occasionally engages in alcohol consumption.

The patient experienced three months before admission, a right unilateral nasal obstruction associated with mild pain and recurrent épistaxis, leading to repeated visits to the emergency department for nasal packing. This symptomatology prompted the performance of a cervico facial CT scan which demonstrated a right ethmoid lesion with lysis of the roof and papyraceous lamina, a complementary MRI scan revealed a massive endonasal and ethmoidal lesion extended to the maxilla, the frontal sinus, the medial wall of the orbit, with infiltration of the cribriform lamina and meningeal irritation [Figure 1, Figure 2]. A biopsy was

performed at this location that was in favour of grade II olfactory neuroblastoma. The extension assessment by a cervical-thoracic-abdominal CT scan revealed only two centimetric lower right jugulo-carotid adenopathies, without any other lesions of suspicious appearance. this case was discussed in a multidisciplinary medical meeting, and the decision was to proceed with initial chemotherapy using CISPLATIN and ETOPOSIDE, followed by reassessment for potential surgery followed by adjuvant radiotherapy. The patient received three cycles of chemotherapy with good tolerance and a 30 percent reduction of the initial tumor volume observed on the assessment MRI. then he underwent a large surgical excision with right cervical lymph node dissection, the pathological examination of the surgical specimen revealed olfactory neuroblastoma with some necrotic areas and significant mitotic activity, suggesting Hyams grade III, it invades the right maxilla, the right frontal and ethmoidal sinuses, the medial wall of the orbit, the base of the skull, and the frontal meningeum, with tumoral margins. The examination of cervical lymph dissection revealed the presence of three invaded nodes out of 27 nodes removed. These nodes were located in lymph node areas III and IIb, and there was no capsular penetration observed. Following the Multidisciplinary Consultation Meeting decision, we have settled on the indication for postoperative radiotherapy at a dose of 54 Gy for levels I, IIb, and III on the right, and a dose of 54 Gy on the tumor bed, with a boost up to 66 Gy on the tumor bed of the right nasal ethmoid, where there were positive margins. The patient presented during the treatment a radiodermitis grade 2 and a radiomucitis grade 2 which were treated, and the therapeutical follow-up was marked by a clinical improvement of these toxicities with regaining of weight, but on the other hand, persistence of ageusia and xerostomia.

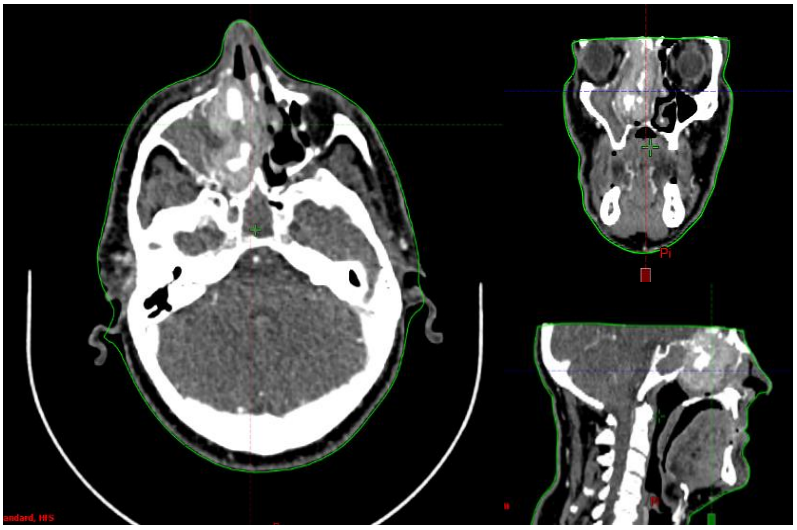

Figure 1: Cervico facial CT scan in three distinct sections showing a right ethmoid lesion with lysis of the roof and papyraceous lamina

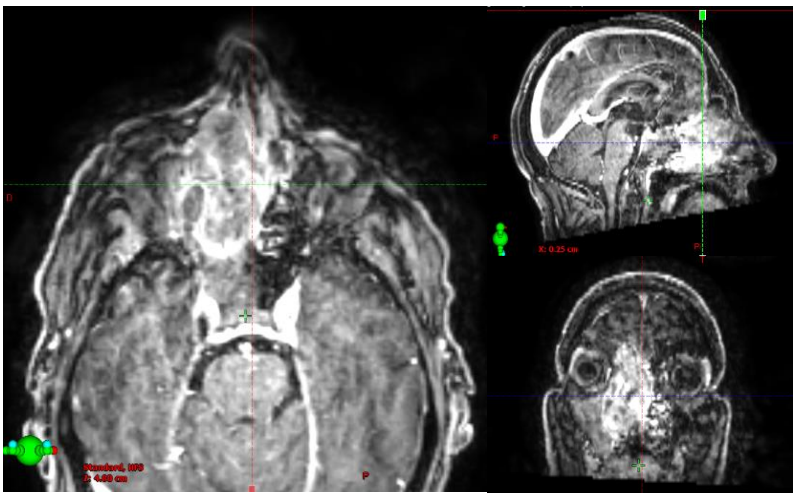

Figure 2: T1 cervicofacial MRI with gadolinium injection, showing a massive endonasal and ethmoidal lesion extended the maxilla, the frontal sinus, the medial wall of the orbit, with an infiltration of the cribriform lamina and meningeal irritation

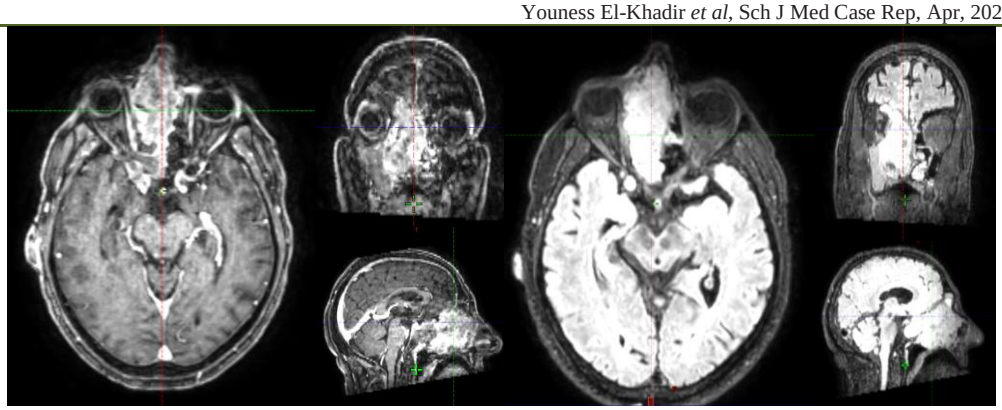

Figure 3: Cervicofacial MRI in T1 injected and T2 sequences indicating a 30% reduction in tumor size after neoadjuvant chemotherapy

DISCUSSION

Olfactory neuroblastoma, also known as esthesioneuroblastoma, is an uncommon malignant tumor of neuroectodermal origin exhibiting neuroendocrine differentiation. These tumors originate from the olfactory epithelium [1]. Olfactory neuroblastoma constitutes approximately two percent of all sinonasal tumors, with an incidence of 0.4 cases per million in the population [2]. Typically, individuals diagnosed with olfactory neuroblastomas present at a mean age of 53 years, and the majority of cases occur in the age range of 30 to 70 years. In terms of gender distribution, there is a moderate male predominance, as indicated by a 59:41 male-to-female ratio in a series sourced from the Surveillance, Epidemiology, and End Results (SEER) database [3].

Olfactory neuroblastoma typically manifests with nasal obstruction as the predominant symptom associated with a nasal cavity mass. Additional local signs include epistaxis, nasal discharge, and pain. Invasion into adjacent structures can give rise to specific symptoms including Anosmia, Orbital Extension, Eustachian Tube Obstruction and frontal headaches. Paraneoplastic syndromes, though rare, may occur due to hormone production [4, 5]. The diagnosis is established through a tissue biopsy, typically obtained during a thorough examination of the nasal cavity. Unfortunately, delayed diagnosis is a frequent occurrence. Early recognition and timely biopsy are critical in ensuring prompt and effective management of olfactory neuroblastoma, highlighting the need for heightened awareness and thorough investigation in suspected cases. Imaging studies, including CT and MRI, are essential for diagnosing and staging olfactory neuroblastoma. These modalities help differentiate the tumor from other causes of nasal obstruction and provide valuable information about the extent of the disease [6, 7]. PET/CT can be beneficial in identifying lymphatic metastases [8], while somatostatin receptor-based imaging (SRI) holds promise for detecting and staging olfactory neuroblastoma[9]. The combination of these imaging techniques is crucial for accurate diagnosis, staging, and guiding treatment decisions, particularly in cases with locally advanced or high-grade disease. The staging of this tumor lacks a universally accepted system, with the Kadish and Dulguerov systems being the most commonly used. Kadish System is based on primary tumor extent, and lymph node or distant metastases, it includes 4 stages, Stage A: Confined to the nasal cavity, Stage B: Involvement of one or more paranasal sinuses, Stage C: Extension beyond the nasal cavity and paranasal sinuses, and Stage D: Regional lymph node or distant metastasis [10] . In the the other hand, Dulguerov System is a modified TNM-based classification providing potential superior prognostic stratification [11] . Meta-analysis suggests better discrimination of overall survival, especially in Kadish stage C patients [12] .

Olfactory neuroblastoma is graded using the Hyams system (I-IV), correlating with prognosis. Histologically, low-grade tumors display lobulated patterns and fibrillary stroma, while high-grade tumors show sheet-like growth, reduced sustentacular cells, and increased mitotic activity [13]. Molecularly, it is genetically diverse, with mutations in TP53, PIK3CA, NF1, CDKN2A, and copy number alterations in FGFR3 and CCND1 [14]. Differential diagnoses include sinonasal undifferentiated carcinoma (SNUC) and neuroendocrine carcinomas, with IDH2 mutations causing diagnostic challenges. "Olfactory carcinoma" has been suggested for cases with ambiguous features [15]. Immunohistochemistry is crucial for accurate diagnosis, using markers like Calretinin and neuroendocrine markers [16]. Overall, understanding the pathology involves a multifaceted approach considering grading, molecular findings, and differential diagnosis.

Surgery, radiation therapy (RT), and/or chemotherapy are all used in the treatment of olfactory neuroblastomas, however, the optimal paradigm lacks confirmation from randomized clinical trials due to the rarity of the disease and the limited numbers of patients included in the studies [17]. Surgery is the primary treatment for olfactory neuroblastoma but is generally limited to selected patients with early-stage and low-grade disease, and most generally a combined-modality approach with radiation therapy is preferred for better outcomes [18, 19]. The factors influencing the

surgical approach include tumor extent, patient comorbidities, and surgical team experience. Observational studies favor a combined craniofacial approach, leading to improved en bloc resection, local control, and survival compared to the transfacial approach [20, 21]. Craniofacial resection generally yields superior outcomes, compared to lesser surgery which can be proposed for early-stage tumors [21]. RT alone is less satisfactory, and it is primarily reserved for poor surgical candidates. However, it plays a major therapeutic role in combination with surgery for improving disease control, disease-free and overall survival [22]. Postoperative RT for tumours without high-risk features, suggests a minimum dose of 54 Gy in 30 treatments over six weeks, using highly conformal techniques like intensity-modulated radiation therapy (IMRT) and proton therapy (IMPT), which are now the standard to minimize toxicity to adjacent critical structures [23, 24]. The role of chemotherapy lacks established guidelines [25]. While neoadjuvant chemotherapy's benefit is unclear in adult patients, it is often included in the plan for unresectable tumors, advanced stage, or poor prognosis[19, 25]. Moreover, it can provide clinically useful palliation of patients with advanced olfactory neuroblastoma who are not candidates for definitive surgery or RT, though There is limited data to recommend any specific chemotherapy regimen, such patients should be enrolled in clinical protocols whenever feasible [26]. There are no formal guidelines for follow-up, emphasizing the need for extended clinical and imaging monitoring, as approximately 10 to 20 percent of olfactory neuroblastoma patients may experience local or regional recurrence for at least 10 years after initial therapy [27]. Surveillance involves baseline brain MRI with maxillofacial imaging at 2-3 months post-treatment, followed by 6-month intervals for about 2 years, then yearly checks until 5 years post-treatment. PET/CT and somatostatin receptor-based imaging may detect metastases, especially in high-risk patients. For high-risk cases, it should extend beyond 5 years, with potential additional imaging at 1-2 year intervals [27, 28].

CONCLUSION

Olfactory neuroblastoma, a rare malignancy, requires a comprehensive approach involving surgery, radiation, and potential chemotherapy. Despite limited guidelines, a combined-modality approach, including craniofacial surgery and advanced radiation techniques, shows improved outcomes. The role of chemotherapy remains uncertain, often considered for unresectable or high-grade tumors. Follow-up lacks formal guidelines, emphasizing extended clinical and imaging monitoring for recurrence detection, particularly in high-risk cases, contributing to better long-term outcomes.

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