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OLFACTORY ESTHESIONEUROBLASTOMA: STUDY OF 5 CASES AND REVIEW OF THE LITTERATURE

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ABSTRACT

Introduction: Esthesioneuroblastoma is a rare malignant tumor, which develops from olfactory neuroepithelium and is one of the rarest tumors of the nasal cavity. The aim of this study is to specify through a review of the literature, histoclinic characteris- tics, therapeutic terms and prognostic factors of this tumor. **Material and methods:** a retrospective study concerning five cases of olfactory neuroblastoma treated in the department of radiation therapy at the departmentof radiotherapy University hospital Center Fes Morocco. **Results:** The mean age of our patients was 40 years. Clinical symptomatology was dominated by nasal obstruction and epistaxis. Four patients were classified as Kadish C and one patient as Kadish D. Four patients underwent surgical treatment, 3 of them had postoperative radiotherapy. One patient was above all therapeutic resources. One patient is in complete remission with a mean follow-up of 3 years. **Conclusion:** olfactory esthesioneuroblastoma is a rare sinonasal malignant tumor, characterised by clinical polymorphism and local agressivity. In spite of the surgery and the radiotherapy, the forecast remains reserved in the long term.

KEYWORDS: Olfactory neuroblastoma, Imagery, Immunohistochemestry, Surgery, Radiotherapy.

1. INTRODUCTION

Olfactory esthesioneuroblastoma, also called "esthesioneurocytoma", "neuro-epithelioma" or most commonly "olfactory neuroblastoma", is a rare malignant tumor developed at the level of neuro epithelial elements of the olfactory placode.[1] It often has rhinologic symptoms, and ocular or neurological signs might be or appear in the second place. The CT scan and the MRI both allow aprecise locoregional assessment.[2] The diagnosis is anatomopathological, and the treatment is essentially based on surgery and radiation therapy.

This tumor raises managments issues, due to the late diagnosis and to the mportant expansion, which might impede a complete exereis of the tumor.

We propose, through this study and literature reviw, precising the histo clinical characteristics, as well as the different anatomo clinical classifications of the olfactory esthesio neuroblastomas exploring the elements of prognosis, as well as drawing an adopted therapeutic protocol to this tumor.

2. MATERIALS AND METHODS

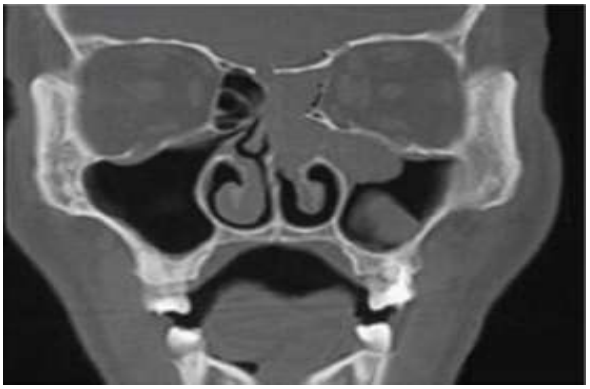
The present study is retrospective and descriptive carried out during a 4 year period (2012 to 2016) and based on five observations about olfactory esthesioneuroblastomas compiled at the Radiotherapy department of the Hassan II University Hospital (CHU Hassan II) of Fez.

3. RESULTS

Our series of study included 3 men and two women, with an age ranging from 21 to 64 ans an average age of 40, and no particular exposing to risk factors were noted. The average time taken by the patient oconsult was 6 months and ranging from 2 months to 1 years, the reason for consultations were mainly the ocular and rhino sinus signs. Imparticular, a unilateral and perament nasal obstruction was present in 2 cases, an epistaxis of low abondance resistant to treatment was noted in 2 cases, also, some nasal sinus pains were witnessed in 3 cases. Ocular signs were noted in 3 cases and took the form of exophtalmos for 2 female patients, and a low visual acquity for one patient. Some neurological signs consisted of headaches, were noted in one case; the physical examination, using the nasal endoscopy performed for 4 of our patients, showed a circonferential process of the nasal cavity in 3 cases. A total filling of the nasal cavity was witnessed in 3 cases and a deviation of the nasal septum to controlateral side in 1 case.

The fundoscopic examination, performed for all our patients, showed signs of vascular damage in 1 case. Besides, the neurological examination indicated a trismus in an other case. The examination of lymph

nodes showed some palpable cervical lyphadenopathies for 1 patient. A facial CT scan was carried out for our 5 patients and showed a Kadish stage C tumor of nasal sinus cavities in 4 cases and a Kadish stage D in 1 case. An axpansion to the orbital cavites in 2 cases and to the base of the skull in 1 case. Facial MRI was perfomed for 3 patients, and the tumor bondaries were extended more than what CT scan showed before.



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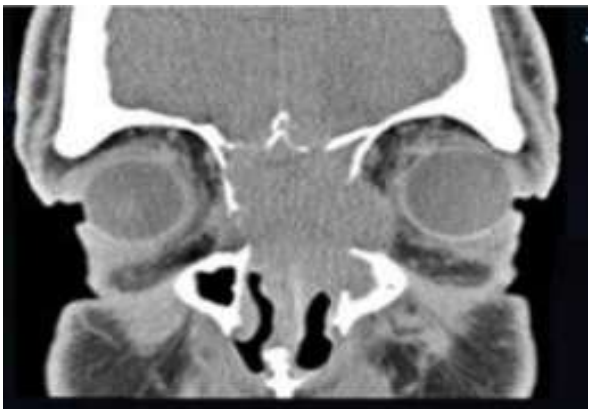

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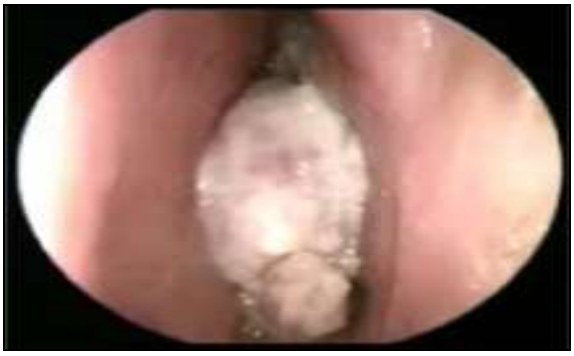
Figure. 1: (A) coronal CT scan showing a tumor mass occupying the left nasal fossa, left maxillary sinus and left ethmoidal cells. (B) Heterogeneous left naso-ethmoidal process of tissue density with endocranial extension and homolateral orbit.

The diagnosis of olfactory esthesioneuroblastoma was only retained on the basis of the anatomopathological examination of the biopsies. On the microscopic level, the two predominat criteria were a lober and compact shape (Figure 2). The tumor cells were small with rounded nucleolis. Cytoplasm was less abondant, without nuclear membrane and with a proeminent fibrillated matrix. According to the histologic grading of Hyams two cases were stage I, two others were stage II and one case was stage III.



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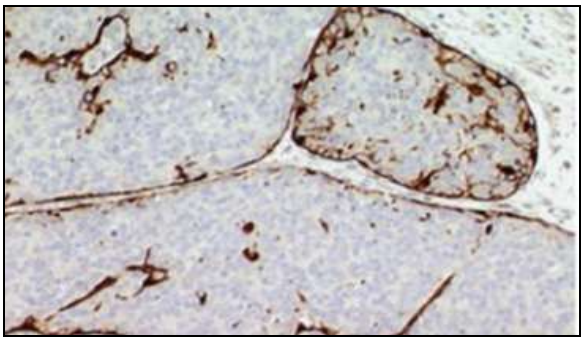

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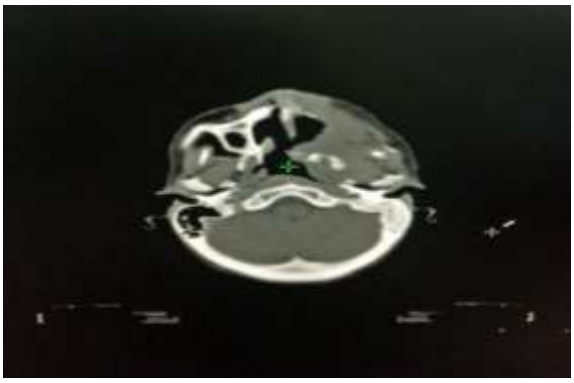
Figure. 2: (A) Endoscopic view showing a budding process of the left nasal fossa. (B) The lobules are underlined by a network of PS100 positive sustentacular cells.

An extended assenssment included a thoraco abdominal CT scan done for 3 patients and also a chest X -Ray for two patients, an abdominal sonography for the two other cases, some lymphadenopathies were found in two patients.

Four patients had surgeries from which three by the intransal approach, and the 4th by open surgery with extended lymp node dissection. A female patient was judged for above any treatment due to the important locoregional expansion of the tumor, then she had a symptomatic treatment (Observation N° 2). The surgical treatment was followed by radiation therapy for 3 patients and one patient had palliative chemotherapy. A complete remission was achived for only one patient after 3 years follow up.



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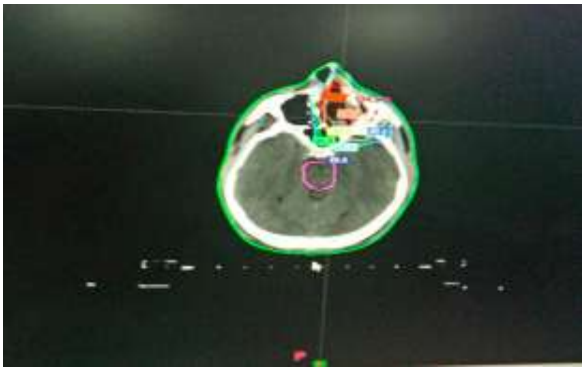

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Figure. 3: (Observation N 1): (A) CT scan Simulation, (B) Dosimetric CT scan.

A evolutionary pursuit was noted in 1 case: 3 months after the exclusive surgical treatment. A tumor recurrence occured in 2 cases, and one patient got out of the hospital and passed away later. The table 1 summaries the observations of our patients.

Tableau. 1: summary of observations.

Case	Age	Sexe	Timeline of the consultation	clinical symptoms	Staging	Treatment	Evolution
1	25	M	12mois	-Nasal Obstruction. -Exophtalmos. -low visual acquity -Headaches.	Stage C	-Surgery radiation therapy 66Gy	Full remission
2	30	M	8mois	-Epistaxis, -nasal sinus pains -Swelling of the hemiface	Stage D	Symptomatic treatment	patient deliverad to family
3	21	M	2mois	-Nasal Obstruction. Epistaxis, anosmia -Low visual acquity -Nasal sinus pains -Headaches	Stage C	-Surgery radiation therapy 70Gy	Reccurence
4	64	F	3mois	-Nasal obstruction Epistaxis anosmia exophtalmos -cervical lymphadenopathy	Stage C	surgery	evolutionary pursuit
5	63	F	4mois	-Nasal obstruction -nasal sinus pains	Stage C	-palliative radiation therapy -palliative chemotehrapy	passed away

4. DISCUSSION

The olfactory esthesioneuroblastoma was first described in 1924 by Berger and al.[2] Therafter, 1000 cases were noted in the literature.[3] It is a rare tumor that represents 1,2% of the overall malignat nasal sinus pains and 3 to 6% of all the nasal tumors.[2, 3, 4, 5] The increase of the cases published during the post years corresponds more with the rise of the disease frequency[6]; In most series this tumor effects also sexes[7] even if some authors report a slight female predominance.[6] The disease occurs at any age, but two frequency peaks was described: between the age of 10 and 20, and between 50 and 60.[3, 5, 9] No risk factor was clearly identified in the literature. However, some studies evoked a possible role of Nitrosamines, wood dust and some genetic abnormalities.[10]

Clinically speaking, in 75% of the cases, the tumorl is discovered by rhino sinus signs, mainly nasal obstruction and epistaxis, anosmia, rhinorrhea and nasal sinus pains.[11] In fact, the one sideness and the gradual worsening of the symptomatology that should draw attention.[4] The ophtalmic damage with orbital invasion is observed in 20 to 30% of cases[2, 5], which causes an exophtalmos, adecrease of the visual acuity, and even an ophtalmoplegia. The presence of ocular signs, in the first place, shows a late stage of the disease. In our series, we found exophtalmos for 2 patients. The neurological signs

with an endocranial expansion are more rarely observed (less than 10% of cases).[2, 5] 2 patients from our series has reported headaches, even if only oneof them has an endocranial expansion shown on the CT scan. A pain syndrome, the presence of cervical lymphadenopathies, or a paraneoplastic syndrome are rare as well.[12] However, in our series, some nasal sinus pains were observed at 3 of our patients. The endoscopic examination showedthe the tumor takes a polypoid shape, with a clor changing from grey to dark red, friable and hemorrhagic.[2,5] The ophtalmogical examination is mandatory in the frequence of ocular signs. The neurological examination should be systematic due to the proximity to the basal skull and the frequent endocranial expansionn; for our patients, the neurological examination revealed an ophtalmoplegia in one case. The examination of the cervical lympnodes is also systematic, especially that the esthesioneuroblastomais associated with lymphophilia. In fact, a patient from our series presented palpable cervical lymphadenopathies, cencerning radiology, the standard sinus radiography is pointless in the initial assenssment of the nasal sinus neoformations.[13] The imaging of this type cancers essentially acquires the CT scan and the MRI which are complementary.[13] The scan, with coronal and axial iamges before and after the injection of contrast agent, is considered to be prefferd axamination to show a dense homogeneous opacity that might cantain intratumoral calcifications and which moderately increase after the injection of the contrast agent.[5] Precising the exact limits of the intra cranial expansion and detectins the invasion of the anterir section.[2,5] Depending on the expansion, Kadish proposed (in 1976) a clinical classification in 3stages[1,2,14]

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

This classification was modified by Monita in 1993.[12] Most recently, Dulguerov[14,15] proposed a more precise classificationbasedon the TNM classification and using the CT scan and MRI.

- T1: Nasal and / or sinus tumor, keeping an air space between the tumor and cribriform plate.
- T2: Tumor touching and even eroding the cribriform plate.
- T3: Intracranial extradural tumor and/ or an orbital damage.
- T4: Intracranial intradural tumor.

The current recommended classificationd are one of Kadish modified by Morita, and the other of Dulguerov.[8,13] In our series, the radiological staging was done according to the classification of Kadish. Thus, 4 patients were classified stage C and a patient was stage D. The diagnosis of the esthesioneublastoma raised by the imaging, is histological[13], and it is based on the morphology and immunohistochemistry. This one is recommended for the low grade types[13], and it is essential high grade types where it allows eliminating differential diagnosis such as: lymphoma, adenocarcinoma, plasmocytoma, melanoma, rhabdomyosarcoma, paraganglioma and Ewing sarcoma. There are no specific markers of olfactory esthesioneurblastomas, but a revealing profile that marks the double differentiation of the damage.[16] It shows the positivity of the neuroendocrine markers, and the S100 protein that has a histoprognostic value, and the usual negativiy of epithelial markers. The histological examination allows precising the histological grade of Hyams.[15] In our series, 2 cases were classifed Hyams grade I, 2 cases were grade II, and one case was tage III. According to the recommendations of REFCOR, the treatment of the esthesioneuroblastoma is proposed depending on its ability to be surgically removable, a complete resection surgery, macroscopic and microscopic, with safetymargins, followed by a radiotherapy of the tumor site and the first node bridges, which is considered to the standard curative treatment of sinus esthesioneuroblastoma (Grade C recommendation) (13]. There is no standard access, still any surgical access should take into consideration two aims[17], on the one hand, the ability to control all the anatomical limits of the tumor and the cribrifom plate; on the other hand a one piece cardcinological resection that -if possible- avoids the tumor fragmentation or the sectioning.[17] Essentielly, there are three approaches: craniofacial, transfacial and currently the most often adapted one is the endonasalendoscopic surgery when it comes to stages A and B of Kadish.[13] The surgical access is ether transfacial, by performing a para lateral nasal rhinotomy (for A and B Kadish stages), or through low frontal incision is there is a damage of the skull base.[9]

If there is an orbital extension, the attitudes are extremly nuanced but the majority of surgeons have a conservative approach toward the eyeball; since there is no significant difference in case of exenteration on survival or recurrence rates. If the tumor cannot be surgically removed, the treatment is multimodal and includes a first line chemotherapy, and an eventual radiation therapy followed by a craniofacial surgery (professional consensus).[13] The preoperative radiotherapy, eventhough adopted by some canters, is most a standard.[3,8] This radiation therapy targets the tumor site as well as lymph node area the radiation dose might be 45 to 60 Gy if the tumor volume is important.[18] The olfactory esthesioneuroblastoma is a tumor withe a very poor prognosis,-; the survivalis about 50%of 5 years and 30% of 10 years. The local and locoregional recurrences represent 60%[20], and they might be early or late, which justifies a life -long supervision of the patients. Our experience witnessed two lowal reccurences after 8 months and two years. The distant metastases were noted in 35 to 40% of cases[20], and the were manly lymphnode, pulmonary or bone metastases.[18]

In our series, we did not witness any visceral metastasis; the prognosis factors of the esthesioneuroblatomas are

very blurring bacause of the small number of patients in every series. the main prognosis factor is the clinical stage of the diagnosis. Age, gender, and ethnicity were not noted as prognosis factors. The Hyams histological grade seems also to be a significant prognosis factor with a 56% srvical rate for the low grades I and II versus a 25% rate for higher grades III and IV. The other factors are presented by TNM stage and the treatment; in fact, the survival, when associating surgery and radiation therapy, is higher than the case of using only radiotherapy or isolated surgery.

5. CONCLUSION

The olfactory esthesioneuroblastoma is a rare and locally aggressive tumor of the nasal sinus cavities, which represents diagnosis diffiulties and therapeutical managment issues. The most accepted tretment in the litterature is the cranio-facial anterior resection, followed by a post operative radiation therapy for the localized stages.[21] The endonasal endoscopic sugery seems to be increasingly recommended.[22] Nevetheless, this tumor still has a poor prognosis and recurrence chances.

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