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Case Report

Esthesioneuroblastoma presenting as diplopia and proptosis in a young female patient. Case report and review of the literature

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Esthesioneuroblastoma is a rare, primary sinonasal malignant tumor with an incidence between 3%-6% of all the sinonasal malignancies and estimated occurrence rate of 4 in 10 million individuals. We report the case of a 36 years old female patient admitted for progressive lower gaze diplopia and proptosis, diagnosed using Computer Tomography (CT), Magnetic Resonance Imaging (MRI) and histopathology examination with highly differentiated grade C esthesioneuroblastoma. Treatment included total surgical removal via endonasal approach and adjuvant radiotherapy with good prognostic. Diplopia and proptosis are rare presentations of esthesioneuroblastomas; a biopsy should always be performed in case of a nasosinusal infiltrating tumor. The current staging system, Kadish and Hyam's scales proved to be useful instruments in choosing the appropriate treatment and also in predicting the survival rate of these patients. Long-term follow-up is mandatory due to the extended interval for disease recurrence, sometimes up to 10 years since the diagnosis.

Keywords: esthesioneuroblastoma, sinonasal malignant tumor, diplopia, proptosis, chronic sinusitis, endoscopic nasal surgery, Kadish scale, Hyam's scale

INTRODUCTION

Esthesioneuroblastoma, also known as olfactory neuroblastoma, is a rare, primary sinonasal malignant tumor of neuroectodermal origin, developing from the basal cells of the upper nasal cavity olfactory epithelium. Recent studies report its incidence to be between 3%-6%

of all the sinonasal malignancies with two age group peaks, in the 1-2 decades and 5-6 decades of life, without proven sex difference and an occurrence rate of 4 in 10 million individuals (Barnes, 2005).

Since it was first described in 1924, approximately 1200 cases were diagnosed with more than 80% being described in the last 25 years.

Because of its anatomical location, patients usually present nonspecific symptoms including unilateral nasal obstruction (70%), epistaxis (50%), anosmia, rhinorrhoea, facial pain, headache, hyperlacrimation, in most cases

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Figure 1. Head Computer Tomography showing a soft tissue structured proliferative process located in the right nasal cavity extending through the bone hiatus and invading the right maxillary sinus, and eroding the nasal septum.

initially leading to consider this as paranasal benign disease and delaying the diagnosis. In very rare cases it presents with exophthalmos and visual disturbances when there is invasion through the cribriform plate in the anterior skull structures.

Histological findings divide this tumor into low- and high-grade esthesioneuroblastoma with an aggressive, uncontrolled growth of the latter, capable of rapid widespread metastasis through hematogenous and lymphatic routes, disseminating to the lungs and bones (Malouf et al., 2013).

There are no class I treatment guidelines for managing this malignant tumor but small sized studies have shown superior results in patients that underwent surgical resection and radiotherapy. Although a recent review of the literature published in 2010 questions these results,

showing no superiority in associating these therapies, the current management of most cases includes both treatments, with chemotherapy association in recurrent or high-grade cases (Kane et al., 2010).

CASE PRESENTATION

We report the case of a 36 years old female patient who was admitted in our clinic for progressive lower gaze diplopia which started within the last 14 days. She was also complaining about progressive nasal obstruction and rhinorrhea in the past year and hyperlacrimation in the last 5 months. She had a history of chronic sinusitis and considered these as being a relapse of her sinusitis thus postponing an appointment to the physician.

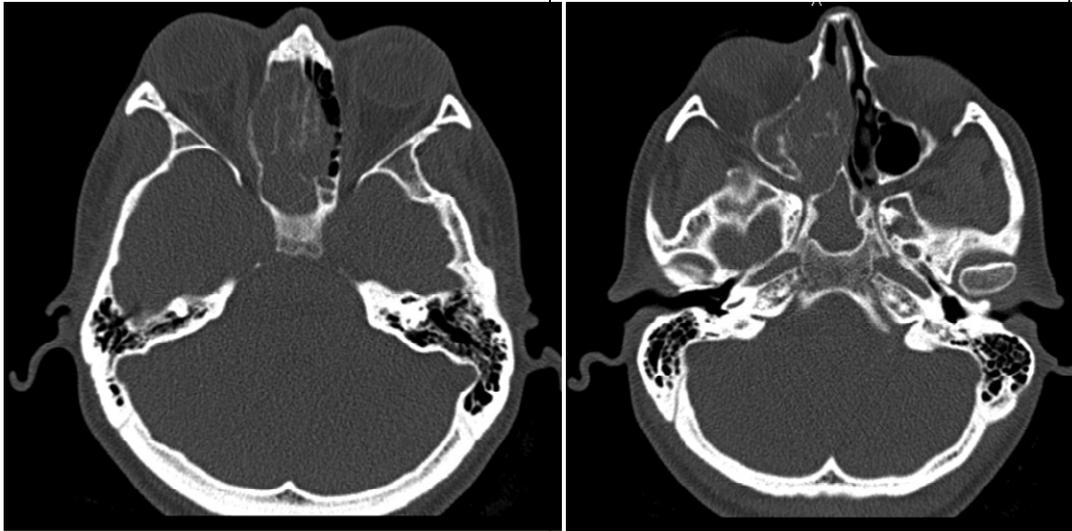


Figure 2,3. Head Computer Tomography showing a soft tissue structured proliferative process located in the ethmoid extending towards the right superior posterior orbital cavity eroding the lamina papyracea.

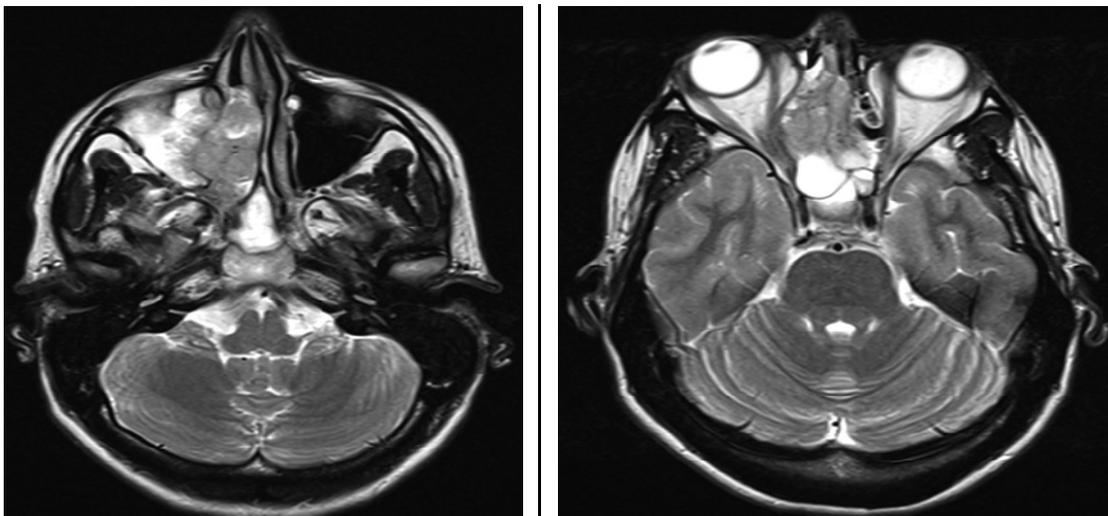


Figure 4,5. Cerebral MRI, transverse T2 sequence, revealing a space occupying lesion located in the mid-half of the right maxillary sinus with extension through the bone hiatus towards the middle meatus, right nasal cavity, invasion of the right ethmoid. The lamina papyracea is bulged by the lesion on its right side and exceeds it toward the superior orbit having small buds insertions that come in contact with the posterior pole of the superior oblique muscle.

The neurological exam revealed anosmia in her right nostril, hyposmia on the left side, lower gaze diplopia, limited adduction of the right eye, right proptosis, with no other neurological deficits and no superficial adenopathies at the clinical examination.

A head Computer Tomography (CT) scan was initially performed showing right nasal cavity mass lesion extending to her right maxillary sinus, ethmoid and eroding the cribriform plate with right superior orbital invasion. There were osteolytic lesions of the ethmoid bone and partial destruction of the nasal septum.

A head Magnetic Resonance Imaging (MRI) was also performed to complete the imagistic work-up. This

showed right nasosinusal proliferating process with extension through the nasal septum, the paramedian and left ethmoidal cells, through the cribriform plate (extradural, the right olfactory bulb could not be identified), and through the papyracea lamina in the right orbit, coming in close contact with the right superior oblique muscle. No signs of cerebral spinal fluid (CSF) fistula were visible, although a small fistulous path could not be excluded because the proliferating process came in close relation with the olfactory bulb and dura mater. There were no signs of cerebral oedema or any other meningoencephalitic abnormalities. No adenopathies were detected.

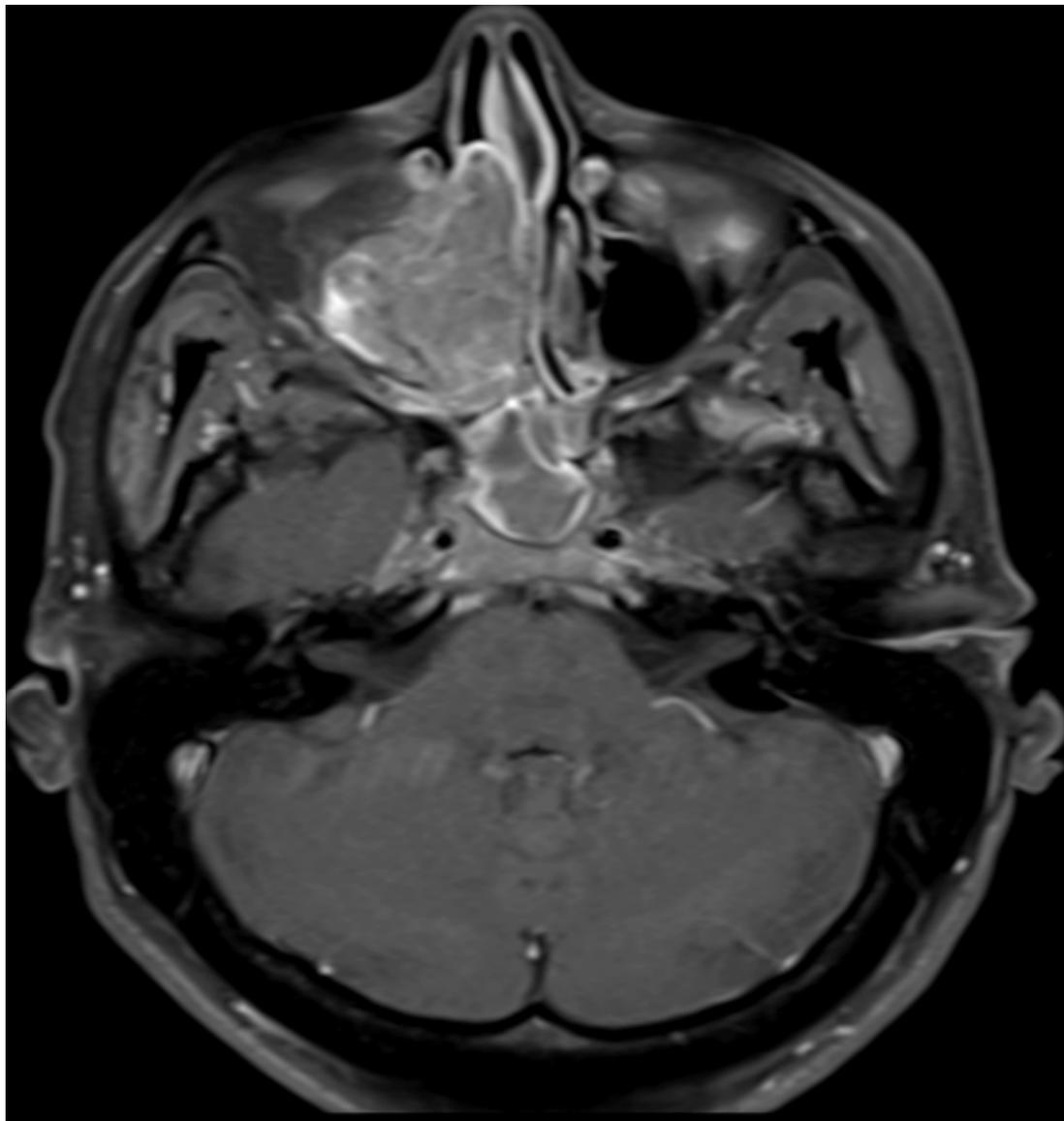


Figure 6. Cerebral MRI with transverse section T1 weighted image with contrast enhancing lesion located in the right nasal cavity extending towards the right maxillary sinus, with disorganized lobular structure.

At this stage, based on clinical and imagistic studies, the tumor aspect suggested an inverted papilloma or an esthesioneuroblastoma, but in order to reach a diagnosis, histopathology examination was required.

The histopathology exam showed a well-differentiated tumor, with no necrosis and no mitoses identified, with no distinguishable rosettes and neurofibrillar stroma. The tumor cells were completely positive for Synaptophysin (+) and Chromogranin A (+), S100+/- (flecking), AE1/3-, Neurofilament (+) positive in the sparse places of neurofibrillary matrix. Cytokeratin flagged the tumor cells only very flimsily. The proliferation marker had a low value (< 1%, ki 67) and lymphoma, melanoma, inverted papilloma of rhinal mucosa or hypophyseal adenoma were ruled out.

These findings suggested a well-differentiated esthesioneuroblastoma but a histological staging was impossible with the obtained tissue.

She was referred to a neurosurgical clinic with experience in the management of this type of tumor, where a multidisciplinary team (Ear-Nose-Throat Specialist, Oro-Maxillo-Facial Specialist and Neurosurgeon) performed an endoscopic transnasal complete tumorectomy. The intraoperative MRI confirmed the complete tumor resection.

No signs of complications were present during the post-op period and the patient could leave the hospital within 10 days.

A radiotherapy (RT) plan was also established; it included 30 sessions of RT that accounted for 60 Gy.

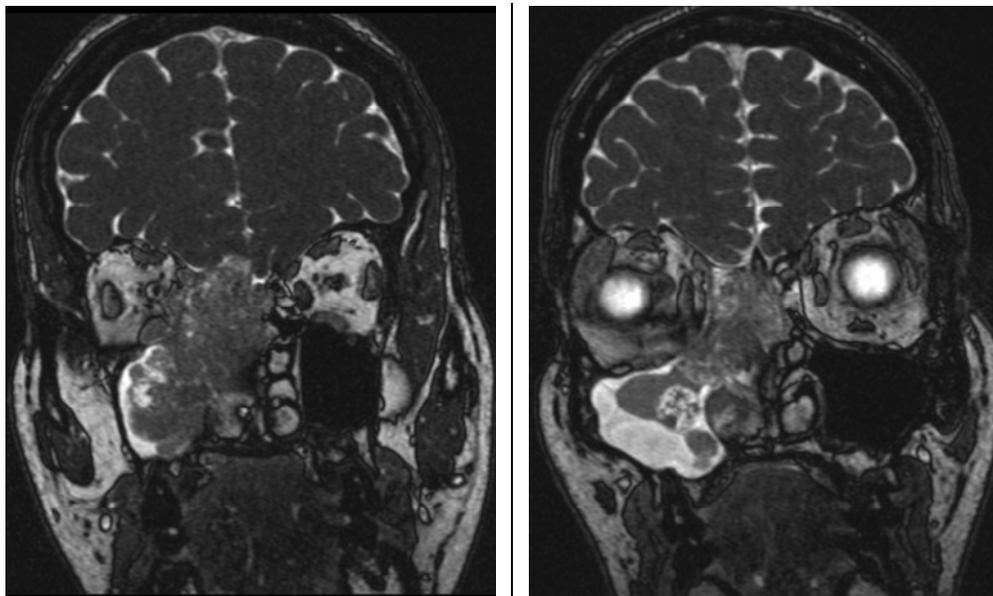


Figure 7,8. Cerebral MRI, coronal T2 weighted image, with the same appearance described before, eroding the cribriform plate, forming a 10 mm bone hiatus at the same level and inserting small intracranial extradural buds, without further identification of the right olfactory bulb. The left olfactory bulb is visible but slightly flattened by the proliferating process that exceeds the midline in the superior ethmoid. The whole space-occupying lesion measures 60mm in craniocaudal diameter, from the right alveolar maxilla floor towards the intracranial extension through the cribriform plate.

We reevaluated the patient one month after finishing radiotherapy; a fibroscopy showed no local signs of tumor recurrence, there was no exophthalmos, and the patient had no neurological deficits besides the right nostril anosmia.

DISCUSSION

The patient, a young female, presented with an infiltrating, proliferating process which invaded the right cranio-nasal and orbital cavities with MRI study suggestive for an inverted papilloma or esthesioneuroblastoma.

In this context a histopathology exam was mandatory for diagnosis - the result concluded that the tumor was indeed a highly differentiated olfactory neuroblastoma, but the Hyam's staging could not be determined due to the low quality of the biopsy specimen. The histological exam also ruled out squamous cell carcinoma, adenocarcinoma, sinonasal undifferentiated carcinoma, hemangioma, melanoma or metastasis, which should be considered for differential diagnosis.

Two scales are currently used for classification and prognosis evaluation of esthesioneuroblastomas. The Kadish scale that is based on the tumor's clinical and imaging aspect and Hyam's scale which is centered on histological and Immunohistochemistry (IHC) analysis.

The Kadish staging has three grades, marked with A, B, and C, representing imagistic findings of tumor

infiltration in the sinus, paranasal sinuses, or extending beyond the horizontal lamina.

In our case, the Kadish scale was C, corresponding to extension beyond the nasal cavity and paranasal sinuses.

Review of the literature data revealed three types of possible direct intracranial extension for olfactory neuroblastomas: cranio-nasal-communicating, orbital-nasal-communicating and cranio-orbital-nasal-communicating tumor (Yu et al., 2009), the latter corresponding to our case.

The Hyam's criteria takes into consideration the histological appearance (lobular architecture, mitotic activity, nuclear pleomorphism, presence of rosettes and grade of necrosis) and IHC analysis, dividing esthesioneuroblastomas into low- and high-grade tumors. First and second stages correspond to the low-grade and have a more benign course, while stages three and four to high-grades with a very aggressive course (Malouf et al., 2013).

Currently, due to the rarity and different extension patterns, esthesioneuroblastomas have no class I treatment recommendations, this resulting in a multitude of treatment regimens including surgery, radiotherapy, or chemotherapy alone, as well as multimodal approaches with combined therapies.

Currently there are two published meta-analysis (2001, 2010) that attempted to review and determine the appropriate treatment, demonstrating no statistically significant difference between surgery alone and surgery

with adjuvant radiotherapy in the case of low-grade tumors (Dulguerov et al., 2001; Kane et al., 2010).

However, the preferred treatment approach combines surgical excision followed by adjuvant radiotherapy (the recurrence rate being lower in the cases treated with both). Additional smaller series from single institutions also concluded that this multimodal approach is the preferred treatment (Argiris et al., 2003; Bachar et al., 2008; Constantinidis et al., 2004; Morita et al., 1993; Ow et al., 2014; Hollen et al., 2013; Platek et al., 2011; Diaz et al., 2005).

Chemotherapy is indicated in cases of high-grade tumors, recurrent or unresectable esthesioneuroblastomas, using different treatment regimens based on clinical experience. (Loy et al., 2006; Porter et al., 2008; McElroy Jr et al., 1998; Kimm et al., 2007; Ow et al., 2014; Herr et al., 2014)

Tumors' anatomical location and extension to the anterior skull structures required developing of multiple surgical approaches. Recent studies suggest no significant difference between open and endoscopic approaches as long as oncological surgical safety principles are obtained, with superior cosmetic results for the latter. Expanded endonasal endoscopic procedures combined with craniotomy are used in cases with major extension (Song et al., 2012; McLean et al., 2007).

In the presented case the multimodal treatment approach was preferred, combining curative excision with nasal endoscopic surgery and adjuvant radiotherapy using a total dose of 60 Gy.

The majority of patients treated with adjuvant radiotherapy in esthesioneuroblastomas receive doses between 50-65 Gy, which are considered to be the highest tolerated doses for the sensible nearby anatomical structures (Kane et al., 2010).

Case studies showed a recurrence rate between 14%-30% at 2 years after diagnosis, an increase to 50% at 5 years and occurrence even after 10 years but with slightly lower incidence in radiotherapy treated patients (Zhang et al., 2010; Gore et al., 2009; Dulguerov et al., 2001; Nakao et al., 2003).

Review of most case series concluded that between 15%- 22% patients had lymph node invasion at the time of the initial diagnosis, this being an important prognostic factor in determining the 5-year survival rate. In the N0 group the survival rate was 64% at 5 years interval, while the N1 stage to 29% survival rate for the same time span (Kane et al., 2010).

To conclude, using an individualized approach based on tumor histopathology, tumor extension and lymph node invasion provides a comprehensive way to determine prognosis and selection of patients that would benefit from aggressive adjuvant treatments.

As mentioned, the present patient with highly differentiated grade C Kadish grading, no lymph nodes invasion and treated with endoscopic resection and adjuvant radiotherapy has a good overall prognosis.

Nevertheless, extensive follow-up is mandatory; we agreed on re-evaluating the patient on a clinical and paraclinical basis according to the following plan: ENT evaluation every 3 months with endonasal fibroscopy in the first year, MRI scan every 6 months for the next 2 years and complete annual reevaluation was recommended afterwards for the next 8 years.

CONCLUSION

We reported a case of esthesioneuroblastoma associated with proptosis and diplopia in a young female patient that had a history of chronic sinusitis and preceding symptoms that were disregarded as sinusitis recurrence.

Thorough clinical and paraclinical investigations are needed to correctly diagnose and treat the patient; esthesioneuroblastoma should be taken into consideration and a biopsy performed in cases presenting with an infiltrating nasosinus tumor.

The Kadish and Hyam's staging system, lymph node status and treatment modality are decisive in choosing the appropriate approach and also in predicting the survival rate in these patients.

Long-term follow-up is mandatory due to the extended interval for disease recurrence, in reported cases even after 10 years since the diagnosis.

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