

Case Report

Management of Esthesioneuroblastoma: A Retrospective Study of 6 Cases and Literature Review

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Keywords

Esthesioneuroblastoma · Treatment · Radiotherapy · Surgery

Abstract

The esthesioneuroblastoma (ENB) is a rare malignant sinonasal tumor of neuroectodermal origin. This study aimed to improve the understanding of the clinical features by reviewing the literature and analyzing the medical records of patients diagnosed with ENB in our institution between 2012 and 2019. A total of 6 cases of ENB were available for analysis. The mean age at the time of diagnosis was 36 years. The main complaints at presentation were the rhinologic signs. Tumors were classified as stage C of Kadisk in 3 cases and stage D in the others. According to TNM (modified by Dulguerov), 2 patients were T3N0M0, one T4N0M0, one T3N1M0, and two T4N1M0. The diagnosis of ENB was based on pathological examination. According to Hyams histological grading, low-grade lesions (Hyams I and II) were seen in 2 cases, high-grade undifferentiated lesions (Hyams III and IV) were seen in 4. Of the 6 patients, 4 received surgery. The surgical approaches mainly included an endoscopic endonasal resection in 2 cases, a cranial-facial resection surgery in 1 case, and an expanded endoscopic endonasal approach in combination with craniotomy in 1 case. Four patients received adjuvant radiotherapy (RT). RT dose ranged from 60 to 70 Gy. A total of 3 patients had lymph node metastasis and received RT of the neck. Chemotherapy was delivered in 2 patients. After a mean follow-up of 4.5 years, 4 patients were free of recurrence. Unfortunately, 1 patient died from a progressive disease 6 months after RT. ENB is a rare locally aggressive tumor of the

nasosinusal cavities. The first-line treatment for resectable tumors should include primary surgical resection with adjuvant RT. However, this tumor remains of poor prognosis. Therefore, long-term close follow-up based on symptoms, endoscopy, and imaging is essential.

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Introduction

Olfactory esthesioneuroblastoma (ENB) also called esthesioneurocytoma, neuroepithelioma, or more commonly olfactory neuroblastoma is a rare malignant tumor originated from the olfactory epithelium of the upper nasal cavity [1], slowly evolving with frequent recurrences after more than 10 years. The diagnosis is pathological and the treatment is mainly based on surgery and radiotherapy (RT).

Due to the small number of affected patients, there are no randomized trials on the subject. The only publications are mainly case reports, retrospective studies, and retrospective meta-analyses. There is no consensus on the overall management of this pathology. This study aimed to improve the understanding of the clinical features by reviewing the literature and analyzing the medical records of patients diagnosed with ENB in our institution.

Materials and Methods

Patients diagnosed with ENB and received treatment at the department of Radiotherapy in Hassan II University Hospital of Fes, between 2012 and 2019 were reviewed retrospectively. Available data of gender, age, clinical presentation, tumor site, tumor subtype, treatment, treatment outcome, follow-up, and vital status were extracted from the medical records of patients.

The follow-up of the patients ended on June 2021. Overall survival was defined as the time from the first diagnosis to death from any cause or date of last follow-up.

Results

A total of 6 cases of ENB were available for analysis. The clinical features are summarized in Table 1. Three patients were males and 3 were females. The mean age at the time of diagnosis was 36 years (range, 18–62). No particular risk factor exposure was noted. The main complaints at presentation were rhinologic signs with nasal obstruction in all cases, recurring epistaxis was noted in 2 cases, hyposmia or anosmia were noted in 3 cases. Ophthalmological symptoms such as exophthalmia, diplopia, and decreased visual acuity were noted in 4 cases, and tearing in 1 patient. Neurological signs such as headache were noted in 2 cases. No paraneoplastic syndrome was noted. There was a delay between the appearance of clinical signs and the histological diagnosis with an average of 6, 8 months (range 4–14 months). Endoscopic exam of the nasal cavities was performed in all of our patients. A proliferate tumor of the nasal fossa was revealed in all cases, with a total filling of the nasal cavity in 3 cases.

The ophthalmologic examination found exophthalmos in 4 cases and decreased visual acuity in 2 cases. A fundoscopic exam performed on all of our patients revealed signs of vascular distress in 3 cases. Neurological examination showed ophthalmoplegia in one case and trismus in another. Examination of the lymph node areas shows palpable cervical lymphadenopathy in 3 cases. The initial radiological assessment included a CT of the facial cavity in

Table 1. Clinical features of 6 cases with ENB

Case number	Age, years	Gender	TNM within Dulguerov	Kadish staging	Hyam's grading	Initial treatment	RT dose	Follow-up, months	Vital status
1	62	F	T4N0M0	C	III	None	None	1	DOD before TRT
2	18	M	T3N1M0	D	II	Surgery + RT	66	24	NED
3	26	F	T3N0M0	C	III	Surgery + RT	66	30	NED
4	27	M	T4N1M0	D	III	CRT	70	6	DOD
5	23	M	T3N0M0	C	I	Surgery + RT	66	74	NED
6	59	F	T4N1M0	D	III	Surgery + CRT	70	96	NED

NED, no evidence of disease; DOD, dead of disease.

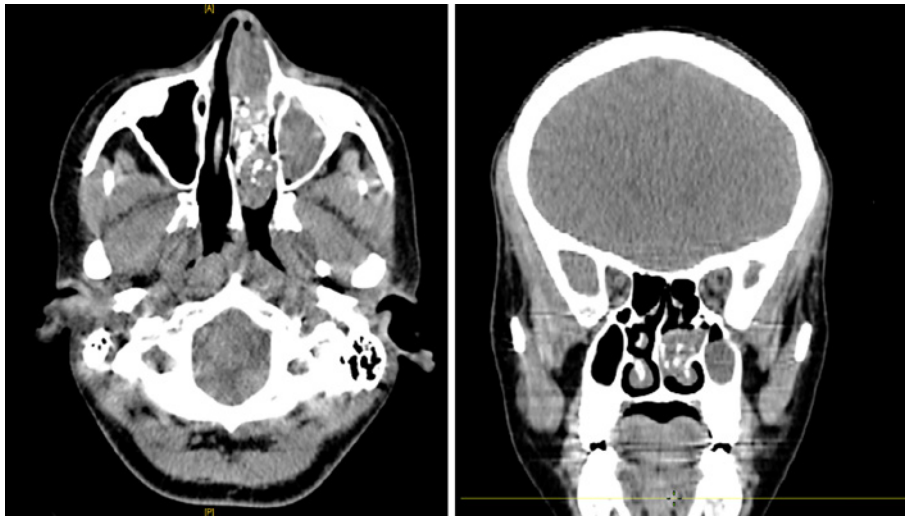


Fig. 1. Tumor process of the left nasal fossa, containing calcifications, lysing the bony septa and enhancing heterogeneously after contrast measuring 66 × 28 × 46 mm.

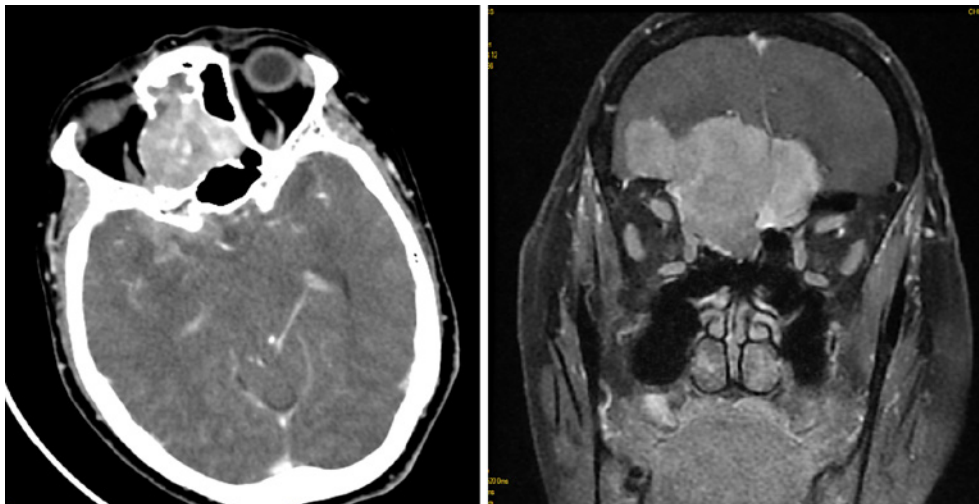


Fig. 2. Voluminous tumoral process of the anterior level of the skull base lateralized to the right (a), with endocranial extension (b).

all cases and a cervical/cerebral MRI in 4 cases to evaluate the locoregional tumor's extent and establish a staging according to the Kadish classification and TNM classification according to Dulguerov (shown in Fig. 1, 2).

It revealed a tumor invading the nasal cavity and/or the paranasal sinuses with an extension to the eye socket in all cases, an extension to the sphenoidal sinus and/or the cribriform plate in 3 cases, an extension to the cerebral parenchyma in 3 cases, and the presence of regional lymph node metastases in 3 cases. The tumor was classified as stage C of Kadisk in 3 cases and stage D in the others. According to TNM (modified by Dulguerov), 2 patients were T3N0M0, one T4N0M0, one T3N1M0, and two T4N1M0.

The diagnosis of ENB was based on pathological examination. Microscopically, tumor cells were round and small, within a fibrillated intercellular stroma. According to Hyams histological

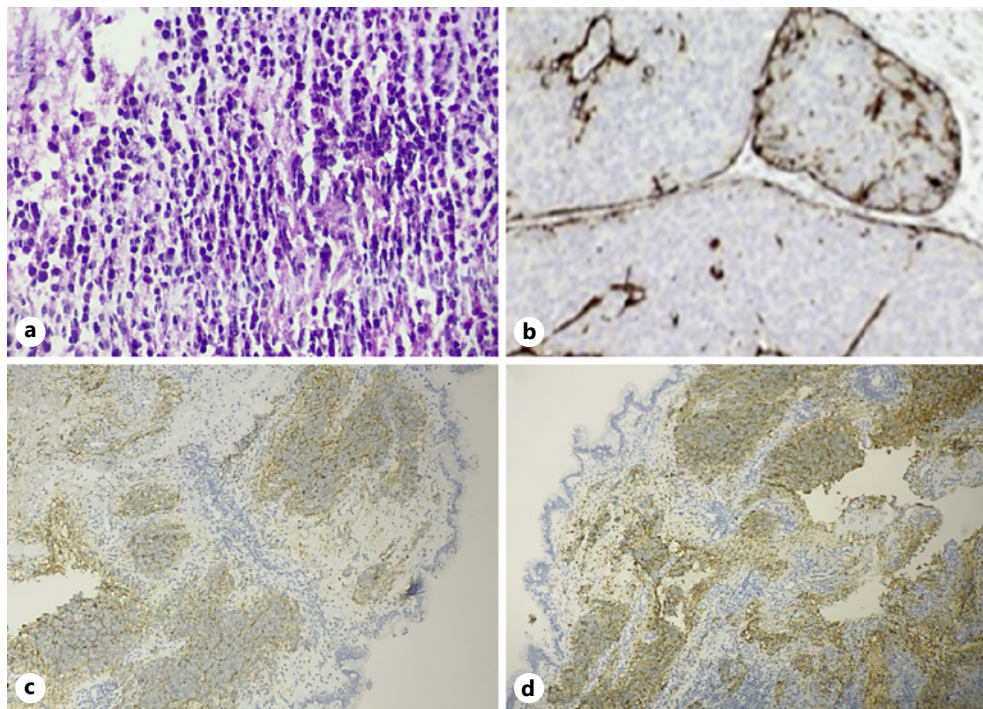


Fig. 3. Histological and immunohistochemical features of ENB. **a** Tumor cells are round and small within a fibrillated intercellular stroma. **b** The lobules are underlined by a network of PS100 positive sustentacular cells. **c** Positivity of chromogranin. **d** Positivity of synaptophysin.

grading, low-grade lesions (Hyams I and II) were seen in 2 cases, high-grade undifferentiated lesions (Hyams III and IV) were seen in 4.

In immunohistochemistry, the expression of the anti-neuron-specific enolase antibody was positive in all samples. Variable positivity was observed for synaptophysin, chromogranin, specific markers of neuroendocrine differentiation, cytokeratins, vimentin, “Epithelial Membrane Antigen” and CD56 (shown in Fig. 3).

A chest-abdominal CT was carried out in all cases. No distant metastases were revealed.

Patients diagnosed with ENB received surgical resection, RT, and chemotherapy, or a combination of these methods. Of the 6 patients, 4 received surgery. The surgical approaches mainly included an endoscopic endonasal resection in 2 cases, a cranial-facial resection surgery in 1 case, and an expanded endoscopic endonasal approach in combination with craniotomy in 1 case. Four patients received adjuvant RT. It was indicated in cases of incomplete resections, macroscopic residue and in cases of high-grade or locally advanced tumors. Definitive RT was done due to inoperable tumor burden. Chemotherapy was delivered in 2 patients. The regimens used for chemotherapy included etoposide and cisplatin.

RT was planned as 3D conformal or as intensity-modulated RT (IMRT). Each patient was immobilized with a custom-made thermoplastic cast in the supine position. All subjects were scanned with 3 mm slice thickness. Scanning started from the top of the head to the bifurcation of trachea. All gross tumor volume images were contoured. The clinical target volume was defined as the grossly detectable tumor volume plus regions at risk. A Planning target volume with a margin of 5 mm was added to the clinical target volume. The treatment was administered 5 days per week with a single dose of 2 Gy for all patients. Radiation dose ranged from 60 to 70 Gy. A total of 3 patients had lymph node metastasis and received RT of the neck.

One patient died before any treatment due to involvement of cerebral parenchyma. After a mean follow-up of 4.5 years, 4 patients were free of recurrence. Unfortunately, 1 patient died from a progressive disease 6 months after RT.

Discussion

Epidemiology

ENB, also called olfactory neuroblastoma, was first described by Berger et al. [2]. Its starting point is the olfactory epithelium located in the upper part of the nasal cavities. This is a rare tumor that accounts for 3% of all endonasal neoplasms [3]. The real incidence of ENB remains difficult to establish because current histological techniques allow a better diagnosis of these lesions. In fact, out of just over 1,000 published cases of ENB, 80% were published in the past 20 years [4].

There appears to be a slight male predominance. The age incidence has a bimodal distribution, with peaks at 11–20 years and 40–60 years, the highest incidence at 51–60 years [5]. No familial case of ENB has been reported in the literature and no genetic predisposition to cancer has been associated with ENBs. In addition, no environmental factors have currently been discovered [6].

Clinical Presentation

The clinical manifestations upon diagnosis are nonspecific and dependent on the local or regional tumoral extension [7]. ENB is a unifocal tumor, and the symptoms are often unilateral [6]. In 75% of cases, the tumor is revealed by rhinological signs [8], mainly nasal obstruction and epistaxis, elsewhere, it is anosmia, rhinorrhea. Ophthalmologic involvement with invasion of the orbit is observed in 20–30% of cases leading to exophthalmia, visual disturbances, or even ophthalmoplegia. The presence of eye signs indicates a late stage of the disease [3]. Patients also could have local pain or headache. The symptoms may be associated with a mass in the neck and/or paraneoplastic syndrome such as Cushing's syndrome, malignant hypercalcemia, hyponatremia due to inappropriate antidiuretic hormone secretion, and even an opsomyoclonus syndrome [9]. In our series, we found exophthalmos in 4 patients with a reduced visual acuity in 2 cases, and a cervical lymphadenopathy in 3 cases, which indicate a locally advanced disease.

On endoscopic examination, the tumor appears as a polyploid formation in the nasal cavity, varying in color from gray to dark red, obstructive, friable, and bleeding on contact [10]. Ophthalmologic examination is mandatory due to the frequency of ocular signs. Neurological examination should be systematic given the proximity of the tumor to the base of the skull and the frequent endocranial extension [11, 12]. In our series, ophthalmoplegia was revealed in one case.

Examination of cervical lymph nodes is important since the ENB is lymphophilic. Despite everything, the symptomatology at the beginning of the disease remains very common and nonspecific, which often leads to diagnostic delay, even worse by the slow growth of the tumor [13].

Standard sinus radiography has no value in the initial assessment of nasal-sinus neoplasms. Imaging of this type of cancer mainly involves computed tomography and MRI which are complementary. On the CT-scan, all cases had intranasal polypoidic lesion which may contain intratumoral calcifications with an epicenter located on a unilateral olfactory recess responsible for an asymmetrical enlargement in the olfactory system and extending to the cribriform plate [14, 15]. CT provides the best information about the tumor and its local invasion into surrounding bone structures. On MRI, the tumor appears in hypo or iso signal in T1, with a clear hypo signal of the areas of necrosis, whereas in T2 the tumor appears in iso or hypersignal and is clearly enhanced by the injection of gadolinium. The contribution of MRI is important

in improving the preoperative assessment of these tumors by estimating tumor spread into surrounding soft tissue areas, such as the anterior cranial fossa and the retromaxillary space. Orbital extension is also closely evaluated on FAT-SAT sequence MRIs [16]. Octreotide scintigraphy may be useful in confirming the preoperative diagnosis of certain head and neck neuroendocrine tumors, such as paragangliomas, Merkel cell carcinomas, medullary thyroid carcinomas, and ENBs [17].

Regional extension to the cervical lymph nodes must be evaluated clinically, via an MRI/cervical CT and a PET-FDG scan. The PET scan makes it possible to diagnose the presence of cervical lymphadenopathy that is not detectable on a CT in nearly 20% of cases [18]. A chest-abdominal CT and/or hepatic ultrasound are indicated when searching for pulmonary and hepatic metastases [16].

Tumoral Staging

Kadish et al. [9] proposed (in 1976) the first historical classification in 3 stages based on tumoral diffusion from the nasal cavities toward adjacent anatomical structures. It was modified by Morita and colleagues [19] with the addition of a stage D for patients presenting cervical or distant lymph node metastases. Then, Dulguerov and Calcaterra [20] proposed in 1992 a new classification closer to the TNM classifications usually used, which makes it possible to better evaluate regional and distant extension. Three of our patients were classified as stage C of Kadish and 3 as stage D.

Histological Characteristics

The diagnosis of ENB is histological; it is made on the basis of morphology and immunohistochemistry. ENB is conventionally constituted, in variable proportions, by the association of circumscribed lobules and cell nests within a fibrillated intercellular stroma. Neuroepithelial cells are small, round, monomorphic and organized in Homer wright rosettes in 30% or pseudo-rosettes of Flessner Wurtenstein in 70% of cases. In low-grade forms, tumor cells have a small, uniform nucleus with fine chromatin and a discrete nucleolus. In high-grade forms nuclear pleomorphism, more frequent mitosis and patches of necrosis are observed. According to this histological criteria, Hyams grading evaluates the aggressiveness of the primary tumor. It describes 4 stages of differentiation, ranging from indolent forms to aggressive and metastatic forms (grade I [differentiated] to grade IV [undifferentiated]) [21, 22].

In immunohistochemistry, ENB presents a diffuse positivity of “Neuron-Specific Enolase” (NSE), synaptophysin and chromogranin, specific markers of neuroendocrine differentiation. Variable positivity is observed for vimentin, cytokeratins, “Epithelial Membrane Antigen” and CD56 [19]. PS-100 positivity is visible on the periphery of the tumor. The Ki-67 proliferation index is high, between 10 and 50% [23, 24]. In our series grade 1 was observed in 1 case, grade II in 1 case, and grade III in 4 cases.

Treatment

The treatment approaches for ENB still remain controversial, although it is generally believed that A multimodal treatment combining surgery and RT provides the best results [25]. Among the first studies carried out on the subject that of Foote et al. [19] which included 49 patients. There was not a significant difference between the survival of patients treated by surgery alone and those treated by surgery and RT. However, the author specifies that the patients treated with bitherapy initially had locally advanced disease. They concluded on a better survival after treatment with bitherapy. At the same time, Dulguerov and Calcaterra [20] showed superior survival for patients who had been treated with bitherapy. According to the meta-analysis by Dulguerov et al. [26], on articles published between 1990 and 2000, the 5-year survival after surgery alone is 48%, after RT alone 37%, while survival after surgery

and RT is 68%. In Chao meta-analysis, the survival of the group benefiting from a bitherapy is much higher than that of the groups benefiting from monotherapy, whatever the stage [27]. These data were confirmed by Ward et al. [19] with a 15-year disease-free survival of 83% for patients treated with surgery and RT, against 23% at 5 years and 0% at 15 years for patients treated with surgery alone. In addition, according to this study, postoperative RT of the tumor bed significantly reduces the risk of distant lymph node metastases. Other studies have found similar results [28–30].

In our series, patients received Surgery and adjuvant RT for resectable disease, Surgical resection has been the mainstay of treatment in ENB. With the development of surgical techniques, from open craniofacial resection to the development of endoscopic surgery, endoscopic surgery has been welcomed as a treatment for ENB. Any surgical approach must meet two objectives [31]: on the one hand, the possibility of controlling all the anatomical limits of the tumor and the cribriform plate; on the other hand, performing a carcinological resection, avoiding tumor fragmentation.

Endoscopic surgery was usually limited to the nasal and paranasal cavities, but in recent years, the indication of endoscopic surgery is progressively expanding. Harvey et al. [32] reported that the endoscopic approach has better survival results than craniofacial resection in advanced Kadish C stage patient. Also, endoscopic surgery can achieve high negative margin even in advanced tumors, which is an important prognostic factor for survival outcomes [31, 33].

Radiation therapy is now part of the “gold standard” for the treatment of ENB associated with total surgical resection. For some authors, the only indication for surgery without complementary RT would be Kadish A stage tumors with clean resection margins [6]. A study showed the efficacy of RT (50 Gy) combined with concurrent chemotherapy in the neoadjuvant treatment of widely extended ENB, not operable upon diagnosis. When combined therapy is used, preoperative doses of 45 Gy and postoperative doses of 50–60 Gy are indicated, depending on the status of the surgical margins. Doses of 65–70 Gy are delivered with irradiation alone in patients with inoperable tumors. The usual fraction dose is 1.8–2.0 Gy [34, 35].

Because of the proximity of ENB to the optic nerves, the optic chiasm, and the brainstem, insufficient dose delivery is a major reason for treatment failure. Modern RT technology provides alternatives to the conventional technique used to treat these tumors. IMRT can limit the radiation dose to nearby normal tissues without compromising tumor control [36]. Compared with conformal RT (CRT), IMRT has better survival outcomes and less adverse reactions. Proton beam therapy is a safe and effective modality for ENB. It could limit secondary effects by saving healthy peritumoral soft tissue [37].

In case of cervical metastases, conventional treatment includes lymph node dissection combined with cervical irradiation. However, prophylactic neck RT in patients without cervical metastases upon diagnosis remains controversial [38]. Some authors showed that prophylactic lymph node irradiation in adults reduces the risk of cervical nodal failure but did not improve final survival outcomes [39]. For others, prophylactic RT does not prevent these lymph node relapses, and it could be omitted [40].

Even if the role and type of chemotherapy remains to be defined, its usage in addition to surgery and RT seems to benefit patients’ survival [41]. Indications for chemotherapy concern high-grade lesions, positive or borderline resection margins, cases of tumoral relapse, nonoperable tumors and regional or distant metastatic forms [6].

A potential molecular target for ENB is overexpression of cell surface somatostatin receptors. Somatostatin analogs appear to be a safe and effective option for unresectable, locally extensive, or metastatic ENB. They may be of future use [42].

ENB is a tumor with a very poor prognosis. Survival is approximately 50% at 5 years and 30% at 10 years. Local recurrence is of highest risk followed by metastatic recurrence, it represents 60%. These recurrences can be early or late, thus justifying long-term monitoring

of these patients. Distant metastases are observed in 35–40% of cases. The prognostic factors of ENB are highly controversial due to the low number of patients in each series. The main prognostic factor is the clinical stage at the time of diagnosis. Unfavorable prognostic is associated with higher Kadish stages, lymph node extension, and distant metastases [43–45]. In another study, orbital and/or intracranial extension represented a factor of a poor prognostic [46]. The histological grade of Hyams also appears to be a significant factor in the prognosis with 56% survival for low grades (I and II) versus 25% for high grades (III and IV).

Conclusion

ENB is a rare locally aggressive tumor of the nasosinusal cavities. The first-line treatment for resectable tumors should include primary surgical resection with adjuvant RT. Endoscopic endonasal surgery seems to be increasingly indicated. Postradiation complications decreased with current techniques like IMRT and protontherapy. Nevertheless, this tumor remains of poor prognosis. Therefore, long-term close follow-up based on symptoms, endoscopy, and imaging is essential.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case series. Written informed consent was obtained from participants for publication of the details of their medical case and any accompanying images. Study approval statement was not required for this study in accordance with local and national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Zenab Alami: investigation, writing – original draft, writing – review and editing, Fatima Zahrae Farhane: investigation, writing – original draft, Amina Bouziane: investigation, review and editing, Samiya Mhirech: investigation, review and editing, Sara Amrani Joutei: investigation, review and editing, Wissal Hassani: investigation, review and editing, Touria Bouhafa: investigation, writing – original draft, writing – review and editing.

Data Availability Statement

The data support the findings of this study are included within the article.

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