CASE REPORT

Esthesioneuroblastoma: A case with prolonged disease control

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Abstract: Esthesioneuroblastoma, a rare tumor arising from the olfactory vault, varies from being indolent to extremely aggressive. Owing to its rarity, the diagnosis, staging, and treatment of the disease are not well defined. According to a number of small observational retrospective studies and case reports, the disease’s actual treatment involves surgery, radiotherapy, and/or chemotherapy (either as a single treatment or used in combination), depending on the disease’s staging. Optimal treatment has not been standardized, particularly regarding the role of chemotherapy. We describe a case of advanced esthesioneuroblastoma with prolonged disease control, subjected to a multimodal therapy with surgery, radiotherapy, and chemotherapy, illustrating the benefits of this approach in managing a patient with esthesioneuroblastoma. Herein, we analyze the most important and controversial issues of this type of neoplasia.

Keywords: esthesioneuroblastoma; nasal cavity; surgery; radiotherapy; chemotherapy


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Introduction

Esthesioneuroblastoma was first described by Berger and Luc[1] in 1924. It is a rare tumor, accounting for 1%–5% of all malignant neoplasms of the nasal cavity and only 1,400 cases have been described thus far, mostly in small retrospective series and case reports[2]. Owing to the heterogeneity and paucity of randomized data, there is no consensus on disease treatment and treatment mostly depends on tumor staging. Surgery, radiotherapy, and chemotherapy are the available options and can be used on their own or in combination. Chemotherapy is mostly reserved for the advanced disease stage; however, its real benefit is difficult to establish, especially in the neoadjuvant and adjuvant settings[3,4].

Herein, we describe a case of advanced esthesioneuroblastoma with prolonged disease control, of which the treatment was based on a multimodal approach with surgery, radiotherapy, and chemotherapy. In addition, we also analyze the most important and controversial issues of this type of neoplasia.

Ethics statement

All procedures were performed in accordance with the ethical standards of the Helsinki Declaration (1964, recently amended in 2013) of the World Medical Association.

Case report

A 35-year-old male with no relevant clinical background was referred to our institution in December 2010. An ethmoidal lesion was detected from a cranial-encephalic computed tomography (CE-CT) scan during an investigation of a four-month-long frontotemporal headache that was associated with vomiting, photophobia, and anosmia. Subsequently, a brain magnetic resonance imaging (B-MRI) scan was performed and it showed an ethmoidal mass invading the cribriform plate and the anterior cranial fossa (Figure 1), suggesting ethmoidal neoplasia. A staging cervico-thoracic CT (CT-CT) scan showed no metastasization.

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Figure 1. Brain magnetic resonance imaging during diagnosis. T1-weighted: (A) Axial slice; (B) Coronal slice; (C) Sagittal slice. Ethmoidal mass can be seen destroying the cribriform plate and invading the anterior cranial fossa.

A cranio-facial resection (CFR) was performed in January 2011 with a gross total resection. Histopathology was compatible with esthesioneuroblastoma, showing small-blue-round cells in a rosette formation. Immunohistochemistry was positive for synaptophysin and neuron-specific enolase (NSE) (Figure 2), and negative for chromogranin, S100, and cytokeratins.

Since the post-operative period was affected by S. pneumoniae meningitis complications, the patient only underwent complementary three-dimensional conformal radiotherapy in June 2011. The B-MRI reevaluation (Figure 3) and CT-CT scan in September 2011 showed no signs of recurrence and the patient remained in follow-up.

However, a cervico-thoraco-abdominal-CT scan done in January 2012 revealed multiple lung micronodules, as well as mediastinal and hilar adenopathies (with the longest diameter being approximately 5 cm) (Figure 4). The biopsy of the latter confirmed it as esthesioneuroblastoma metastasis. In March 2012, the patient started chemotherapy with cisplatin 80 mg/m² (day 1) + etoposide 100 mg/m² (day 1–3), Q21 days. After four cycles, the re-evaluated CT-CT scan showed the disappearance of the lung micronodules and a decrease of the mediastinal adenopathies, observation that are compatible with a partial response according to the Response Evaluation Criteria In Solid Tumors (RECIST) guide. In August 2012, we ran four additional cycles of CT-CT scan, generating evidence of a stable disease according to RECIST. At this point, chemotherapy was stopped and the patient has had a 45-month progression free survival (PFS) to date (Figures 5 and 6).
Figure 2. Photomicrographs. (A) Hematoxylin & Eosin (original magnification 400X): Small-blue-round cells with voluminous and hyperchromatic nuclei, with occasional rosettes; (B) Immunohistochemistry staining (original magnification 400X). (B1) Synaptophysin; (B2) NSE.

Figure 3. Brain magnetic resonance imaging two months after radiotherapy. T1-weighted: (A) Axial slice; (B) Coronal slice; (C) Sagittal slice. There is an absence of intracranial lesions with residual and stable inflammatory tissue in the ethmoidal cells.
Figure 4. Cervico-thoracic computed tomography (axial slices) at relapse (January 2012). Mediastinal adenopathies (A and B), hilar adenopathies (C), and lung micronodules (D).

Figure 5. Brain magnetic resonance imaging at last follow-up (February 2016). (A) Axial slice (T1-weighted); (B) Coronal slice (T2-weighted); (C) Sagittal slice (T2-weighted). There is no evidence of local recurrence.
Figure 6. Cervico-thoracic computed tomography at last follow-up (February 2016). Evidence of stable imagiological decrease of metastatic disease (A and B: Mediastinal adenopathies; C: Hilar adenopathies; D: Absence of lung micronodules).

Discussion

Esthesioneuroblastoma represents a rare tumor, accounting for 1%–5% of all malignant neoplasms of the nasal cavity[3,5,6]. It originates in the olfactory neuroepithelium, arising from embryonic olfactory placodes, and has a better prognosis than neuroendocrine neoplasm[5]. The tumor commonly appears as a mass in the upper nasal cavity in the cribiform plate region, originating from the lower nasal cavity within one of the paranasal sinuses[7,8], or intracranially with no intranasal component[3].

A population-based study over a 30-year period showed that this tumor affects both genders and can occur at any age, with a peak age between 40–70 year-old[9]. There is no specific symptomatology for esthesioneuroblastoma as delays ranging from 6 to 12 months between establishing symptoms and diagnosis have been reported[10]. The most frequent clinical manifestations are nasal obstruction (70%), epistaxis (46%), rhinorrhea, and headache. Anosmia, otalgia, and ocular pain are often present due to the neoplasm’s invasion to adjacent structures[2,3,11,12]. During its growth, it extends to the skull base and can spread to the brain or spinal cord. Cervical ganglia, lung, and bone are the main localities of metastasization.

Histology is essential for the diagnosis of esthesioneuroblastoma, characterized by small-blue-round cells in a rosette formation[13]. Differential diagnosis includes undifferentiated or neuroendocrine sinusal carcinomas, lymphoma, melanoma, Ewing sarcoma, and rhabdomyosarcoma. Immunohistochemistry is crucial, wherein esthesioneuroblastoma usually exhibits diffuse positivity for synaptophysin (65%), neuron-specific enulase (NSE), and less frequently, chromogranin. Results are negative for cytokeratins, epithelial membrane antigen, vimentin, desmin, UMB45, and leucoytic common antigen[3,5].

CT and MRI are essential tools to identify tumor staging; CT provides better information about bone invasion, along with local and distant metastatic spread[14] whereas MRI is useful for evaluating adjacent soft tissue structure invasion[15]. Staging is usually performed via the modified Kadish classification[4,16] (Table 1) and the Dulguerov-Calcaterra classification[3], based on the tumor-
node–metastasis (TNM) staging (Table 2). Esthesioneuroblastoma has a typical initial slow growth, mostly in the nasal cavity or perinasal sinus, thus contributing to its frequent diagnosis at advanced stages. This is illustrated by the results of a population-based study where only 17% of the staged patients had the disease confined to the nasal cavity (Kadish A), 54% had local disease beyond the nasal cavity (Kadish B and C), and 29% had regional or distant metastasis (Kadish D). Our case showed a locally advanced disease at the point of diagnosis (Kadish C) after a four-month symptomatic period, which is in line with the majority of cases described.

### Table 2. Dulguerov-Calcaterra staging system

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor involving the nasal cavity and/or paranasal sinuses (excluding sphenoid), sparing the most superior or ethmoidal cells</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor involving the nasal cavity and/or paranasal sinuses (including the sphenoid) with extension to or erosion of the cribriform plate</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor extending into the orbit or protruding into the anterior cranial fossa</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor involving the brain</td>
</tr>
<tr>
<td>N0</td>
<td>No cervical lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Any form of cervical lymph node metastasis</td>
</tr>
<tr>
<td>M0</td>
<td>No metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present</td>
</tr>
</tbody>
</table>

The biological behavior of esthesioneuroblastoma varies between indolence and extremely aggressive, with a five-year overall survival (5y-OS) of 45%–70%. Advanced Kadish stage tumors, intracranial extension, cervical metastasization, and positive resected margins have been identified as negative prognostic factors. In a localized disease, the mainstay treatment is surgery, followed by radiotherapy. This is supported by several studies that demonstrated superior outcomes for this combined approach when compared to just undergoing surgery or radiotherapy alone. In the meta-analysis by Dulguerov et al., patients treated by surgery and radiotherapy had a 5y-OS of 65%. In contrast, patients treated only with surgery or radiotherapy had a 5y-OS of 48% and 37%, respectively. This combination is particularly useful in managing locally advanced disease (Kadish C) and that with positive margins. Currently, a combined craniofacial approach that allows en bloc resection is usually performed, offering better local control and survival compared to a unique transfacial approach. Standard radiotherapy dosage is between 55–65 Gy, preferably introduced with intensity modulated radiotherapy techniques, in order to minimize toxicity to adjacent structures. Patients showing positive diagnosis of the lymph nodes have worse 5y-OS rate at 29% versus 64% for patients with no cervical lymph-node metastasis. Thus, nodal dissection and radiotherapy should be considered for patients with cervical metastasis. Prophylactic irradiation of cervical nodes is still a point of controversy; 14%–33% of patients develop cervical metastasis in the course of the disease, but there are no randomized data for this approach and salvage therapy. Proton beam therapy could be an option, particularly when higher doses are needed or the involved structures are quite close to each other. Our patient did not undergo cervical prophylactic irradiation. Interestingly, he relapsed with lung and ganglionar mediastinical metastasis without any cervical evidence, which were topographically expected. Biopsy is important to confirm the metastasis of esthesioneuroblastoma.

Chemotherapy is usually reserved for advanced stages of the disease. To improve the outcome, chemotherapy has been used in neoadjuvant and adjuvant treatments of locally advanced tumors; however, the survival data reflecting the outcome of chemotherapy are variable and chemotherapy’s additional benefit, compared to just undergoing surgery or radiotherapy alone, remains uncertain. In a study reported by a group from the University of Virginia, patients with Kadish stage C received preoperative sequential chemotherapy (two cycles of vincristine + cyclophosphamide ± doxorubicin) and radiation therapy, followed by craniofacial resection. The 5- and 15-year survival rates reported for this group were 72% and 60%, respectively, which are similar to other values reported without the use of chemotherapy. There is limited experience in the metastatic setting owing to the rarity of this subset of patients. The types of schedules and the optimal duration of treatment have also not been determined. Analogous to other related neuroendocrine tumors, cisplatin-based schedules (mainly associated with etoposide) are most frequently used. The use of non-platinum combinations such as irinotecan + docetaxel or doxorubicin + ifosfamide + vincristine have also been reported. In our patient,
after an early relapse six months after the end of the initial treatment, a palliative chemotherapy with cisplatin + etoposide was performed, with an imagiological partial response after four cycles. Thereafter, four more cycles were performed with evidence of a stable disease. After achieving an optimal response, we decided to withdraw the chemotherapy treatment and the patient remains under follow-up without disease progression.

**Conclusion**

Our patient represents an advanced case of esthesioneuroblastoma (Kadish C) and was treated with a surgery and radiotherapy combination approach to afford prolonged disease control, despite an almost six-months delay between the two treatment approaches (due to an infectious complication). After an early relapse with distant metastasis, chemotherapy performance seemed to have been preponderant in the disease control and contributed to the longer PFS. Our case reinforces the importance of a multimodal approach in managing esthesioneuroblastoma, especially regarding the use of chemotherapy in recurrent disease.

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**Conflict of interest**

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

**References**


