VIA MEDICA

CASE REPORT

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Aggressiveness of esthesioneuroblastoma: a rare case report and review of literature

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ABSTRACT

Introduction. Esthesioneuroblastoma, also known as olfactory neuroblastoma, is a rare malignant neuroecto dermal nasal tumor with distinctive clinical, histopathological, radiological, and molecular features. It arises from olfactory receptors in the nasal mucosa or the cribriform plate of the ethmoid bone. It is generally slow-growing; fast-growing tumors may lead to widespread metastasis. Here, we present an atypical case of aggressive esthesioneuroblastoma treated with a multimodality approach.

Case description. A 28-year male, presented with a painful swelling over the right cheek lasting for 5 months. The patient underwent surgery, and histopathology of the surgical specimen revealed a small round blue cell tumor with widespread positivity for synaptophysin and CD 56. The histopathological appearance and immunohistochemical profile of the biopsy tissue confirmed esthesioneuroblastoma. Owing to subtotal resection, the patient received adjuvant radical radiotherapy to the local site and lymph nodes. Three months post-radiotherapy, a CECT scan showed a partial response, so the patient received intravenous chemotherapy. However, the patient had local disease progression; establishing the aggressivness of esthesioneuroblastoma in our patient. The patient is alive with residual stable disease after 2.5 years from the initial diagnosis and is follow up.

Conclusion. Esthesioneuroblastomas are uncommon tumors and owing to their slow-growing nature, the patient may neglect them. There is a wide spectrum of clinical presentations and outcomes in such patients, and as the literature on esthesioneuroblastoma is scarce due to its rarity, this case report seeks to contribute to a better understanding of such uncommon malignancy in terms of its clinical presentation, behavior, and outcomes.

Key words: esthesioneuroblastoma, external beam radiotherapy, olfactory neuroblastoma, round blue cell tumor, VAC regimen, VIP regimen

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Introduction

Esthesioneuroblastoma, also known as olfactory neuroblastoma, is an uncommon malignant neuroectodermal nasal tumor with distinctive clinical, histopathological, radiological, and molecular features. It is thought to arise from the specialized sensory neuroepithelial olfactory cells present in the Jacobson's vomeronasal organ, nervous terminals, sphenopalatine ganglion, ectodermal olfactory placode, autonomic ganglia of the nasal mucosa, and the olfactory neuroepithelium. Olfactory neuroblastomas are generally slow-growing, but fast-growing tumors may lead to widespread metastasis. Here, we present an atypical case of an aggressive type of esthesioneuroblastoma treated with a multimodality approach.

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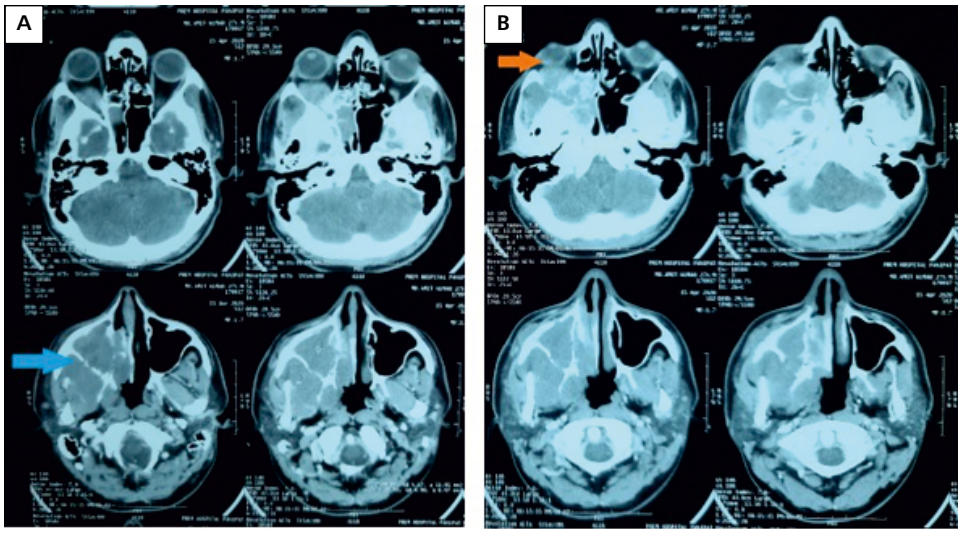

Figure 1. Post-operative CECT of face and neck showing large, solid, soft tissue attenuating mass in the right maxillary sinus (blue arrow in **A**), invading the postero-lateral and medial wall and the same mass also encroaching superiorly through the dehiscent roof into right orbit extraconal space (orange arrow in **B**)

Case summary

A 28-year male, without any prior illness, presented with a painful swelling over the right cheek lasting for 5 months. The swelling was insidious in onset. It started with a right upper molar toothache, and was rapidly progressive in nature, non-mobile, and hard on palpation. There was no history of bleeding or discharge from the swelling. The patient was a non-smoker, non-alcoholic, and had no associated history of fever, weight loss, anorexia, headache, chest or abdominal discomfort.

With these symptoms, he first attended a private hospital where radical surgery was attempted. But, the post-operative post-operative contrast-enhanced computed tomography (CECT) scan, revealed a heterogenous mass of size: 6.3 × 3.5 × 3.9 cm in the right maxillary sinus, implicating subtotal resection. The mass eroded the postero-lateral & medial wall and roof of the maxillary sinus with concomitant erosion of the right pterygoid plate and extension into the intra-orbital floor and right sphenoid sinus (Fig. 1A, B). The CECT of the neck further revealed multiple bilateral cervical lymphadenopathies, the largest being 1.7 × 1.1 cm in the right level II region. Histopathology of the surgical specimen revealed a small round blue cell tumor (Fig. 2A, B), with a perivascular pseudo-rosette formation, which also infiltrated the underlying bony hard palate. The neoplastic cells showed widespread positivity for synaptophysin and cluster differentiation 56 (CD 56) immunocytochemical stain and negativity for cytokeratin (CK), vimentin, and cluster

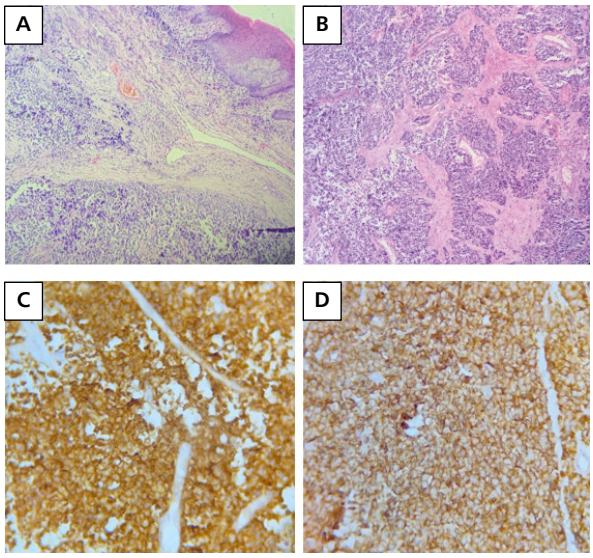

Figure 2. Photomicrographs; **A.** Hematoxylin-eosin stain (H & E stain), original magnification × 10, showing hyperplastic stratified squamous epithelium covered soft tissue and revealing diffuse infiltration by a small round blue cell tumor; **B.** (H & E stain), magnification × 20, displaying malignant small round blue cells with high nucleus-cytoplasm (N:C) ratio: Cytoplasm (N:C) ratio, condensed nuclear chromatin inconspicuous nucleoli, and scanty cytoplasm; **C.** IHC stain, magnification × 20, immunohistochemical study (IHC) illustrating the neoplastic cells with widespread positivity for CD 56; **D.** IHC stain, magnification × 40, demonstrating widespread positivity for synaptophysin

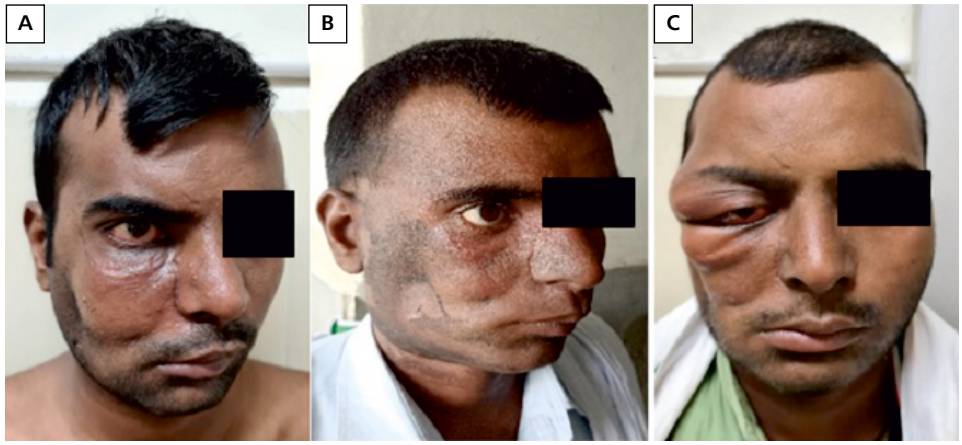

Figure 3. A. A post-operative clinical photograph showing swelling over the right cheek; **B.** Post-adjuvant radiotherapy clinical photograph showing a decrease in the size of swelling revealing partial response; **C.** A clinical photograph taken 3 months after radiotherapy showing diffuse right periorbital edema and erythema of the right eye indicative of progressive disease

differentiation 117 (CD 117 or c-kit) (Fig. 2C, D). The histopathological appearance and immunohistochemical profile of the biopsy tissue confirmed it to be a case of esthesioneuroblastoma.

The patient then visited our department for further treatment. Given the residual disease, the patient was treated with post-operative external beam radical radiotherapy of 60 Gy (gray) in 30 fractions over 6 weeks locally to the primary tumor and 50 Gy in 25 fractions over 5 weeks to the bilateral neck region. Three months post-radiotherapy, a CECT scan revealed a heterogenous mass of size: 4.3 × 3.1 × 3.0 cm suggestive of a partial response. The patient was given 6 courses of 3-weekly intravenous combination chemotherapy with a VAC regimen (vincristine 1.4 mg/m^2, doxorubicin 40 mg/m^2, and cyclophosphamide 750 mg/m^2). A post-chemotherapy assessment revealed persistence of gross disease in the local area (loco-regional failure). Further, the patient was given 6 courses of 2nd line intravenous combination chemotherapy with the 3-weekly VIP regimen (etoposide 100 mg/m^2, ifosfamide 1.4 g/m^2, and cisplatin 100 mg/m^2). Even after that therapy, the disease progressed and this established the aggressivness of esthesioneuroblastoma in our patient. Nevertheless, the patient is still alive with residual disease after 2.5-years from the initial diagnosis.

Discussion

The esthesioneuroblastoma (ENB) is a rare malignant tumor of neuroectodermal origin arising from olfactory receptors in the nasal mucosa or the cribriform plate of the ethmoid bone. Since its initial description by Berger and Luc in 1924 [1], different nomenclatures have been proposed, but the most common are "esthesioneuroblastoma" and "olfactory neuroblastoma". It is a sinonasal malignant tumor frequently invading the brain through the cribriform plate. Thought to arise from olfactory neuroepithelial cells, this tumor has an inclination to spread in adjacent structures by direct local invasion and regional lymphatics spread. Within ENBs, tumors with different biological behavior ranging from localized forms with slow progression to aggressive and metastatic forms at onset are seen. Given its very low incidence, these physiognomies make the study of ENB intricate. The optimal therapy is multimodality treatment involving different medical specialties. Establishing a careful histopathological diagnostic and treatment planning based on a multidisciplinary approach is of paramount importance. The treatment of ENB correlates with the extent of the lesion, with surgery being the mainstay of therapy, followed by post-operative irradiation. Neo-adjuvant chemotherapy is indicated in large unresectable tumors and metastatic forms, although there is no standardized universal regimen. The role of adjuvant and salvage chemotherapy in recurrent and residual cases has also been studied intensively to improve outcomes.

Epidemiology and clinical presentation

Esthesioneuroblastomas are rare neoplasms and only infinitesimal cases have been reported in the global literature so far. ENBs have a bimodal distribution and 2nd and 6th decades are the most common age of presentation [2]. There appears to be a slight male predominance [3]. Among presenting symptoms, epistaxis and nasal blockage are most predominant with localized pain; cheek swelling is another common symptom [4]. At initial diagnosis, around 50–60% of cases have local spread or distant metastases, and generally present as

headaches, proptosis, visual disturbances, or even a neck mass. Overall cervical node metastasis is 27% [5]. Polypoid friable mass in the nasal cavity or the nasopharynx is the usual finding in physical examination; it usually bleeds on touch. An ocular examination is a must as in all sinonasal masses.

Differential diagnosis

Esthesioneuroblastoma presents as a large swelling on the face around the maxillary region. It must be distinguished from squamous cell carcinoma of the maxillary antrum (nose and para nasal sinus squamous cell carcinoma), adenocarcinoma of the salivary gland, inverted papilloma olfactory neuro epithelioma, lymphoma, soft tissue sarcoma (especially Ewing's sarcoma), melanoma, rare small cell carcinoma, Merkel cell carcinoma, and metastatic tumors. Imaging is of little value in its differentiation, and the final diagnosis mostly relies on histopathological and immunohistochemical profiling. Homer-Wright rosettes are considered to be diagnostic of esthesioneuroblastoma with positivity for synaptophysin, CD 56, and neuron-specific enolase (NSE).

Surgical resection

Surgery is the mainstay of treatment in all resectable cases. Surgery alone (open or endoscopic) with an adequate negative margin appears to be enough for small, early-stage tumors with close follow-up and adjuvant radiation kept in reserve in case of recurrence [1]. Complete resection with preservation of vital structures can be done by a craniofacial approach. Routine neck dissection is not indicated in clinically N0 patients, because of the low incidence of neck node metastasis in early-stage ENBs. However, in patients with advanced-stage disease, the cervical metastatic rate escalation to 44% potentiates the need for neck dissection (primary or post-radiation) [6].

Radiotherapy

Radiotherapy (RT) is considered adjuvant therapy after surgical resection, as definitive treatment in inoperable tumors and for palliation of metastatic sites [2, 7]. The RT technique for the primary lesion is similar to that of paranasal sinuses. The conventional anterior field is enough for disease confined to the ethmoid. Beam arrangement can be modified according to disease extension into the orbit or maxillary sinus. Neck irradiation can be given electively or in presence of neck masses [6]. In a combined modality of treatment, a pre-operative dose of 45 Gray (Gy) and a post-operative dose of 60 Gy are given; whereas 70 Gy is needed when definitive RT is planned [8]. The usual fraction dose is 1.8 to 2.0 Gy; a high dose per fraction (exceeding 2 Gy) increases the possibility of late sequelae such as blindness, bone and brain necrosis.

In our case, due to subtotal resection, adjuvant radiotherapy was given to the primary site at a dose of 60 Gy in 30 fractions over 6 weeks. Adjuvant radiation therapy to the neck was also given at a dose of 50 Gy in 25 fractions over 5 weeks. Concurrent chemotherapy was not given to increase the patient's chances of survival.

Chemotherapy

Chemotherapy is considered a secondary treatment, adjunct to surgery and radiation therapy. Chemotherapy can be given in neo-adjuvant settings in unresectable cases, as concomitant with radical radiation and salvage therapy in recurrent cases and metastatic diseases. Neo-adjuvant platinum-based chemotherapy was explored in a lot of case series, and an approximately 70% response rate was reported [9]. Platinum-based chemotherapy was also tried in concurrent and adjuvant settings with variable outcomes. For advanced and residual diseases, therapeutic trials with combination chemotherapy regimens have been conducted. Different combinations of thiotepa, cyclophosphamide, doxorubicin, vincristine, nitrogen mustards, etoposide, cisplatin, ifosfamide, and actinomycin-D have been explored in the literature to improve tumor control and increase the chances of survival [10–13]. Tyrosine kinase inhibitor (TKI) and imatinib have also been tried in some case reports with c-kit positive tumors [14]. Our approach was to use the combination chemotherapy of vincristine, doxorubicin, and cyclophosphamide as the first line and a combination of etoposide, ifosfamide, and cisplatin as the second line in recurrent disease settings with partial response.

Conclusion

The optimal treatment of ENB demonstrates the benefit of adjuvant therapy, particularly radiation therapy. Patients with locally advanced high-grade tumors should receive aggressive treatment with combined modalities such as surgery, radiation therapy, and chemotherapy rather than monotherapy [15]. Here, we have described a case of aggressive esthesioneuroblastoma in a 28-year male. Even using the combined modality approach of adjuvant radiation therapy and chemotherapy to treat a visibly aggressive tumor does not ensure a favorable outcome. Our case demonstrates that subtotal resection is an independent index of poor outcome, with trauma during resection leading to more chances of local progression. More case reports and case studies are needed to evaluate the right approach to the management of aggressive esthesioneuroblastoma.

Conflict of interest

Authors declare no conflict of interest.

Consent

All authors declared that written informed consent was obtained from both the patient and his carer for the publication of this article and accompanying images. However, the patient's identity is not disclosed anywhere in the article.

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