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Esthesioneuroblastoma

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Abstract

Introduction: Esthesioneuroblastoma (ENB) is a rare malignant tumor developed at the expense ofthe neural-olfactory epithelium, and it is among the rarest cancer of nasal cavity. It is usually manifested by rhinological symptoms, the ocular damage may be inaugural or appears during the evolution of the secondary orbital damage. Computed tomography and magnetic resonance imaging allow a very precise general and loco-regional assessment. The diagnosis is anatomo -pathological .and treatment usually relies on surgery and radiotherapy

Materials and Methods: retrospective study of 12 cases within ENT department of the CHU HASSAN II of FEZ over a .period of 15 years

Results: The average age of our patients was 45 years without gender predominance. The average consultation period was 8 months. Rhinosinus syndrome was the predominant clinical symptom, sometimes associated with ophthalmologic or neurological symptoms. All the patients benefited from a radiological assessment which allows to objetify the tumor as well as its locoregional extensions. Four cases of intracranial expansion have been detected. Of the 12 cases, 10 patients received surgical treatment (either endonasal removal for six patients, combined way for three patients, or external way (paralateronasal type of Moure) forone patient) followed by complementary radiotherapy. Evolution has been satisfactory. In the remaining 2 cases, treatment was only palliative (chemotherapy or radiotherapy) due to the extension of the tumor

.

Conclusion: Esthesioneuroblastoma (ENB) is a rare tumour, first described by Berger in 1924; it mainly affects men and usually occurs during the second and third decades. Clinicaly , it's revealed most often by rhinological symptoms (uniform or bilateral nasal obstruction, epistaxis, anosmia). Neurological symptoms are common and ophthalmologic manifestations, such as exophthalmia, reflect tumor extension into the orbital. The diagnosis can only be made by anatomopathology. Treatment is based on surgical removal combined with radiochemotherapy.

Keywords: Esthesioney\uroblastoma; Nasal Obstruction; Epist axis; Surgery; Radiotherapy

Introduction

Esthesioneuroblastoma or olfactory neuroblastoma is a rare malignant tumor of the nasal cavities, developed at the expense of the olfactory epithelium [1,2]. Since its first description by Berger and Luc in 1924 as olfactory esthesioneuroepitheluim [3]. Limited series have been reported in the literature reflecting the difficulties of the diagnosis.

Through a retrospective study from January 2004 to December 2019, we will analyze a series of 12 patients with esthesioneuroblastoma who were collected at the ENT department of the CHU Hassan II of Fez.

The objective of our work is to study the different epidemiological, clinical and therapeutic parameters of this disease, and then we will use the literature as a foundation to make the point of the etiopathogenic hypotheses, the diagnostic means and the therapeutic modalities available to us for the management of these tumors.

Materials and Methods

This is a retrospective study spanning 15 years within the time frame of 2004 and 2019, involving 12 patients from the ENT department of the CHU Hassan II of Fez. Cases included in our study are men and women of different ages, who have been seen and treated for esthesioneuroblastoma at the ENT department of the CHU Hassan II of Fez.

Results

Between 2004 and 2019, we had the opportunity to treat 12 cases of esthesioneuroblastoma. There were 5 men and 7 women. The patient's age ranged from 26 to 70 years with a mean of 48 years. The average consultation period was 8 months with extremes ranging from 2 months to 14 months. Almost all the patients showed symptoms of nasal obstruction and epistaxis followed by anosmia, face swelling and Rhinorhea in half of the cases. On the other hand, ophthalmologic signs were observed in three cases.

Clinical examination via the Endoscopy revealed the tumor and allowed us to do the biopsy which confirmed the diagnosis.

The radiological assessment (CT and/or MRI) revealed the tumor and its loco-regional extensions. Two cases of intracranial expansion have been identified.

An extension assessment has been realized for all our patients to establish a TNM classification: the majority of the cases had tumors classified between T2 and T3 (6 cases), 2 cases classified as T1 and 4 cases as T4. Cervical lymphadenopathy was found in 2 cases and distant metastases in only one case.

Of the 12 cases, 10 patients received curative treatment (first surgery followed by radiotherapy of 50-60Gy) using either the endonasal way for 6 patients, paralateronasal of Moure way for only onepatient or combined wayfor 3 patients. For the other 2 patients the lesion was invading adjacent structure, and they have benefited of palliative treatment: chemotherapy included cyclophosphamide (650 mg/m2) with vincristine (1. 5 mg/m2 with a maximum dose of 2 mg/m2).

The majority of patients have progressed well after five years of decline.

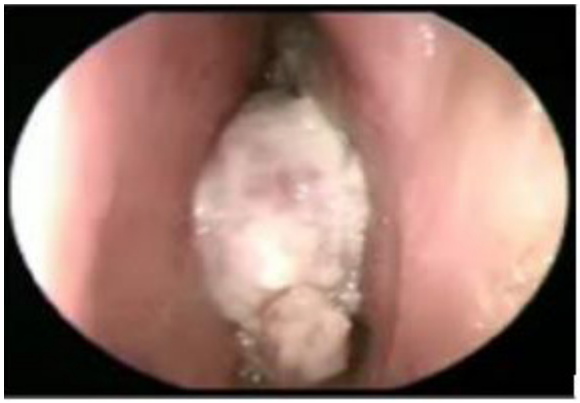

Figure 1: Endoscopic aspect of a budding process of the left FN. (Iconography of the service)

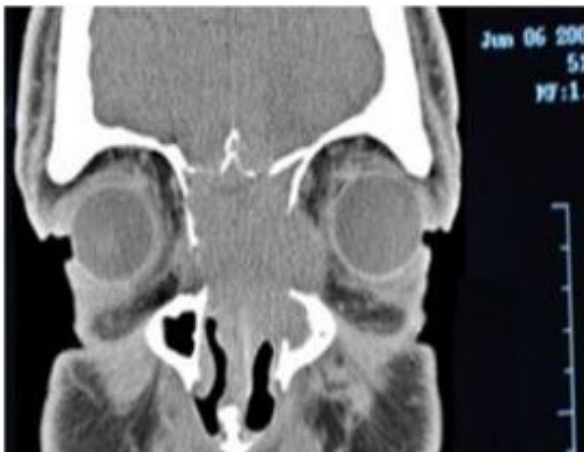

Figure 2: axial facial CT showing left naso-ethmoidal heterogeneous process and tissue density with endocranial extension and towards the homolateral orbit. (Iconography of the service)

case	age	Gender	Presenting symptoms	TNM classification	treatment	**Evolution** (5-year follow-up)
1	51	M	-nasal obstruction. -Epistaxis, anosmia. - Headaches.	T4N1M0	Palliative chemotherapy. (cyclophosphamide-vincristine)	Died after the 2nd cure of chemotherapy
2	65	F	-Nasal obstruction. -Epistaxis, anosmia.	T2N0M0	Tumor resection by endoscopic endonasal approach (EEA), followed by radiotherapy additional 50 Gy	Comptete Clinical and radiological remission
3	50	M	-Nasal obstruction. -Rhinorhea, Epitais	T3N0M0	Tumor resection by EEA followed by radiotherapy.	Complete remission.
4	63	M	-nasal obstruction. -Epistaxis -Tumefaction of the right hemiface.	T4N1M1	Palliative chemotherapy. (cyclophosphamide - vincristine)	Died 2 months after starting treatment.
5	35	F	-nasal obstruction. -anosmia, epistaxis. -Headaches.	T3N0M0	Surgical resection by Paralateral nasal pathway + external radiotherapy.	Good clinical evolution
6	40	F	-nasal obstruction. -decrease in visual acuity. (DVA) -Epistaxis.	T2N0M0	Surgical resection by EEA	Good clinical evolution
7	26	f	.nasal obstruction- .Epistaxis- .Exophthalmia-	T3N0M0	Surgical resection by EEA followed by radio- .therapy	Good clinical evolution
8	40	H	.nasal obstruction- Epistaxis- Exophthalmia- DVA-	T4N0M0	Combined tumor resection followed by complementary radiotherapy ((60 Gy	Good evolution on a current follow-up of 2 .years

9	60	f	.Nasal obstruction-Epistaxis-	T1N0M0	Surgical resection by EEA	Complete remission
10	70	H	.Nasal obstruction-Epistaxis-rhinorrhea-Exophthalmia	T3N0M0	Combined tumor resection followed by complementary radiotherapy	No recurrence on a follow-up of 18-month.
11	40	f	.Nasal obstruction-Epistaxis-	T1N0M0	Surgical resection by EEA	Complete remission
12	54	f	.Nasal obstruction-.Epistaxis-.anosmia-DVA-	T3N0M0	Combined tumor resection followed by complementary radiotherapy	Complete Clinical and radiological remission

Discussion

Esthesioneuroblastoma is a rare tumor which represents 3% of all nasal tumors [2, 4]. In almost all published series, the authors report a small number of patients treated in the same institution, and the dispersion of these cases over time (often over a long period of time). It is a tumor that occurs at all ages with 2 frequency peaks, one between 11 and 20 years, the other between 50 and 60 years. It affects both sexes with a slight male predominance.

Authors	Number of cases / Number of years	Age/ extremes of ages	Sex ratio (H/F)
NAKAGAWA [5]	22 cases over 8 years	49 years (27-83)	10/12
GAYE [6]	12 cases over 7 years	20 years (11-66)	7/5
LAPIERRE [7]	10 cases over 12 years	56 years (32-83)	7/3
CHAHED [8]	3 cases over 10 years	54 years (23-85)	1/2
KERMANI [9]	7 cases over 26 years	36 years (11-63)	2/5
Our study	12 cases over 15 years	48 years (26-70)	5/7

Histopathogenism of esthesioneuoblastomas is little known although Volrath and Altmannsberger may have induced neurofactory tumors using nitrosamines [6, 10]. The role of viruses, especially adenoviruses, is not clearly established in their carcinogenesis. However, on tumors developed spontaneously in cats, viral sequences have been found in the genome of tumor cells [10].

In a study analyzing the cytogenetic characterization of one case, numerous chromosomal aberrations were reported mainly involving chromosomes 2q, 5, 6q, 17, 19, 21q and 22, as well as Trisomy 8 [11]. Another study reported the presence of deletion of chromosomes 1p, 3p/q, 9p and 10p/q and amplifications of 17q, 17p13, 20p and 22q [12].

Ethesioneuroblastoma etiopathogenesis makes us discuss their membership in the PNET (Peripheral Neuro-Ectodermal Tumors) family to be discussed because of the frequency of T (11.22) translocation reported in Ewing's sarcoma [13].

The clinical manifestations of Ethesioneuroblastoma can't claim any sign of its own, especially since several symptoms can be associated, and often reflect an extensive intranasal process [10, 14, 15]. A well-conducted clinical examination of the ENT sphere is required to establish an early diagnosis.

Clinical Presentation

Clinical signs are dominated by either nasosinus symptoms or by objectifying the externalization of the lesional process beyond the nasosinus cavities. The fortuitous discovery on systematic histological analysis of a polypectomy is rare.Cervical lymphadenopathy is exceptional [4, 16, 17]

The symptoms are often late and especially not spe-

cific to a malignant process. Their banal nature and the high frequency of inflammatory or infectious pathologies of the nasosinus cavities explain that the diagnosis of these tumors is often suspected in the presence of fortuitously based on imagery [16,18]. Because of these non specific symptoms, certain characteristics must be taken into consideration: the one-sidedness, at least at the beginning, and the age of the manifestations that progressively lead to a worsening of the symptoms.

The esthesioneuroblastoma is characterized by high clinical variability and manifests itself in 3/4 of cases as ENT call signs [19, 20]. Eye signs are associated in 11% of cases [13, 19].

The CT/MRI pair allows the precise assessment of tumor extension. Indeed, MRI is crucial to clarify orbital and endocranial extension and also to differentiate between tumor mass and inflammatory retention. In advanced forms, the MRI aspect is a dumbell-shaped tissue process centred in the upper nasal cavity and extending into the intracranial [21,22].

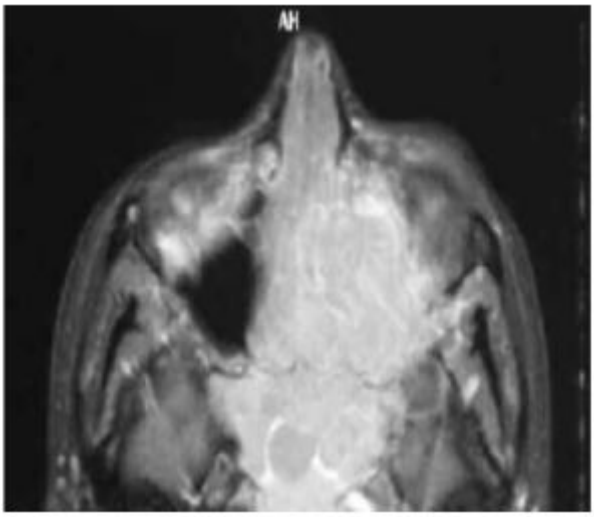

Figure 3: MRI T1 with gadolinium: large mass located in nasal fossas. Spreading to the left maxilla sinus invading the left orbit. Spreading to the anterior portion of skull base. Involvement Affectation of inferior orbital fissure and right cavernous sinus. [23]

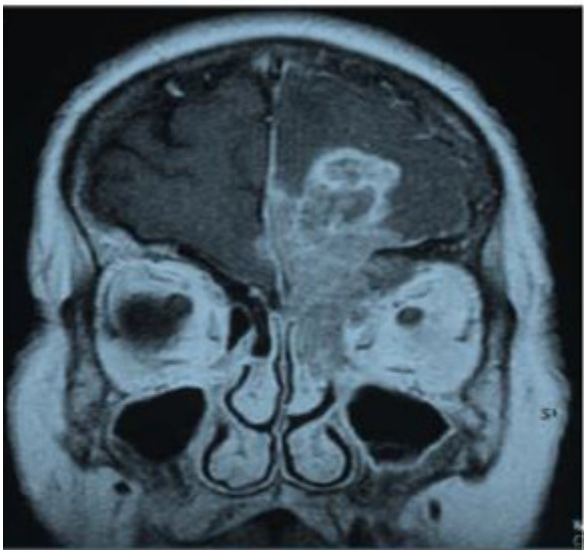

Figure 4: MRI T1 with gadolinium: Intrasinusal solid mass (left side) with extensionspreading to anterior cerebral fossa. [23]

Based on the extension, Kadish proposed (in 1976) a classification with three clinical stages [24]:

-Stage A: Tumor limited to the nasal cavity.
-Stage B: Tumour limited to the nasal cavity and sinuses.
-Stage C: Tumour extended beyond the nasal cavities and sinuses.

This classification was modified by Morita in 1993 [25] More recently Dulguerov [26] proposed a more accurate classification based on the TNM classification and using CT and MRI:

- T1: Tumor involving the nasal cavity and/or paranasal sinuses (excluding sphenoid), sparing the most superior ethmoidal cells.
- T2: Tumor involving the nasal cavity and/or paranasal sinuses (including the sphenoid), with/without extension to or erosion of cribiform.
- T3: Tumor extending into orbit or protruding into anterior cranial fossa, with/without dural invasion.
- T4: Tumor involving the brain.

Pathology

The histopathological aspect of esthesioneuroblastoma may be confusing with some small cell naso-sinusal tumors, especially in less differentiated forms. Immunohistochemistry is therefore a great help. In differentiated forms, the histological study shows lobules separated by conjunctivo-vascular partitions. Small to medium tumor cells have most often a roundnucleated nucleus and a clearly visible chromatin. The cytoplasm, which is not very abundant or moderately abundant, is poorly limited. Mitotic activity is highly variable [24, 27, 28]. Less frequently, the tumor is poorly differentiated, made up of diffuse layers of lymphocytoid cells, the tumor stroma is not very abondant and contains a prominent capillary network. The existence of a fibrillar fund -cytoplasmic, Flexner rosettes or Homer pseudorosettes -Wright (HW) is very revealing [29]. Hyams described a 4-grade histopathological classification system that relies primarily on the level of cell differentiation, the presence of neuronal stroma, the number of mitosis and the degree of necrosis (Table I [30]).

Grade	Lobular architecture preservation	Mitotic index	Nuclear polymorphism	Fibrillary matrix	Rosettes	Necrosis
I	+	None	None	Prominent	HW rosettes	None
II	+	Low	Moderate	Present	HW rosettes	None
III	+/-	Moderate	Prominent	Present	FW rosettes	Rare
IV	+/-	High	Marked	Absent	None	Frequent

HW: Homer Wright; FW: Flexner–Wintersteiner.

[**Table 1:** The Hyams histological grading system: HW rosettes, FW rosettes [30

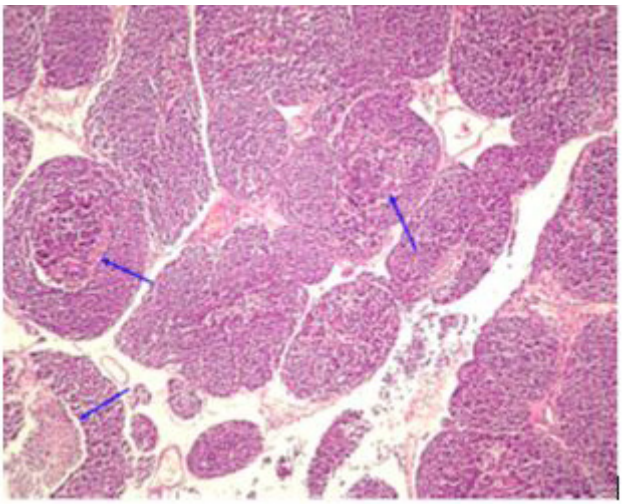

Figure 5: General appearance of the tumor. The cells are arranged according to a lobular pattern, separated by loose fibrovascular fibers. Necroses are visible in same central lobules (arrows) [29]

Treatment

Due to the rarity of esthesioneuroblastomas, the main source of assistance in making therapeutic decisions is the analysis of the results obtained by the authors who published their cases [30, 31, 32].

There is no standardized management of these tumors. The difficulty in establishing a better therapeutic strategy relies mainly in the small number of patients treated in the same institution, and in the dispersion of these cases over time (often over a long period of more than 20 years), which leads to a heterogeneous results [32,33].

Traditional treatment strategies are based on surgery or radiation therapy as single or combined modalities. More recently, chemotherapy has been introduced into the therapeutic arsenal of these tumours. Although there is a favourable consensus on the need for surgery, there is no agreement on the most appropriate surgical technique or on the use of complementary therapeutic methods [33, 34].

There is no standard surgical approach, however, there are two objectives: On the one hand, the possibility of controlling the entire anatomical limits of the tumor and the screened blade; On the other hand, carrying out a truly carcinological removal in monobloc, avoiding if possible Tumor fragmentation or excision by fragmentation [30]. There are basically three approaches: craniofacial, transfacial, and currently endonasal surgery is increasingly being used mainly in Kadish stages A and B [35]. The first surgical pathway is either transfacial performing a paralatero-nasal rhinotomy (for Kadish stages A and B), or by the upper subfrontal way if the base of the skull is reached [35, 36].

In the case of an orbital extension, attitudes are extremely nuanced, but most surgical teams are currently conservative towards the eyeball; due to the lack of significant differences in survival or recurrence rates when exempted. Esthesioneuroblastoma has a high local failure rate. As a result, most institutions have adopted surgical resection followed by postoperative radiation therapy as a standard treatment approach [35].

Postoperative radiation therapy has been shown to improve local disease control. However, for early-stage disease (Kadish A) with negative resection margins, the role of postoperative radiation is still questionable and surgery alone may be sufficient [37, 38]. The dose of radiation therapy used usually ranges from 55 to 65 Gy [39]. Due to the complexity of the anatomy and the location and proximity of various critical structures, there was always a concern about potential complications of adjuvant radiation; However, with the advancement of radiation technologies, compliant techniques such as Intensity Modulated Radiation (IMRT) and Proton Beam Therapy have shown better results in improving local control and minimizing toxicity and complications of nearby critical structures. [13,40]

The philosophy of treatment chemotherapy patients with esthesioneuroblastoma is based on the premise that these tumors share some histological features with other chemosensitive neural crest tumors (for example neuroblastomas, high-grade neuroendocrine carcinomas and PNETs) [41]. This theory has been proven by a variety of published retrospective analyses [42,43]. While another study has suggested that perioperative chemotherapy may be harmful [44].

The most commonly used schemes Cyclophosphamide (650 mg/m2) with vincristine (1. 5 mg/m2 with a maximum dose of 2 mg/m2) every 3 weeks for a total of 6 cycles [35].

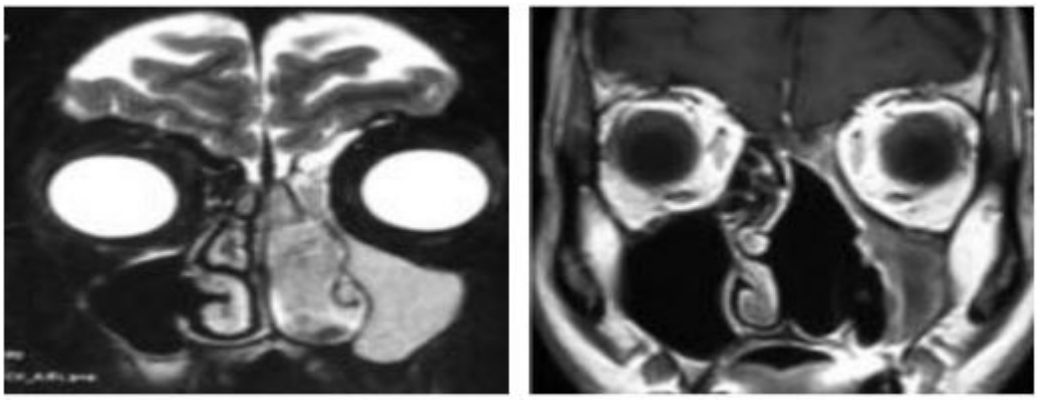

Figure 6: coronal section of MRI. (a) pre-operative, (b) One year after treatment (Iconography of ENT department)

Despite treatment, esthesioneuroblastoma remains a malignant tumor with a fazzy prognosis, since the overall survival at 5 years is of the order of 50%, and local or locoregional recurrences are very common [35].

Factors that affect the prognosis include:

- Local extension assessed according to the Kadish classification
- The histopathological grade of Hyams[30].
- Age: the prognosis would be better in a young person after adjustment on the stage. General condition and weight loss at diagnosis would rather be related to treatment tolerance and the risk of complications [45].
- Presence of cervical lymphadenopathy when the desease is discovered :

  - A meta-analysis carried out in 2008 found that the disease control was 29% in patients with lymph node invasion, compared with 64% in the opposite case [10].

  - Survival at 5 years is 0% if lymphadenopathies are present, compared to 65% if not [13].

- The presence of distant metastases: indicates a very disappointing prognosis [13, 35].
- Diffuse marking at the PS 100and a low proliferation index to Ki 67: correlated with a better prognosis [35]

Conclusion

Esthesioneuroblastoma is a rare malignant tumor of the olfactory placode with an unknown etiology. It is characterized by clinical polymorphism, and a banality of symptoms that cause patients to reach advanced stages with significant locoregional invasion. Imaging (CTM and/or MRI) often makes it possible to evoke the diagnosis. It is an essential contribution to the evaluation of the pre-therapeutic, the determination of surgical tactics, and serves as a reference for assessing therapeutic response.

The precise diagnosis can only be made by anatomopathology. The treatment is not yet codified, but the radio surgical association seems to give the best chance of survival. Chemotherapy is reserved for advanced stages of the disease, inoperable tumours and incurable recurrences. Despite treatment, esthesioneuroblastoma remains a malignant tumour with a fuzzy prognosis, as the overall survival at 5 years is around 50%, and local or locoregional recurrences are very common.

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