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**Case Report**

# Olfactory Neuroblastoma Presenting as a Submandibular Mass

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**Abstract:** Background: Olfactory Neuroblastoma is a rare, locally aggressive malignant neoplasm arising from the olfactory epithelium, which causes metastasis by lymphatic and haematogenous routes, with most common site being the cervical lymph nodes. Materials and Methods: Clinical history was retrieved from discussion in the Head and Neck multidisciplinary team meeting and medical records. Routine macroscopic and microscopic histological examination along with appropriate immunohistochemistry was performed. In addition, we include the review of literature of olfactory neuroblastoma metastatic to different sites. Results: A 75 year old female presented with a left submandibular mass which on biopsy was diagnosed as high grade neuroendocrine carcinoma requiring further investigation for characterising it as primary or metastatic. The histological diagnosis proved difficult and doubtful, till after five months when on follow up investigation a skull base lesion was identified, this on biopsy was confirmed to be an olfactory neuroblastoma. Conclusion: It is important to think laterally and consider metastatic tumours when evaluating neuroendocrine lesions in the submandibular region as this can be the first manifestation.

**Keywords:** Olfactory Neuroblastoma, Metastasis, Submandibular Gland

## 1. Introduction

Olfactory neuroblastoma (also known as esthesioneuroblastoma) is a rare neuroectodermal tumour, arising in the upper portion of the nasal cavity from the olfactory epithelium, first described by Berger in 1924 as 'esthesioneuroepitheliome olfactif' and accounts for approximately 3% of all sinonasal tumours [1, 2]. Metastases are usually synchronous or metachronous in patients with an established diagnosis of olfactory neuroblastoma, with cervical lymph nodes being the common site.

## 2. Case Report

A 75 year old female presented with a left sided submandibular mass, with no previous history of malignancy and no other lesions being evident on the routine body scans. The biopsy from the mass showed a neuroendocrine neoplasm. As primary neuroendocrine lesions of the salivary glands are very rare, the case was reported with the suggestion to rule out metastatic tumours, which are more common.

The head & neck, chest and abdomen scans were unremarkable. The serum calcitonin and CEA levels were within normal range. The multidisciplinary team decided to excise the left submandibular gland with a limited neck dissection.

The histology from the excision showed a salivary gland replaced by a solid tumour with small round cells, hyperchromatic nuclei, granular chromatin, inconspicuous nucleoli, nuclear moulding, high nuclear / cytoplasmic ratios and frequent mitosis [Figures 1, 2, 3, 4]. Extensive lymphovascular invasion with positive level II and III lymph nodes was evident. Tumour cells were strongly and diffusely positive for neuroendocrine markers chromogranin,

Synaptophysin and NF [Figures 5, 6] and showed focal cytokeratin expression; they were negative for TTF1, CK7, CK20, CEA, actin and calcitonin. The proliferation fraction by MIB 1 was approximately 15-20% [Figure 7].

Five months after the excision, an Octreotide scan showed uptake at anterior skull base, which on biopsy was confirmed to be an olfactory neuroblastoma. Following which an anterior composite resection was performed, demonstrating an olfactory neuroblastoma, Hyams III/IV and Kadish C. The tumour was protruding into the anterior cranial fossa without brain involvement and was staged Dulguerov T3. Positive surgical margin was noted focally.

On review, both the submandibular lesion and ethmoidal lesion showed similar morphology and the submandibular lesion was interpreted as metastatic olfactory neuroblastoma. The patient had post-operative radiotherapy and is currently on follow up.

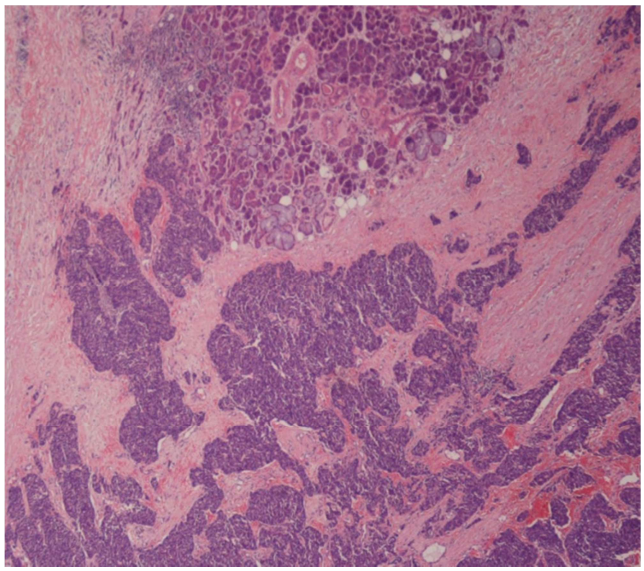

***Figure 1.*** *Submandibular gland involved by a high grade neuroendocrine tumour- metastatic olfactory neuroblastoma; no lymphoid tissue seen (excision specimen). (H&E 40X).*

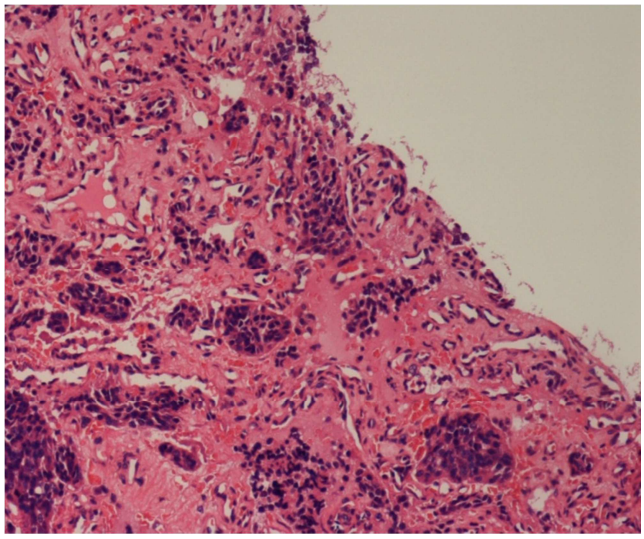

***Figure 2.*** *Core biopsy of the lesion showing similar pattern. (H&E 40X).*

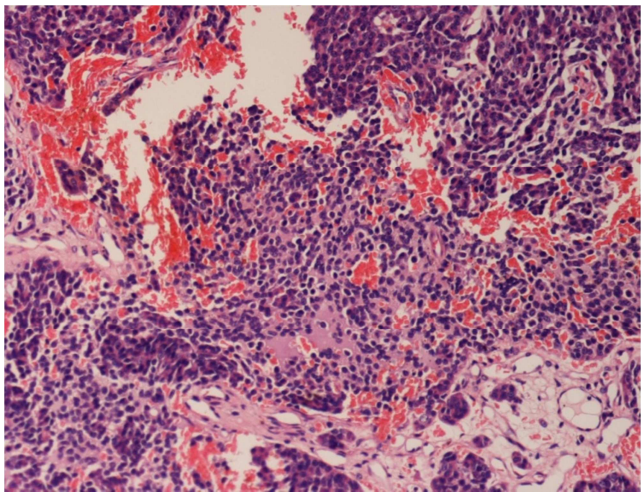

***Figure 3.*** *Tumour showing lymphovascular invasion. (H&E 40X).*

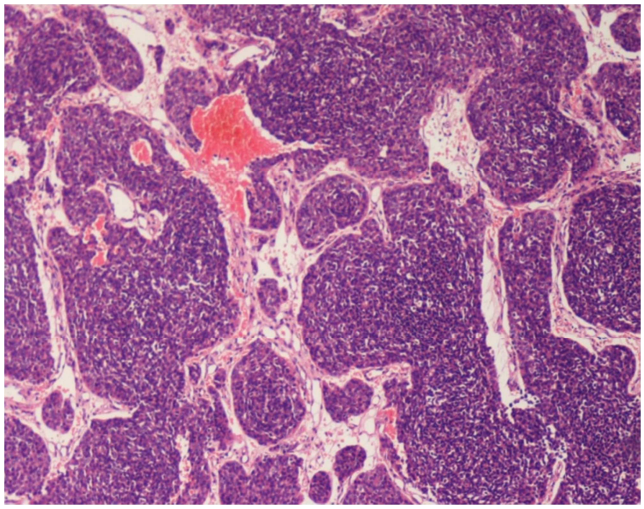

***Figure 4.*** *Organoid pattern showing small round cells with hyperchromatic nuclei, granular chromatin, inconspicuous nucleoli, nuclear moulding and high nuclear-to-cytoplasmic ratios. (H&E 100X).*

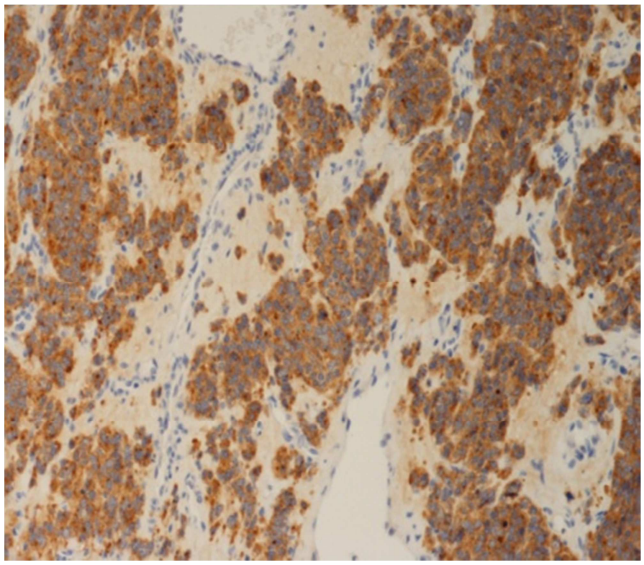

***Figure 5.*** *Tumour shows NF positivity. (NF 100X).*

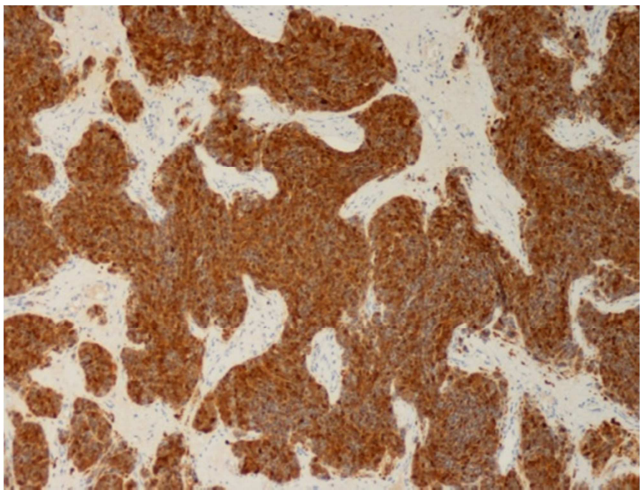

***Figure 6.*** *Synaptophysin showing tumour positivity. (Synaptophysin 100X).*

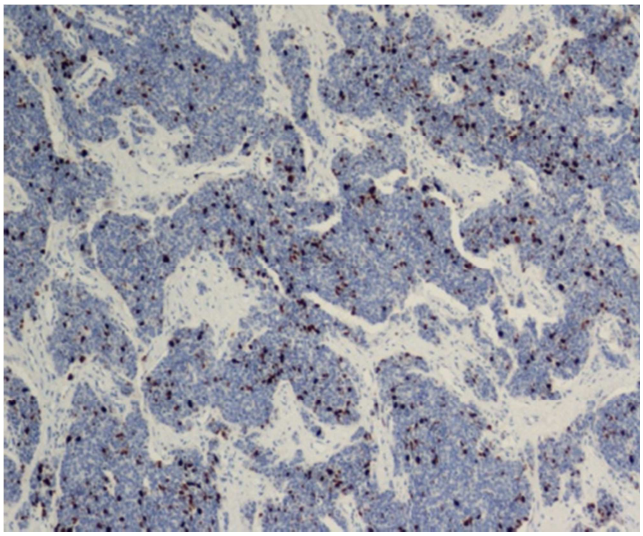

***Figure 7.*** *MIB1 showing proliferation fraction of up to 20% (MIB1 100X).*

## 3. Discussion

Olfactory neuroblastoma (ON) arises in the upper portion of the nasal cavity, with rare cases reported in lower nasal cavity and maxillary sinuses. Also there are cases of intracranial and intrasellar ON reported without an apparent intranasal component [3, 4]. The tumour was initially reported to be bimodal in age distribution, recent data however show an even distribution with a peak in fifth and sixth decades of life; ON has been reported in ages ranging from 2 to 90 years [2]. There are no well documented etiological agents or association with occupational exposure reported in literature.

A slight male predominance has been noted and the most common symptoms reported were unilateral nasal obstruction and epistaxis; with less common symptoms being anosmia, headache, proptosis, visual field defects and epiphora [2]. The challenges in characterization of ON are that they have a variable biological activity, ranging from relatively indolent to both locally aggressive and metastatic.

Metastasis usually involves cervical lymph nodes and the incidence reported ranges from 10-44% in literature [5]. The retropharyngeal lymph node metastasis needs to be assessed radiologically, given the clinical difficulty and the fact that they are not always included in neck dissections [6]. Nalavenkata et al in their study showed that histological grade was higher in patients with primary neck disease versus delayed neck disease and that ipsilateral nodal disease most commonly involved level II followed by level III and level IV. Positive surgical margin was associated with higher risk of delayed neck disease as compared to clear surgical margins [7, 8].

The sites of distant metastasis reported in various large scale and single case reports are brain, spinal cord, meninges, bone, bone marrow, lung, liver, dermal, breast, heart, parotid and thyroid gland [9-21] and Table 1. Buohliqa et al [18] have reported three unusual recurrences, distinctly distant from the primary site, raising the questions of what constitutes real recurrence versus embolic metastasis especially around the paranasal sinuses.

Histologically, ON are submucosal proliferation composed of cells arranged in lobules and nest showing increased nuclear/cytoplasmic ratios with characteristic salt and pepper nuclei. Nucleoli are inconspicuous. Neurofibrillary background is present particularly in low grade lesions.

The histological grading system was proposed by Hyams in 1988 on the basis of Armed Forces Institute of Pathology experience [22]. The grading from I to IV was based on a combination of lobularity, nuclear uniformity, mitotic figures, necrosis and presence of neurofibrillary background. Kadish proposed the staging system in 1976 as follows: A -limited to nasal cavity, B - involving the nasal and paranasal cavities and C - tumour extending beyond nasal and paranasal cavities [23]. Dulguerov et al proposed a TNM staging system, including the tumour characteristics, cervical neck nodal staging and distant metastasis [24].

Olfactory neuroblastoma presenting as primary submandibular mass can be a real diagnostic and therapeutic challenge as demonstrated by our case. Primary neuroendocrine tumours (NET) of salivary glands are exceedingly rare and represent a diverse group of neuroendocrine neoplasm ranging from well-differentiated to high grade neoplasm [25-27]. Meacham et al in their study on primary head and neck neuroendocrine carcinomas noted that these tumours are more prevalent in parotid, paranasal sinuses and supraglottic tumours [27]. A histological diagnosis of NET should be rendered only after complete clinical and radiological work-up to rule out metastatic origin which are more common especially lung and cutaneous metastasis.

Gnepp et al have described small cell carcinoma of salivary gland origin to be subdivided into small cell ductal carcinoma and small cell neuroendocrine carcinoma as they appear to arise from the ductal cells of the intercalated duct: one which contains cells that differentiate towards squamous/ductal cells, and other which contain neuroendocrine-like granules [25]. These tumours have better prognosis as compared to other neuroendocrine neoplasm.

Histologically, the list of differential diagnosis must include metastatic small cell carcinoma, Merkel cell carcinoma, rhabdomyosarcoma, metastatic medullary carcinoma of

thyroid, small cell melanoma and lymphoma. Microscopically, it is challenging to distinguish small cell neoplasm; however some helpful clues like presence of rhabdomyoblast in rhabdomyosarcoma, amyloid in medullary carcinoma of thyroid, melanin pigment and prominent nucleoli in melanoma, while diffuse infiltrate of dischoesive cells with large nuclei and clumped chromatin is helpful in identifying lymphoid neoplasm. The absence of immunoreactivity with TTFI, CK20, calcitonin, muscle, melanoma and lymphoma markers, together with the clinical and radiological correlation was required in excluding the other neuroendocrine tumours from lung, cutaneous, thyroid, soft tissue and lymphoid origin.

Salivary gland mass as sites of small cell carcinoma metastasis has been reported by Salama et al which demonstrated primary lung small cell carcinoma in three cases and breast carcinoma in one case [28]. Gulati et al showed a case of bronchial carcinoid metastatic to submandibular salivary gland [29].

***Table 1.*** *ON distant metastasis excluding cervical lymph node metastasis reported in literature (*More than one site involved).*

| Study | No. of cases | Site of metastasis | Time to distant metastasis |
|---|---|---|---|
| Chatterjee et al 1996[9] | 1 | Right ventricular wall | 13 years later |
| Shetty et al 2000[10] | 1 | Breast | During radiotherapy |
| Mrad et al 2005[11] | 1 | Breast | 2 years |
| Bachar et al 2008[12] | 3/39 | Bone, lung, retroperitoneum | Up to 39 months later |
| Mattavelli et al 2009[13] | 1 | Trachea | 18 months |
| Chew et al 2011[14] | 1 | Subcutaneous tissue | 4 years later |
| Tural et al 2011[15] | 11/18 | Spinal cord + meningeal (2), brain (6), bone marrow* (3), bone (1), lung (1) | 5.2-66.5 months |
| Larbcharoensub et al 2014[16] | 1 | Breast | 7 months |
| Ilson et al 2015[17] | 1 | Neck and left lung nodule | 2 years |
| Buohliqa et al 2015[18] | 3/3 | Maxillary sinus (2), sphenoid sinus (1) | 51 months -7 years |
| Banuchi et al 2016[19] | 13/57 | CNS (6), bone (3), leptomeningeal (4), dermal (1) | 9-134 months |
| Hussaini et al 2016[20] | 1 | Parotid gland | 30 and 40 months |
| Rahman M et al 2017[21] | 1 | Thyroid gland | 7 years |
| Current study 2019 | 1 | Submandibular gland | 5 months prior to primary diagnosis |

# 4. Conclusion

Neuroendocrine tumours, especially presenting as metastatic tumours, are difficult to localise by histology alone and varied series of test would be required before the final tumour localisation. Our case suggests that ON needs to be included in the list of differential diagnosis when dealing with unusual tumours of salivary glands with endocrine morphology.

# Conflicts of Interest

The Author's declare that there is no conflict of interest.

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