Esthesioneuroblastoma, or olfactory neuroblastoma (ONB), is a rare malignant tumor of the olfactory neuroepithelium, which is normally confined to the superior one third of the nasal septum, cribriform plate, and superior turbinates but may extend to the base of the skull and intracranial space. ONB accounts for only 3% of all intranasal tumors, and its etiology remains unclear. The tumor can affect both children and adults, with a bimodal peak incidence between 11 and 20 years and between 51 and 60 years. Controversy exists regarding the origin, diagnosis, and management of ONB, mainly because of its rarity and the fact that most institutions treat only a small number of patients with this diagnosis. Many cases go unrecognized because of difficulties in the diagnosis of this tumor as a result of nonspecific initial symptoms (nasal obstruction, recurrent epistaxis). There are rare reports of ONB arising in the nasopharynx, ethmoid sinus, and maxillary sinus. We report a rare case of a very large ONB in a pediatric patient. The clinical appearance of the tumor and diagnostic procedure are discussed, and cases published in the literature are reviewed.

Report of Case

A 3-year-old boy presented with an 18-day history of a swelling in the right maxilla according to the report of the mother. Extraoral examination showed significant facial asymmetry (Fig 1). The patient had no palpable neck lymph nodes, and his medical history was noncontributory. Introral clinical examination showed an extensive, reddish soft-tumor mass in the right maxilla (measuring 3 cm in diameter), which extended from maxillary first molar to the right maxillary tuberosity, not exceeding the midline (Fig 1).
2). Computed tomography (CT) of the facial sinuses showed an expansive, solid, infiltrative tumor involving the nasal cavity and septum, maxillary sinus, orbital cavity, and oral cavity (Figs 3, 4). CT of the upper abdomen, pelvis, and skull showed no anomalies, and there was no evidence of metastases. The clinical diagnosis was a malignant tumor whose origin needed to be established. An incisional biopsy was performed, and histopathologic examination showed the proliferation of neoplastic cells containing uniform round nuclei, inconspicuous nucleoli, and scant cytoplasm and exhibiting intense basophilia and pleomorphism. The stroma was fibrous and vascularized (Fig 5). An immunohistochemical panel was applied to identify the nature of the tumor (Table 1). Immunohistochemistry showed that the tumor was positive for synaptophysin (Fig 6), neuron-specific enolase (NSE) (Fig 7), and Ki-67 (Fig 8).

The definitive diagnosis of ONB was established based on the combination of clinical, radiographic, and histopathologic characteristics obtained by hematoxylin-eosin staining.

**FIGURE 2.** Intraoral photograph showing extensive tumor mass in right maxilla.


**FIGURE 3.** Axial CT scan showing expansive and infiltrative tumor involving nasal cavity and septum, as well as oral cavity.


**FIGURE 4.** Coronal CT scan showing expansive and infiltrative tumor involving nasal cavity and septum, maxillary sinus, orbital cavity, and oral cavity.


**FIGURE 5.** Histopathologic section showing proliferation of neoplastic cells (hematoxylin-eosin stain, original magnification × 400).

and immunohistochemistry. After establishment of the definitive diagnosis, Radiolabeled Metaiodobenzylguanidine (MIBG) $^{131}$I whole-body scintigraphy was performed, which showed an extensive primary neuroblastoma in the region of the right maxilla. The treatment of choice was chemotherapy by a neuroblastoma protocol: cyclophosphamide (150 mg/m$^2$), Doxorubicin (35 mg/m$^2$), vincristine (1.5 mg/m$^2$), platinum (90 mg/m$^2$), and Teniposide (250 mg/m$^2$). During therapy, the drug doses had to be reduced by 25% because of nephrotoxicity, and there was a treatment delay because the patient had contracted chickenpox. Nevertheless, the response to treatment was good, and a significant reduction in the tumor was observed (Fig 9). After the chemotherapy sessions, the patient was submitted to resection of the remaining tumor. Two weeks after surgery, the patient received 6,000 cGy radiation divided into 30 fractions. Control assessment 3 months later showed no evidence of locoregional recurrence or systemic metastases. The patient’s parents were advised to have the child undergo regular follow-up (Fig 10).

**Discussion**

ONB, also known as esthesioneuroblastoma, arises from the olfactory neuroepithelium and presents with a peculiar biologic behavior.$^5$ These tumors are characterized by a variable clinical behavior and can be extremely aggressive depending on age, clinical stage, and genetic mutations. The fact that ONB is rare and that its clinical presentation and microscopic features

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Immunostaining</th>
</tr>
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<tbody>
<tr>
<td>CD10</td>
<td>Negative</td>
</tr>
<tr>
<td>CD20</td>
<td>Negative</td>
</tr>
<tr>
<td>CD3</td>
<td>Negative</td>
</tr>
<tr>
<td>Cytokeratin 20</td>
<td>Negative</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>Negative</td>
</tr>
<tr>
<td>Desmin</td>
<td>Negative</td>
</tr>
<tr>
<td>LCA</td>
<td>Negative</td>
</tr>
<tr>
<td>MIC 2 (CD99)</td>
<td>Negative</td>
</tr>
<tr>
<td>NGFR</td>
<td>Negative</td>
</tr>
<tr>
<td>NSE</td>
<td>Positive</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>Positive</td>
</tr>
<tr>
<td>Ki-67</td>
<td>Positive (+ + +)</td>
</tr>
</tbody>
</table>

**Table 1. IMMUNOSTAINING OF NEOPLASTIC CELLS FOR ANTIBODIES USED**

Abbreviations: LCA, leukocyte common antigen; NGFR, nerve growth factor receptor.

can be confused with other diseases explains the diagnostic difficulties.

ONB is most frequently found in the upper third of the nasal cavity and affects individuals of any age. No gender preference has been reported. ONB is more prevalent among young adults and is rare in individuals aged younger than 10 years. The age range of ONB reported in the literature is between 14 and 79 years (Table 2). However, our case is very rare because the tumor affected a 3-year-old child.

The most common symptoms of ONB are nasal obstruction and epistaxis, followed by headache and nasal swelling. Other symptoms include anosmia, proptosis, diplopia, paresthesia, facial pain, and tooth mobility, if the oral cavity is involved. In our case an extensive mass involving the nasal septum, maxillary sinus, and orbital, nasal, and oral cavities was observed, which was clinically characterized by a tumor aspect, reddish color, soft consistency, and painful symptoms, associated with an extensive swelling in the right maxilla. These features are similar to those of other cases reported in the literature. Table 2 lists the cases of ONB extending to these anatomic sites published between 1958 and 2010. Our case is the second report of ONB affecting the oral cavity.

Because the symptoms of ONB resemble those of various diseases involving the nasal cavity such as sinusitis, the diagnosis of the tumor in its early stages is difficult and the condition is only discovered in more advanced stages when the increase in tumor volume becomes evident. Therefore imaging methods are important to provide data regarding the extent of the tumor and condition of adjacent bone structures, as well as to evaluate the integrity of the cribriform plate, hard palate, and skull base. CT and magnetic resonance imaging are essential methods to define the limits of ONB and to determine possible invasion of adjacent structures. In our case CT of the facial sinuses showed a solid, expansive, and infiltrative tumor.

On the basis of the clinical and imaging features of our case, some diagnostic hypotheses can be raised, including lymphoma, squamous cell carcinoma, adenocarcinoma, rhabdomyosarcoma, melanoma, and undifferentiated carcinomas. Well-differentiated ONB is characterized histopathologically by a lobular arrangement consisting of small lymphocyte-like uniform cells with oval to round hyperchromatic nuclei and scarce cytoplasm. The neoplastic cells form a rosette- or pseudorosette-like pattern. The intercellular material is cosinophilic fibrillar or reticular, and microvascularization is evident. Mitotic figures and necrotic areas are seen in more advanced stages of the tumor. ONB can be classified into 4 stages (grades I, II, III, and IV) according to the degree of differentiation, cellular pleomorphism, mitotic fig-

FIGURE 9. Clinical photograph showing significant reduction in tumor.

FIGURE 10. Intraoral photograph showing significant reduction in tumor mass.
The tumor in our patient was characterized by intense proliferation of round, occasionally spindle-shaped cells that exhibited intense basophilia, pleomorphism, scarce cytoplasm, and few mitotic figures. This morphology is commonly observed in various cancers. The differential diagnosis of ONB, therefore, includes lymphoma, rhabdomyosarcoma, Ewing sarcoma, mucosal malignant melanoma, anaplastic carcinoma, sinonasal undifferentiated carcinoma, and neuroendocrine carcinomas. Within this context, the establishment of the correct diagnosis is important because these tumors often have different prognoses and, consequently, different therapies.

Because ONB is difficult to diagnose, knowledge about the nature of the tumor is essential and can be obtained by use of special stains such as immunohistochemistry. ONB is positive for neuroendocrine markers such as S-100 protein, NSE, chromogranin, and synaptophysin. Tumors such as mucosal malignant melanoma, anaplastic carcinoma, and sinonasal undifferentiated carcinoma included in the differential diagnosis exhibit immunoreactivity to cytokeratins. This was not seen in our case of ONB, which was negative for cytokeratin 20. According to Bist et al and Thompson, ONB is also nonreactive to thyroid transcription factor-1, whereas neuroendocrine carcinomas might be positive. An immunohistochemical panel was applied in our study (Table 1), which ruled out a possible lymphoid origin of the tumor because it was negative for CD10, CD20, CD3, CD99, and leukocyte common antigen antibodies. A muscular origin could also be ruled out because of the absence of staining for desmin. The tumor was negative for nerve growth factor receptor and chromogranin, although some studies have reported immunoreactivity of ONB to these antibodies. On the other hand, positive immunoreactivity of synaptophysin and NSE showed the neural origin of the tumor. In addition, Ki-67 positivity indicated the intense proliferative activity of neoplastic cells.

There is still no ideal treatment protocol for ONB. However, consensus exists that surgical resection of the tumor combined with preoperative and postoperative radiotherapy is the most indicated treatment. According to Ozsahin et al, patients with ONB undergoing surgical resection followed by postoperative radiotherapy possess a better prognosis. In our case the patient was first submitted to chemotheraphy, followed by surgical resection of tumor remnants and postoperative radiotherapy. It is important that cases of ONB are diagnosed as early as possible before expansion of the tumor and invasion of adjacent structures.

Many patients with ONB present with regional lymph node metastases (eg, stomatognathic system) at the time of diagnosis, a fact resulting in a poor prognosis. Metastases are generally a late event and usually involve the cervical lymph nodes. Lung metastases are observed in some cases. However, dissemination to more distant sites has been reported, for example, bone, liver, and breast. Chemotherapy is indicated for patients in advanced stages, who present with recurrence or metastases.

ONB is an uncommon malignant tumor whose clinical presentation and microscopic features might be confused with other diseases. Knowledge of the clinical-pathologic characteristics of ONB is important to establish a correct and early diagnosis, increasing the chances of cure. A delay in the recognition of ONB results in its diagnosis at a more advanced stage and consequent poorer prognosis, as well as a higher chance of recurrence, considering the destructive and metastatic potential of this tumor.

References


Table 2. DISTRIBUTION OF CASES OF ONB WITH INVASION OF MAXILLARY SINUS OR ORAL CAVITY REPORTED IN LITERATURE ACCORDING TO GENDER, AGE, AND LOCAL INVASION

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Gender</th>
<th>Age (yr)</th>
<th>Local Invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castañeda et al</td>
<td>1</td>
<td>M</td>
<td>16</td>
<td>Maxillary sinus</td>
</tr>
<tr>
<td>Myers et al</td>
<td>1</td>
<td>M</td>
<td>79</td>
<td>Oral cavity</td>
</tr>
<tr>
<td>Wei et al</td>
<td>1</td>
<td>F</td>
<td>15</td>
<td>Maxillary sinus</td>
</tr>
<tr>
<td>Unal et al</td>
<td>1</td>
<td>F</td>
<td>14</td>
<td>Maxillary sinus</td>
</tr>
<tr>
<td>Ferreira et al</td>
<td>1</td>
<td>F</td>
<td>72</td>
<td>Maxillary sinus</td>
</tr>
<tr>
<td>Caeiro et al</td>
<td>1</td>
<td>M</td>
<td>17</td>
<td>Maxillary sinus</td>
</tr>
<tr>
<td>Yu et al</td>
<td>6</td>
<td>M and F</td>
<td>15, 39, 47, and 59</td>
<td>Maxillary sinus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>38 and 55</td>
</tr>
<tr>
<td>Current study</td>
<td>1</td>
<td>M</td>
<td>03</td>
<td>Maxillary sinus and oral cavity</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; M, male.

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