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REVIEW ARTICLE

# Advanced olfactory neuroblastoma in a teenager: a clinical case and short review of literature

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## Abstract

**Background** Olfactory neuroblastoma, also called esthesioneuroblastoma (ONB), is a rare neuroectodermal neoplasm that originates from the olfactory epithelium of the nose-sinus tract. It generally occurs with epistaxis, nasal obstruction, diplopia, and anosmia.

**Methods** A 16-year-old female was admitted to our Unit with a complaint of nasal obstruction, recurrent epistaxis, anosmia, and intermittent headache of sixth month's duration. After the ENT consultation, physical examination, endonasal endoscopy, and multiple biopsies were performed. Instrumental images (CT, MRI) have been requested to stage the aforementioned pathology.

**Results** Instrumental images (CT, MRI) showed a mass filling the right nasal cavity and the maxillary bone and involving the cribriform plate without evidence of dural invasion. Craniofacial resection by means of a bifrontal craniotomy combined with a modified lateral rhinotomic transfacial route was performed. The reconstruction of the inferior and medial orbital walls with employing split-thickness calvarial grafts, pedicled galea-pericranium flap rotated downwards was performed. The patient received 56 Gy of external beam radiotherapy over a 6-week period.

**Conclusion** Early diagnosis and treatment coordinated by a multidisciplinary team of ENTs, neurosurgeons, oncologists, pathologists, and radiologists are a prerequisite for a good prognosis. An excellent surgical debulking, negative margins, and subsequent locoregional control of the pathology through radiotherapy is fundamental.

**Keywords** Esthesioneuroblastoma · Olfactory neuroblastoma · Craniofacial resection · Primary reconstruction · Radiotherapy

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## Introduction

Olfactory neuroblastoma (ONB) is an uncommon neuroepithelial malignant tumor arising from the olfactory epithelium in the cribriform plate or nasal vault and showing a long natural history characterized by frequent local recurrence. The tumor has been described for the first time by Berger et al. in 1924 [1]. Esthesioneuroblastoma constitutes about 3–6% of all tumors of the nasal or paranasal cavity and does not show a different prevalence in the two sexes [2–4]. The incidence, estimated at about 0.4 per million, seems to have increased in the last decade [5]. The average age of onset of the disease is between 40 and 70 years [6]. In 1976, Kadish et al. established a system of staging the ONB then modified in 1993 by Morita et al. (Table 1) [7, 8].

The biological behavior of ONB is not predictable ranging from indolent and slow growth to a submucosal spreading, with eventually extension into adjacent structures especially the sinuses, plate, orbit, and brain.

Therapy of this tumor is challenging because of the rarity and biologic variability and because of lack of standard treatment protocols. An interdisciplinary multimodal therapeutic approach is mandatory especially in case of advanced tumors [6, 9, 10].

Generally, a craniofacial approach seems to be advantageous for most tumors [3]. The location of the tumor often makes complete resection difficult, particularly in stage B of Kadish or higher. In this regard, adjuvant radiotherapy treatment is indicated [11]. However, endoscopic surgery proves also to be effective in some cases. RT alone is a possible alternative to surgery, but the multimodal approach remains more effective [12]. To date, as described in the literature, the use of chemotherapy in the treatment of ONB has little significance [3, 11].

We report a case of a young woman with a poorly differentiated ONB of the nasal-orbito-maxillary area, expanding in the anterior basicranium, submitted to a craniofacial resection and immediate primary reconstruction in order to remodel and reconstitute the tissues removed in oncological debulking, promoting both anatomical and functional restoration and improving the patient's quality of life. Subsequently, the patient was subjected to post-operative irradiation.

**Table 1** Esthesioneuroblastoma Kadish staging systems for tumor

| Kadish staging | |
|---|---|
| Stage A | Tumor confined to the nasal cavity |
| Stage B | Tumor involves the nasal cavity + one or more paranasal sinuses |
| Stage C | Extension of the tumor beyond the sinonasal cavities and into the paranasal sinuses, cribriform lamina, orbit, skull-base, and intracranial |
| Stage D | Cervical lymph node involvement or distant metastasis |

## Case report

A 16-year-old female was admitted to our Unit with a complaint of nasal obstruction, recurrent epistaxis, anosmia, and intermittent headache of sixth month's duration. Physical examination revealed a mild right facial swelling and evidence of an endonasal mass that was endoscopically biopsied proving to be an ONB (Fig. 1).

Instrumental images (CT, MRI) showed a mass filling the right nasal cavity and the maxillary bone, infiltrating the alveolar process, eroding the ipsilateral ethmoidal cells, and involving the cribriform plate without evidence of dural invasion (Fig. 2).

The patient underwent a craniofacial resection by means of a bifrontal craniotomy combined with a modified lateral rhinotomic transfacial route. The surgical specimen consisted in a right subtotal maxillectomy with en bloc resection extending to the anterior cranial base (Fig. 3).

The anterior cranial base defect involving the ipsilateral cribriform plate, fovea ethmoidalis, crista galli, and anterior sphenoidal planum, was then isolated employing a pedicled flap of galea-pericranium rotated and stitched at the side of the bone breach obtaining a watertight seal. The reconstruction of the inferior and medial orbital walls was performed employing split-thickness calvarial grafts obtained from the frontal volet. The orbital grafts toward the nasal cavity were then covered using a further pedicled galea-pericranium flap rotated downwards. The antero-lateral wall of the maxilla and the alveolar process were reconstructed with calvarial bone splits, harvested from the parietal area, superimposed, and then anchored to the zygomatic bone and maxillary alveolar bone residue covered on the oral side by a pedicled temporalis muscle transfer and on the vestibular side by cheek tissues flap (Fig. 4).

After closure of the frontal bone window, an alloplastic prosthesis was positioned on the temporal fossa, the calvarian sampling area was protected with titanium mesh, and right

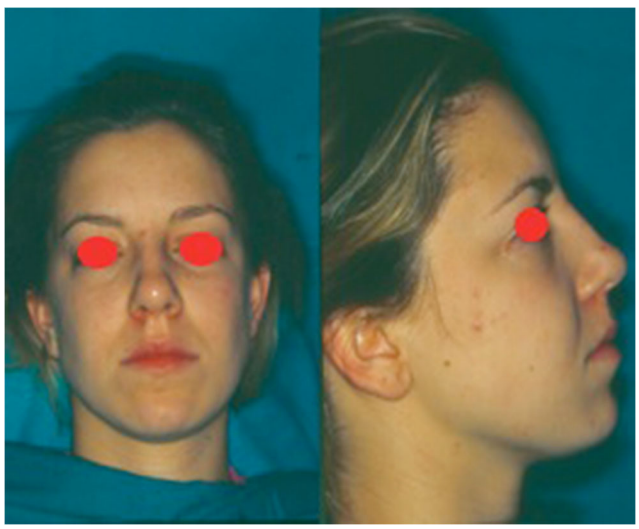

**Fig. 1** Presence of mild right facial swelling and evident endonasal mass

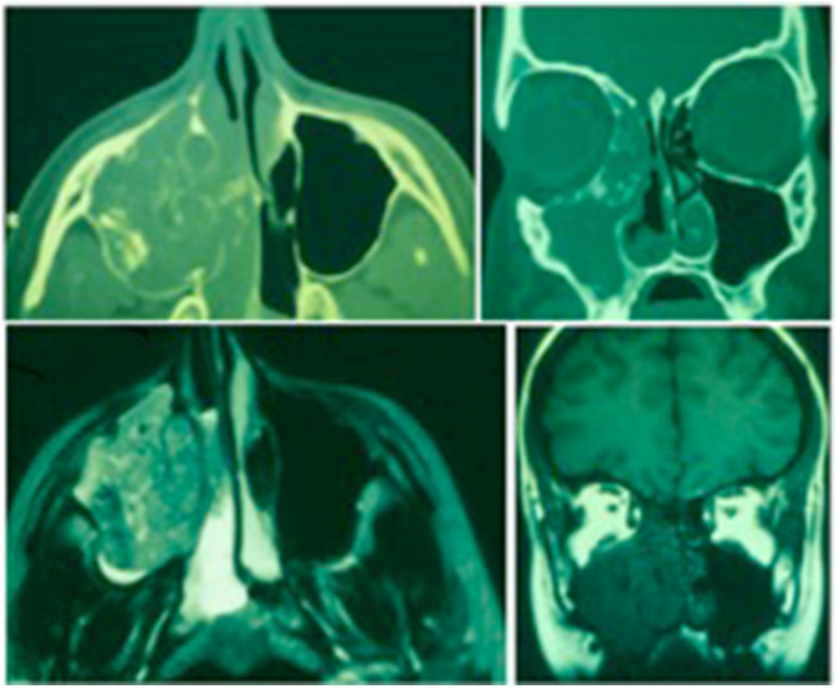

**Fig. 2** CT and magnetic resonance imaging show a mass that fills the right nasal cavity and the maxillary bone. Infiltration of the alveolar process and erosion of the homolateral ethmoidal cells with involvement of the cribrosa plaque. No evidence of dural invasion

medial canthopexy and dacryocystorhinostomy were also performed. Except for a temporary diplopia, the postoperative course was without major complications. The histopathologic study of the specimen exhibits homogenous small cells with uniform round-to-oval nuclei with rosette or pseudo rosette formation and eosinophilic fibrillary intercellular stroma. The surgical margins were reported to be free of disease. The patient received 56 Gy of external beam radiotherapy over a 6-week period. After 6 years of clinic-instrumental follow-up the patient is free of disease (Fig. 5).

## Discussion

ONB is an uncommon neuroepithelial malignant tumor arising from the olfactory epithelium, a structure derived embryologically from the neural crest. First described in 1924 by Berger, it has a histological pattern similar to malignant tumors of sympathetic ganglia, adrenal medulla, and retina and only recently became recognized as a distinct pathologic entity. According to Yin et al., ONB occurs in the fifth and sixth decades of life and age represents an important prognostic factor. No significant gender predilection is present [5].

Over the years, many stages have been described about esthesioneuroblastoma. In 1976, Kadish et al. proposed a system of pretherapy staging, then modified by Morita, during a clinical analysis of 17 patients with ONB [7]. In this staging, the 10-year survival rate varies from 83% for a Kadish stage A to 13.3% in the D stage [5, 13]. In 1988, Hyams et al. instead described a histological and clinical classification correlating prognosis with the degree of tissue necrosis and mitotic activity. A lower degree of Hyams leads to significantly better survival. It represents a prognostic factor of locoregional invasion and therefore orients the choice of adjuvant treatment [13].

Subsequently, also Dulguerov and Calcaterra studied the degree of tumor invasion by radiographic imaging and established a staging system (Table 2) [14].

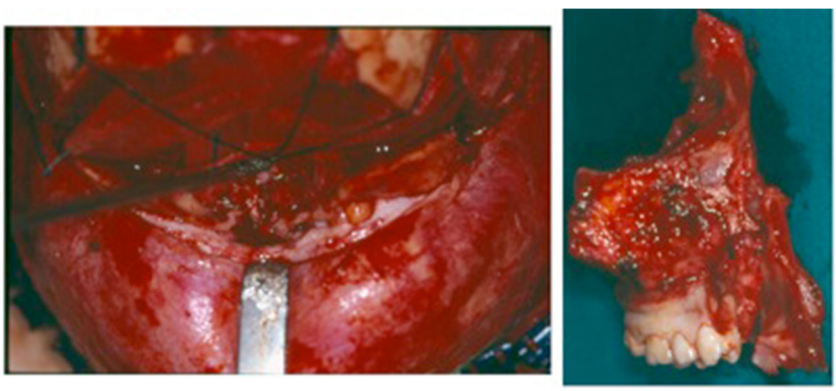

**Fig. 3** Right subtotal maxillectomy with "en bloc resection" extending to the anterior cranial base

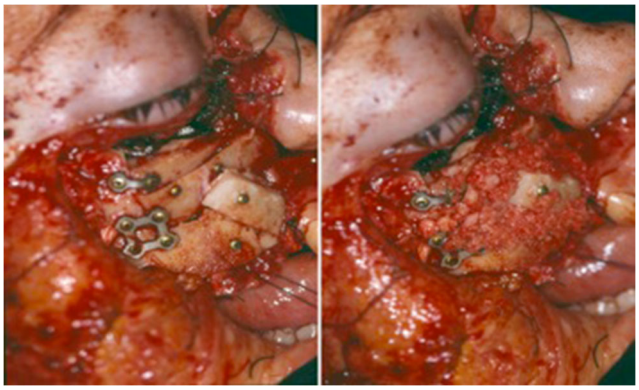

**Fig. 4** Antero-lateral wall of the maxilla and the alveolar process reconstructed by calvarial bone splits, covered on the oral side by a pedicled temporalis muscle transfer and on the vestibular side by check tissues flap

The initial clinical symptomatology includes the presence, more frequently, of unilateral nasal obstruction and epistaxis and, less, of headache, and rhinorrhea. Considering the possible sphenoid and infraorbital extension of the tumor, visual anomalies, and anosmia may occur. In the literature, cases of paraneoplastic syndromes due esthesioneuroblastoma have also been reported [15, 16].

Radiological examinations provide important information on the local extension and tissues surrounding the tumor, thus allowing to establish the best therapeutic choice. CT shows the presence of a homogeneous soft tissue mass, with possible areas of central necrosis or calcifications, depending on the tumor dimensions. The progression of the tumor causes the erosion and invasion of the nearby bone structures. Magnetic resonance imaging is more accurate in the analysis of the degree of invasion of the orbital and intracranial soft tissues.

Histological studies describe ONB commonly well-differentiated, exhibiting the following features: homogeneous small cells, with uniform round-to-oval nuclei, arranged in true rosette or pseudo rosettes patterns, separated by fibrous septa. The surrounding stroma is composed of undifferentiated nuclei and neurofibrillary cords. Marked micro vascularity and palisading of neuroepithelial cells around vessels are present.

Conversely, the undifferentiated ONB is characterized by anaplastic hyperchromatic small cells with numerous mitoses and scant cytoplasm. Conventional light microscopy differentiation

**Table 2** Esthesioneuroblastoma Dulguerov staging systems for tumor (T only)

| Dulguerov modified TNM staging | |
|---|---|
| T1 | Nasal cavity/paranasal sinuses (not sphenoid or superior most ethmoid) |
| T2 | Includes sphenoid with extension to/erosion of cribriform plate |
| T3 | Extends into orbit or anterior cranial fossa without dural invasion |
| T4 | Tumor involving brain |

from other undifferentiated sinonasal small cell neoplasms (such as malignant melanoma, embryonal rhabdomyosarcoma, malignant lymphoma, extramedullary plasmacytoma, and, especially, sinonasal undifferentiated carcinoma and sinonasal neuroendocrine carcinoma) becomes difficult. In these cases, a more accurate diagnosis is supported by identification in tumor cells of chromogranin A, synaptophysin, S-100 protein, and neuron-specific enolase immunohistochemical markers and further by detection of neurosecretory granules with electron microscopy.

Rapid wide spreading metastasis may occur in highly aggressive neoplasm.

The best therapeutic choice involves multimodal treatment, combining the use of surgery, adjuvant radiotherapy, and rarely chemotherapy [17]. Surgical resection is typically performed by transnasal craniofacial resection with or without craniotomy. Alternatively, it is possible to perform an extended endoscopic or endonasal craniofacial resection, obviously depending on the position and extension of the tumor [18].

The importance of adjuvant radiotherapy has been proven in the control of locoregional disease [19]. Indeed Jethanamest et al. showed that the presence of nodal metastases is a negative prognostic factor of survival in patients with ONB [6].

Side effects of acute radiotherapy were conjunctivitis, headache, and dysgeusia. Stomatitis and dermatitis showed improvement after 12 months of follow-up [19].

Primary reconstruction after aggressive surgery is paramount in order to guarantee an adequate functional and cosmetic rehabilitation improving notably the quality life of patients. Cranial bone grafts are particularly useful in the morpho-functional restoration of the 3-D structural support for facial and orbital soft

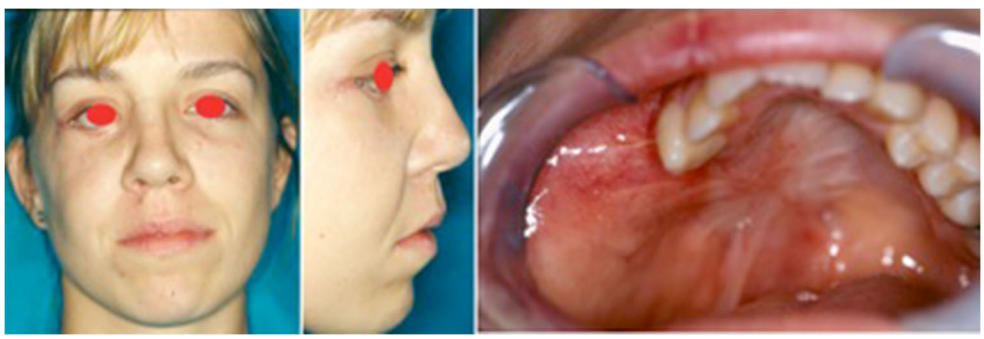

**Fig. 5** Esthetic result after 6 years follow-up

tissues. Peri cranial flaps allow creating a watertight seal between the cranial base and the nasal cavity preventing potentially life-threatening complications. Temporalis muscle flaps demonstrate to be a safe and versatile option in the reconstruction of the hard and soft palate with regard to the recovery of speech, breathing, and feeding capabilities and to cover bone grafts specially in patients who have undergone to radiant therapy.

Miller et al. selectively compared the effect of adjuvant chemotherapy in high-grade Hyams patients. Patients undergoing platinum-based adjuvant chemotherapy did not show more improvement than surgery and adjuvant radiotherapy alone [20].

Despite the best treatment, recurrences can occur; therefore, close lifetime follow-up is mandatory.

## Conclusion

Olfactory neuroblastoma is a rare disease of the head-neck district. Early diagnosis and treatment coordinated by a team including ENTs, neurosurgeons, oncologists, pathologists, and radiologists are a prerequisite for a good prognosis. Excellent surgical debulking, negative margins, followed by a locoregional control of the pathology by radiotherapy, allow a better survival, especially in Kadish lower staging patients.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from the patient included in the study.

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