CASE REPORT

Esthesioneuroblastoma presenting as tooth pain

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ABSTRACT

Esthesioneuroblastoma, also called olfactory neuroblastoma, is a rare malignant tumor originating in the olfactory epithelium in the upper nasal cavity with intracranial extension and may also be associated with secondary sinus diseases. Esthesioneuroblastoma has been observed to cause death by distant metastasis or by invasion through the cribriform plate and secondary meningitis. It usually produces nasal obstruction, epistaxis and less commonly anosmia, headache and pain. We report a case of esthesioneuroblastoma in a 50-year-old female who reported with tooth pain as a presenting symptom.

Key words: Esthesioneuroblastoma, malignancy, neoplasm, olfactory neuroblastoma

INTRODUCTION

Olfactory neuroblastoma or esthesioneuroblastoma is a rare malignant neoplasm of neuroectodermal origin arising from olfactory membrane of the sinonasal tract.[1] It was originally described in French Literature by Berger *et al.* in 1924 who coined the term "esthesioneuroepitheliome olfactif".[2] The various synonyms used for this entity are olfactory esthesio-neuroepithelioma, esthesio-neurocytoma, esthesio-neuroepithelioma, esthesio-neuroblastoma, olfactory neuroblastoma and olfactory placode tumor.[3,4] The first case in American literature was reported by Schall and Lineback in 1951.[2] It represents approximately 2-3% of all sinonasal tract tumors.[3] The incidence has been estimated at 0.4 per million. This tumor has broad histologic spectrum and is often histologically confused with peripheral neural ectodermal tumors and is notorious for its wide clinical behaviors. The common clinical symptoms include nasal obstruction, recurrent epistaxis, hyposomia, rhinorrhea, headache and visual disturbances.[1] Here we report a rare case of esthesioneuroblastoma in a female with presenting symptom as tooth pain.

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CASE REPORT

A 50-year-old female reported to the department of oral medicine with the complaint of pain in the left side of the upper jaw since seven months, which was spontaneous, dull and reduced on taking analgesics. She visited a general dentist five months ago and maxillary left second molar was extracted as it was considered as the causative tooth for pain, however, the patient did not get relief and the pain continued. She noticed swelling of left side of the face, which gradually increased in size and there was a concomitant decrease in size of her left eye opening and the eyeball was pushing superiorly since two months. Her medical and family history was noncontributory and upon general physical examination, all her vital signs were within normal limits. On extraoral examination, a diffuse swelling was seen on the left maxillary area extending from infraorbital margin to mid of the cheek supero-inferiorly and ala of nose to outer canthus of eye antero-posteriorly, which was soft in consistency and tender on palpation [Figure 1a]. Intraorally, swelling was evident on palpation extending from maxillary tuberosity to the vestibule causing vestibular obliteration till the posterior aspect, which was tender and soft in consistency on palpation [Figure 1b].

On the basis of history and clinical examination, a provisional diagnosis of malignant neoplasm of maxillary sinus was considered. Routine hematological investigations revealed the values to be normal. Panoramic and paranasal sinus view showed haziness in left maxillary sinus. The coronal CT revealed a large mass originating in left maxillary sinus with destruction of its medial, superior and postero-lateral wall. Medially, this mass was extending into left nasal fossa

leading to marked luminal compromise on the left side and superiorly extension into left orbit was noticed. Posteriorly it was extending into infra-temporal fossa, left masseteric space and left pterygomaxillary fissure. Partial erosion of anterior maxillary wall, hard palate and lateral pterygoid plate on left side and extension of this mass from lateral maxillary wall into left cheek was also noticed [Figure 2a and b].

Incisional biopsy was performed and on histopathological examination, hematoxylin and eosin stain showed basophilic cells arranged in large lobar sheets with intertwining connective tissue septa. Cells had large round nucleus with minimal pleomorphism and a thin rim of cytoplasm. Pronounced vascularity and formation of pseudorosettes (Homer-Wright type) were seen in some areas, suggestive of esthesioneuroblastoma [Figure 3a and b]. Immunohistochemistry revealed strongly positive neuron-specific enolase among the tumor cells and S-100 showed weak association [Figure 4a and b]. So based on clinical examination and the investigations performed, a final diagnosis of esthesioneuroblastoma was given. The case was referred to the oncology institute for the management and the patient was started with chemotherapy, cisplatin 50 mg (per day) and 5 fluorouracil 1 mg (per day), and recalled after 15 days; there was improvement in the symptoms after which the patient was lost to follow up.

DISCUSSION

Esthesioneuroblastoma is a rare malignant tumor arising from olfactory epithelium and its neural origin was established by Trojanowaski *et al.* in 1982 who demonstrated the presence of neurofilament proteins (NFP) in the tumor cells.[5] Though, it has been reported in patients as young as two years to 90 years, a bimodal age distribution has been noted in the second and sixth decades of life. There are no known etiologic agents for human olfactory neuroblastoma, however, injection of diethylnitrosamine in Syrian hamsters and N-nitrosopiperidine in rats has produced tumors histologically identical to human olfactory neuroblastoma.[3]

The common symptoms associated are unilateral nasal obstruction (70%) and epistaxis (46%), and less common manifestations are anosmia, headache, pain, excessive lacrimation and ocular disturbances. In the present case, the patient complained of pain in left maxillary molar teeth, which is a rare symptom and also, there was decrease in size of left eye, which may be due to superior extension of tumor in the left orbit. The most common site of origin is in the upper nasal cavity in the region of the cribriform plate; other primary sites such as maxillary sinus and nasopharynx have also been reported.[3] Esthesioneuroblastoma is generally believed to be derived from the neurosensory receptor cells of olfactory mucosa. It may also be present as intracranial tumor with an intranasal component.[6] Other sources of origin suggested include sphenopalatine ganglion by Escat, organ of Jacobson, ganglion of Luci by Martin *et al.* and olfactory placode.[3,7] The tumor in the present case was seen to arise from left maxillary sinus and extended to involve nasal fossa, infra-temporal fossa, masseteric space, cheek and the left orbit.

Kadish in 1976 classified esthesioneuroblastoma into three clinical stages. According to this classification, Stage A

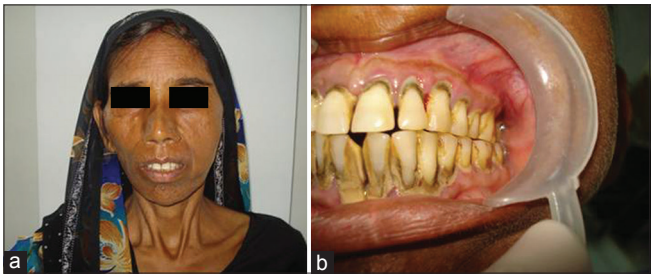

Figure 1: Clinical photograph showing swelling on maxillary region and decrease in the size of the left eye (a). Intraorally, vestibular obliteration was evident (b)

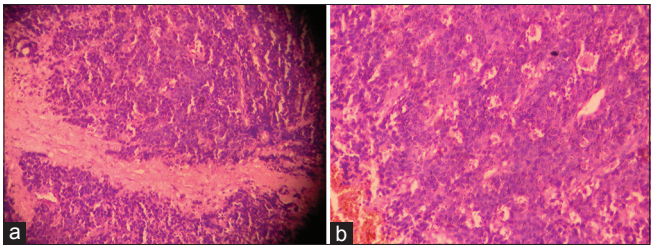

Figure 3: Photomicrograph showing cells arranged in sheets and intervening connective tissue stroma (a) (H&E stain, ×40). Photomicrograph showing cells with large round nucleus, thin rim of cytoplasm arranged in large sheets with intertwining connective tissue septa and formation of pseudorosettes (Homer-Wright type) (b) (H&E stain, ×100)

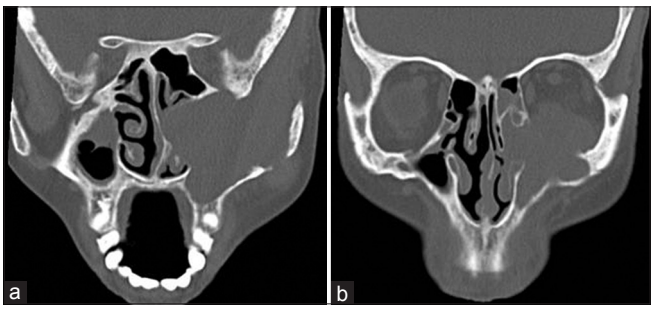

Figure 2: Coronal Computed Tomographic scan showing extension of lesion into sinus and nasal fossa

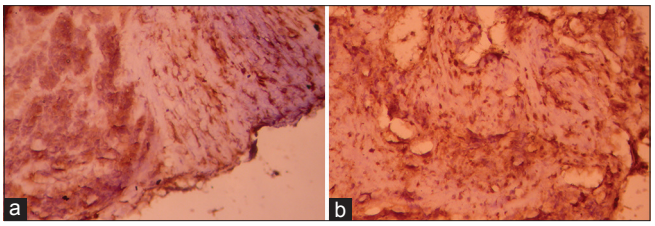

Figure 4: Immunohistochemistry showing strongly positive neuron-specific enolase among the tumor cells (a) (IHC stain, ×200) and weak association with S-100 protein (b) (IHC stain, ×200)

tumors are confined to the nasal cavity, Stage B tumors have paranasal sinus extension and Stage C tumors have extra-paranasal extension including the involvement of the cribriform plate, base of skull, orbit or intracranial cavity. This classification was modified by Morita *et al.* in 1993 who established Stage D in the classification for tumors with metastasis to cervical lymph nodes or distant site.[8] Kadish's classification has been used by various authors and appears to correlate well with the clinical outcome. The present case can be categorized as belonging to Stage C of Kadish's classification.

In evaluation of esthesioneuroblastoma, the extent of disease is best determined by pre- and post-contrast MR imaging in which there is intense signal in T2-weighted images with marked enhancement of T1-weighted images after gadolinium injection. Details of bone erosion (lamina papyracea, cribriform plate and fovea ethmoidalis) are better demonstrated by CT scan.[3] Tumor is presented as homogenous density mass, equal or greater to the surrounding soft tissue and no tumor cysts or calcifications. Contrast enhancement was usually moderate and homogeneous. Coronal images were of value in evaluating extension to the orbit and through the cribriform plate and the anterior cranial fossa.[9] Prado *et al.* (2001) demonstrated the usefulness of Technetinium-99m-ethyl cysteinate dimer (^{99m}Tc-ECD) SPECT in detection of olfactory neuroblastoma.[10]

Obert *et al.* (1960) stated that the characteristic histologic features of olfactory neuroblastoma are plexiform intercellular fibrils, round-to-oval-shaped nuclei with scanty cytoplasm, distinct and sharply defined chromatin, which may be coarse or fine, compartmentation of sheets of neoplastic cells into lobules by slender vascular fibrous septa, true neural rosettes (Flexner-Wintersteiner type) and pseudorosettes (Homer-Wright type). They concluded that if fibrils were absent, then the tumor cannot be classified as neuroblastoma with certainity.[3,7] Histologically neuroblastoma has been classified as olfactory neurocytoma (Pattern I of Mendeloff), a tumor with a sheet of round small cells separated by connective tissue septa and occasionally pseudorosettes; olfactory neuroepithelioma (Pattern II of Mendeloff), a tumor containing round to oval nuclei clear nuclear membrane, scant cytoplasm and rosettes; and a tumor similar to neuroblastomas found elsewhere in the body.[4]

Immunologically, it is most reactive with neuron-specific enolase (NSE) as seen in the reported case. It has shown reactivity with S-100, synaptophysin, NFP, class III beta-tubulin and microtubule-associated protein.[3] Light microscopy can usually establish the diagnosis, but highly undifferentiated tumors make this difficult. In case when light microscopy fails to establish diagnosis, electron microscopy is helpful. Electron microscopy evaluation reveals presence of dense core neurofilaments and neurotubules. Neurosecretory granules having features consistent with those of catecholamines are diagnostic of esthesioneuroblastoma. In addition, Schwann-like cells and junctional complexes may be identified.[3,4]

Esthesioneuroblastoma must be distinguished from lymphosarcoma, transitional cell carcinoma, plasmacytoma, reticulum cell carcinoma, small cell undifferentiated carcinoma and Ewing's sarcoma.[3,4] Small cell carcinoma typically is a submucosal hypercellular proliferation growing in sheets, cords and ribbons; the distinct lobular pattern of olfactory neuroblastoma is absent. The cells are small and hyperchromatic with oval- to spindle-shaped nuclei, absent nucleoli and minimal cytoplasm. Although uncommon, neural-type rosettes similar to those seen in olfactory neuroblastoma can be seen in association with small cell carcinoma. Small cell carcinoma can be differentiated from esthesioneuroblastoma by immunohistochemistry. In contrast to olfactory neuroblastoma, NSE reactivity in small cell carcinoma is more likely to be focal than diffusely positive and the S-100 protein staining, if present, is dispersed throughout the cellular proliferation and not limited to sustentacular cells.[3] Ewing's sarcoma is composed of solid sheets or masses of solid round cells with very little stroma, scanty cytoplasm and ovoid large nuclei; necrosis is common. Glycogen presence can be demonstrated by histochemistry and helps in differentiating with esthesioneuroblastoma. Lymphosarcoma may occasionally show intercellular cytoplasmic strands resembling fibrils. However, their diffuse growth and uniform round cells helps in differentiating them. The characteristic cells of plasmacytoma and so-called cylinders in cylindromas readily help in identifying these tumors. Small cell undifferentiated carcinomas does not contain fibrils and the distinct cytoplasmic borders can be seen.[7]

The current accepted standard of treatment is craniofacial resection followed by adjuvant radiotherapy to a dose of 55-65 Gy for Kadish stages B and C. Small Kadish Stage A disease is treated by surgery alone in some situations by some groups, but most suggest adjuvant radiotherapy for these lesions also. Neoadjuvant chemotherapy has been used in advanced disease and where complete resection is not possible, with cyclophosphamide, vincristine ifosphamide, etoposide and cisplatin combined with preoperative radiotherapy.[11]

The overall five, 10 and 15-year survival rates have been reported to be 78%, 71% and 68%, respectively.[3] Initial multimodality therapy is associated with five-year survival of 80% for low-grade tumors and 40% for high-grade tumors. The most hazardous and often fatal complication is intracranial extension of tumor through destruction of cribriform plate and orbital plates and secondly due to distant metastasis. The majority of the recurrences occur within the first two years. Prognosis has been correlated to clinical staging with five-year survival of 75-91%, 68-71% and 41-47% for stages A, B and C tumors, respectively. Other factors that have been implicated in prognosis include histologic grading, proliferation rate

and ploidy. Histologically lower grade tumors (Grades I and II) have been reported to have a better five-year survival than higher grade tumors (Grades III and IV).[3] The tumor metastasizes widely by both hematogenous and lymphatic routes, approximately 10-60% will experience distant metastasis.[1,3] The most common site for metastasis spread are cervical lymph nodes, and less frequent are lungs, brain, bone, spinal column, breast and abdominal viscera. Metastasis to the central nervous system is infrequent and in spinal cord 80% of metastasis is in cauda equine.[9]

CONCLUSION

Esthesioneuroblastoma is a rare neoplasm of nasal vault. Because of its rarity, this tumor has been difficult to recognize and diagnose pathologically and the wide spectrum of presentation of this tumor has resulted in its frequent misdiagnosis. Thus, the diagnosis of esthesioneuroblastoma demands a specialized and experienced head and neck pathologist, especially as incidence rate is low. Also, esthesioneuroblastoma may present, only as tooth pain as in the present case. So, it may be considered as a possible differential diagnosis, though rare in cases of dento-facial pain of idiopathic cause.

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