Case Report

Maxillofacial esthesioneuroblastoma: A diagnostic complexity

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Abstract Esthesioneuroblastoma is a rare malignant tumor of the sinonasal tract. Oral and maxillofacial pathologists rarely encounter this tumor in their daily practice. Because of their complex anatomic location, non-specific symptoms, varied histomorphology and unfamiliarity, most of the times, the tumor is diagnosed as benign tumor and thereby conservative treatment results in multiple recurrences. A recurrent case of esthesioneuroblastoma in a 24-year-old female patient describing the clinical, histopathological and immunohistochemical features along with differential diagnosis is discussed.

Key Words: Esthesioneuroblastoma, olfactory neuroblastoma, sinonasal tract

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Received: 29.10.2015, **Accepted:** 22.05.2016

INTRODUCTION

Esthesioneuroblastoma also called olfactory neuroblastoma is a rare malignant neuroectodermal tumor of the sinonasal tract region, first described by Berger *et al.* in 1924.[1] According to the World Health Organization, olfactory neuroblastoma is defined as a "malignant neuroectodermal tumor, that is, assumed to originate from olfactory receptor cells present high in the nasal cavity." This justifies the most common site of the tumor being cribriform plate, middle superior nasal structures and anterior skull base.[2,3]

It accounts to about 3–6% of all sinonasal malignancies. These tumors show varied morphology with uncertain histogenesis which results in two extremes, i.e. an indolent growth with more than 20-year survival or an aggressive tumor with limited survival and distant metastasis.[4]

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/0973-029X.185922

Most of the pathologists encounter difficulties in the diagnosis of these malignancies because of their complex anatomic location, non-specific symptoms, variable morphology and unfamiliarity which leads to misdiagnosis as benign tumors. A case of aggressive olfactory neuroblastoma, which recurred thrice following complete surgical excision, is reported.

CASE REPORT

A 24-year-old female patient reported to the Outpatient Department of our hospital complaining of swelling associated with pain on the left side of the face since 1 month. Initially the swelling was about peanut size, which gradually increased to present size, and was associated with pricking and localized pain. Medical history revealed blurred vision and lacrimation for the past 1 week. Her dental history revealed surgical excision

How to cite this article: Raj GS, Rao GV, Kumar MP, Sudheerkanth K. Maxillofacial esthesioneuroblastoma: A diagnostic complexity. J Oral Maxillofac Pathol 2016;20:331-2.

of a tumor in 2007 and subsequent recurrent lesion at the same site in 2013 which was again operated.

At present, extra-oral examination revealed a solitary diffuse swelling in the left infraorbital region of the face measuring approximately 4 cm × 4 cm, extending mediolaterally from the medial canthus of the eye to frontozygomatic region and superioinferiorly from the lower eyelid to 1 cm above the left corner of mouth obliterating the nasolabial fold [Figure 1]. Skin over the swelling was normal with no visible sinus tracts. On palpation, all the inspectory findings were confirmed. The swelling was bony hard with mild tenderness and no local rise in temperature. Intraoral examination showed deficient maxilla and the absence of teeth in relation to 14–28 region [Figure 2].

Computerized tomography revealed a comminuted fracture of the lateral wall of the left orbit with an asymmetric outline of the globe. The posterior wall of left orbit was also incomplete with little soft tissue masses seen protruding into its posterio-lateral aspect. Part of soft tissue was seen extending toward the anterior wall of left maxillary sinus which was completely effaced. Two metal plates were seen, supporting the anterior lateral wall of the left maxillary antrum as artifacts. These plates were presumed to be placed in the previous surgeries [Figure 3].

On reviewing the dental history, clinical and radiological features, a provisional diagnosis of recurrent ameloblastoma of the left infraorbital region was given. The tumor was surgically excised with normal tissue margins surrounding the lesion and the excised specimen was sent for histopathological examination.

Microscopic examination revealed a nasociliary epithelium with adjacent tumor area composed of small round cells arranged in lobular pattern separated by fibrovascular stroma. These tumor cells are arranged in pseudorosettes and glandular patterns, and showed round to oval hyperchromatic nucleus with few presenting salt and pepper chromatin pattern. The adjacent bone tissue is infiltrated by these tumor cells along with new bone formation (osteoid). The stroma is fibro-cellular and -vascular with focal areas of neurofibrillary matrix, giant cells and mitoses [Figure 4].

Based on clinical, radiological and histological findings, a final diagnosis of olfactory neuroblastoma was established. For the confirmation of the diagnosis, immunohistochemistry with a panel of markers was performed [Table 1 and Figure 5], establishing the diagnosis as olfactory neuroblastoma. With the suspicion about the former treated pathologies, past records of the patient were reevaluated and subjected to histopathological and immunohistochemical examination. Histopathology revealed the characteristic features of olfactory neuroblastoma and was confirmed immunohistochemically with the marker neuron-specific enolase (NSE) which showed strong positivity

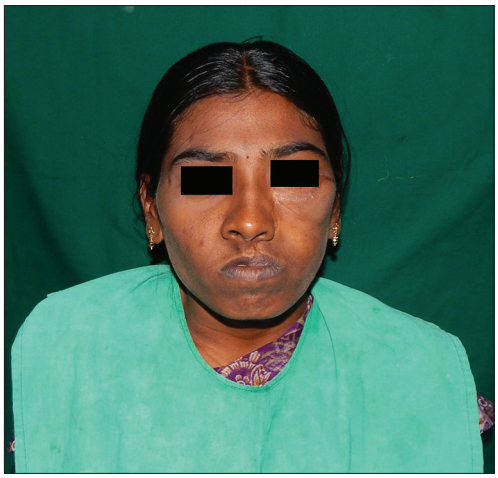

Figure 1: Extraoral photograph revealing infraorbital swelling on the left side of the face

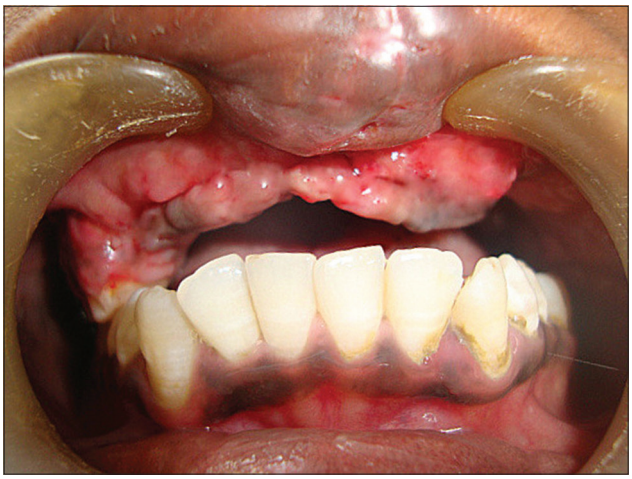

Figure 2: Intraoral examination depicting deficient maxilla and the absence of teeth in relation to 14–28 region

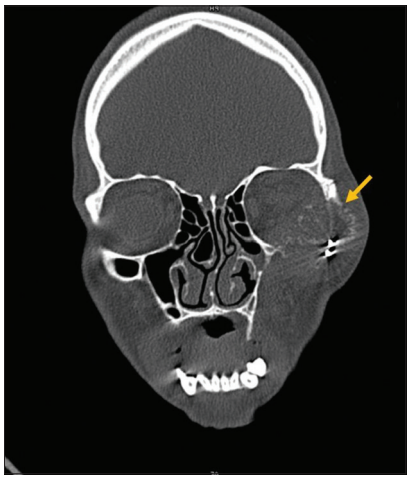

Figure 3: Computerized tomography revealing comminuted fracture on lateral wall and floor of the left orbit with the tumor mass extending into the orbit

[Figure 6]. The patient was referred to the cancer institute for adjuvant radiotherapy.

DISCUSSION

Esthesioneuroblastoma is an uncommon malignant neoplasm representing 2–3% of sinonasal tract tumors.[2] Although there is no much evidence regarding the origin of olfactory neuroblastoma, few studies reported the possible source of this tumor to be specialized neuroectodermal olfactory cells.[5-7]

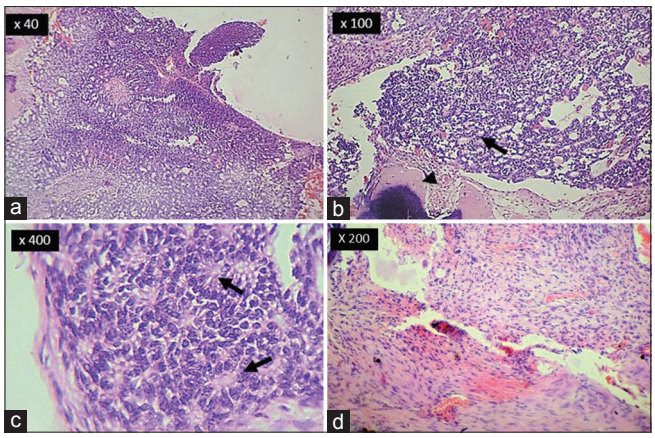

Figure 4: Photomicrograph showing (a) small round cells arranged in sheets and lobules (H&E stain, ×40), (b) rosettes in neurofibrillary matrix (arrow) and new bone formation (arrowhead) (H&E stain, ×100), (c) Homer wright rosettes (arrow) with central neurofibrillary matrix (H&E stain, ×400), (d) fibro-cellular and -vascular stroma (H&E stain, ×200)

Even in the present case, there was an evidence of olfactory epithelium extending along the tumor mass. Other specific sites of origin for this tumor include Jacobson's vomeronasal organ, sphenopalatine ganglion, ectodermal olfactory placode, ganglion of Loci (nervus terminalis) and autonomic ganglia of the nasal mucosa.[8]

Most commonly reported in all age groups with a bimodal peak in second and sixth decade with no gender predilection.[9] In the present case, the female patient first developed tumor at an age of 16 with recurrences noticed at 22 and 24 years. The most common symptoms of olfactory neuroblastoma are nasal obstruction, epistaxis and headache. Tumors in advanced stages usually present orbital symptoms such as proptosis and excessive lacrimation,[2] which were also noticed in the current case report.

Computed tomography (CT) provides the best information about the tumor invasion into bony structures. The CT features

Table 1: Immunohistochemical markers performed

Marker	Reactivity
Epithelial membrane antigen	Negative
Cytokeratin-7	Negative
Caldesmon	Negative
Neuron specific enolase	Strongly positive
Chromogranin	Positive
Ki-67	Positive (labeling index: <10%)
Proliferating cell nuclear antigen	Positive

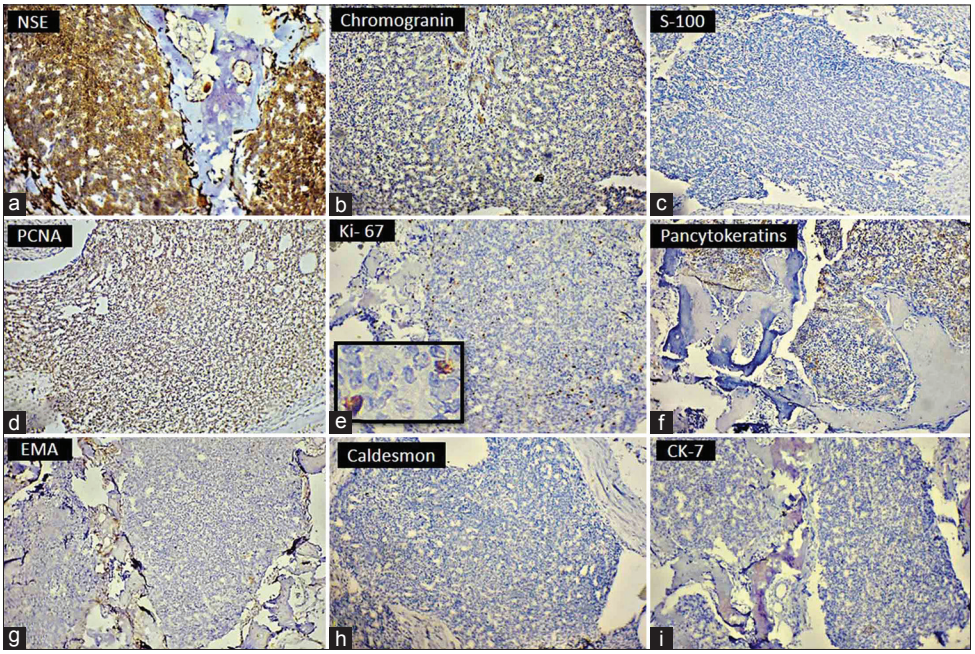

Figure 5: Photomicrograph showing immunohistochemical staining for (a) neuron-specific enolase: strongly positive (IHC stain, x200), (b) chromogranin: positive (IHC stain, x100), (c) S-100: negative (IHC stain, x40), (d) proliferating cell nuclear antigen: positive (IHC stain, x40), (e) Ki-67: positive (labeling index: <10%) (IHC stain, x100) [Inset: showing two positive cells, (IHC stain, x400)], (f) pancytokeratins: focally positive (IHC stain, x200), (g) epithelial membrane antigen: negative (IHC stain, x100), (h) caldesmon: negative (IHC stain, x100), (i) cytokeratin-7: negative (IHC stain, x100). NSE: Neuron-specific enolase, PCNA: Proliferating cell nuclear antigen, EMA: Epithelial membrane antigen

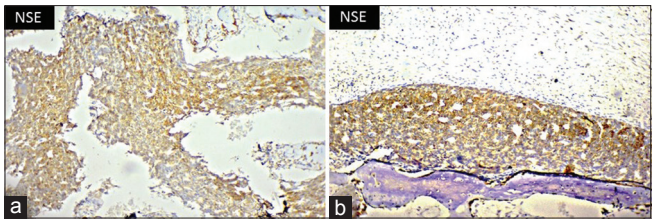

Figure 6: Photomicrograph showing immunohistochemical staining of marker neuron-specific enolase (NSE) showing strong positivity in previously treated pathologies. (a) Section of tumor mass resected in 2007 (IHC stain, x100), (b) Section of tumor mass resected in 2013 (IHC stain, x100)

of olfactory neuroblastoma are nonspecific and so cannot be differentiated from other tumors such as undifferentiated lymphoma, rhabdomyosarcoma, squamous cell carcinoma, extramedullary plasmacytoma and amelanotic melanoma. Definite diagnosis is based on histopathology.[10]

The aggressive nature of this tumor is determined by Kadish staging system,[11] which is based on the clinical spread of the tumor [Table 2]. Morita *et al.* modified Kadish staging system by incorporating Group D for tumors with regional (cervical lymph node) or distant metastases.[12] An extensive research of previous cases of olfactory neuroblastomas revealed their presence in Kadish Stage C. The present case was also categorized under Stage C as the tumor mass was shown to be extending into the orbit. However, Kadish system could not give a definite comparison between the prognosis of surgically operable and inoperable tumors because tumors in the neck, orbit, intracranial portion and distant metastasis were all included in the same stage.[13] Hence, histopathological grading is also mandatory to predict the treatment outcome and survival rate of this tumor.

Histopathologically, Hyams grading system[14] is used to differentiate low-grade (Grade 1 and 2) from high-grade tumors (Grade 3 and 4). Grading is based on few defining features of olfactory neuroblastoma such as lobular architecture, rosettes, neurofibrillary matrix, pleomorphism, mitoses, necrosis and presence of calcifications [Table 3].[8] Two types of rosettes are seen, of which pseudorosettes (Homer Wright rosettes) are the more common. They are characterized by a delicate neurofibrillary and edematous stroma that forms the center of a palisaded arrangement of tumor cells. True rosettes (Flexner–Wintersteiner rosettes) have a tight, "gland-like" annular arrangement.[8] In the present case, most of the tumor cells are arranged in pseudorosette pattern in a fibro-cellular and vascular connective tissue stroma representing a stromal reaction to the proliferating tumor islands.

Histopathological evaluation of our case revealed the tumor in Hyams Grade 2, which is considered as a low-grade

Table 2: Kadish clinical staging system

Stage	Extent of tumor	5 year survival (%)
A	Tumor confined to the nasal cavity	75-91
B	Tumor involves the nasal cavity plus one or more paranasal sinuses	68-71
C	Extension of tumor beyond the sinonasal cavities	41-47

Table 3: Hyams histopathological grading system

Microscopic features	Grade 1	Grade 2	Grade 3	Grade 4
Architecture	Lobular	Lobular	±Lobular	±Lobular
Pleomorphism	Absent to slight	Present	Prominent	Marked
NF matrix	Prominent	Present	May be present	Present
Rosettes	HR	HR	FW	FW
Mitoses	Absent	Present	Prominent	Marked
Necrosis	Absent	Absent	Present	Prominent
Glands	May be present	May be present	May be present	May be present
Calcification	Variable	Variable	Absent	absent

HR: Homer wright, FW: Flexner-Wintersteiner, ±: Lobularity may or may not be present

tumor. However, according to Kadish system, our case can be categorized as high-grade malignancy. Despite its shortcomings, Kadish system is the most commonly used classification system for olfactory neuroblastoma. The other classification systems for olfactory neuroblastoma are according to Biller *et al.*,[15] and Dulguerov and Calcaterra.[16] According to Dias *et al.*, among all classification systems, only Kadish system revealed a statistically significant discrimination among stages for relapse-free survival.[17]

The differential diagnosis included primary intraosseous carcinoma, ameloblastic carcinoma and salivary gland carcinoma. To differentiate whether it was derived from the salivary gland epithelium, a panel of immunohistochemical markers such as epithelial membrane antigen (EMA), cytokeratin-7 (CK-7) and caldesmon was used which showed a negative staining pattern. Hence, the salivary gland tumors were ruled out. As histopathology showed nasociliary epithelium which shows olfactory neural cells, markers specific for neuroectodermal cells, such as NSE and chromogranin, were used which showed a strong positive reaction with NSE and weak positivity with chromogranin. To determine the proliferation rate, immunohistochemical staining with Ki 67 and proliferating cell nuclear antigen (PCNA) was done, which showed the labeling index of Ki 67 to be <10% and strong positivity with PCNA.

Olfactory neuroblastoma is conventionally positive for neuroendocrine markers.[18] The most consistent marker is NSE. Other markers include synaptophysin, neurofilament protein, Class III beta-tubulin, microtubule-associated protein, chromogranin, glial fibrillary acidic protein and

Leu-7. Epithelial markers such as EMA and carcinoembryonic antigen are negative. CKs are usually negative.[19] The present case showed focal positivity for CKs which signifies that there are focal areas of epithelial differentiation which is a common feature of olfactory neuroblastoma.[18] Caldesmon is a marker for neoplastic myoepithelial cells[20] and CK-7 is usually positive for salivary gland neoplasms.[21] Their negative staining in the present case excludes the diagnosis of salivary gland carcinoma. S-100 positivity is mostly seen in the periphery, which represents the Schwann cells or sustentacular cells usually present along the periphery of neoplastic lobules.[19] In our case, S-100 staining was negative which is a common feature seen in high-grade tumors.[19] Ki-67 positivity showed <10% labeling index, which implies that the tumor is well differentiated and associated with long-term survival, whereas poorly differentiated (Hyams Grade 3 and 4) are associated with a high proliferation index.[22] Majority of the features places the current case under low-grade malignancy.

An extensive search of English literature revealed a unique treatment protocol for olfactory neuroblastoma. A combined treatment of surgery and radiation therapy (RT) resulted in a better recurrence -free rate (60–100%) compared with surgery alone (14–56%).[13] Lund *et al.* considered the above combination as the gold standard treatment.[23] In the present case, as the tumor was extended into the orbit (Kadish Stage C) and as the tumor recurred thrice, aggressive surgical excision with adjuvant radiotherapy is the mainstay of treatment.

Elkon included the presence of metastasis and local extension of the tumor (e.g. ethmoidal, nasopharynx, orbital) as negative prognostic factors.[24] Dulguerov and Calcaterra considered tumor recurrence and metastases as significant negative prognostic factors.[16]

CONCLUSION

Olfactory neuroblastoma is a rare malignant tumor with varied clinical behavior. A proper diagnosis should be made through clinical, radiographic and histopathological findings and the tumor should be staged and graded before proceeding to surgery. Aggressive surgical resection and RT is the mainstay of treatment and patients must be followed up carefully as local or regional recurrences are most commonly associated.

Acknowledgements

1. Dr. Radhika M Bavle, MDS, Professor and Head of the Department of Oral pathology, Krishnadevaraya College of Dental Sciences and Hospital, Bangalore, Karnataka
2. Dr. Varsha Jadhav, MD, Department of General Pathology, Mamata Medical College, Khammam, Telangana.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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