

**PRIMARY NEUROENDOCRINE TUMOUR OF MANDIBLE: A CASE REPORT WITH RADIOLOGICAL AND HISTOPATHOLOGICAL FINDING**Monika Gupta\*<sup>1</sup>, Virendra Singh<sup>2</sup>, Anjali Narwal<sup>3</sup> and Rajeev Sen<sup>1</sup><sup>1</sup>Department of Pathology, Pt. BDS, PGIMS, University of Health Sciences, Rohtak, India.<sup>2</sup>Department of Oral Surgery, PGIDS, University of Health Sciences, Rohtak, India.<sup>3</sup>Department of Oral Pathology, PGIDS, University of Health Sciences, Rohtak, India.**\*Corresponding Author: Monika Gupta**

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**ABSTRACT**

Neuroendocrine tumours (NETs) in the oral and maxillofacial region are extremely rare and accounts for only 4% of all cases. As per literature, 46 cases of NETs of maxillofacial region are reported till date. A sixty-four old male presented with swelling right side of face. Clinical examination revealed expansile swelling in the right mandibular region with intraoral extension causing restriction of jaw movement. Biopsy was performed. Microscopic examination revealed monotonous round to oval cells with hyperchromatic nuclei and scanty eosinophilic cytoplasm, infiltrating the fibrocollagenous connective tissue. Immunohistochemistry was performed. Although of uncommon occurrence, with poor prognosis, histopathology and immunohistochemistry is important and most significant tool in differentiating this tumour from other round cell tumours of this area in view of therapeutic connotation. The present case is one of the rarest possibilities as the provisional diagnosis was completely different to the histopathological diagnosis.

**KEYWORDS:** Immunohistochemistry, Mandible, Neuroendocrine tumour, small round cell tumour.**INTRODUCTION**

Malignant tumors of the mandible and maxilla are divided into primary tumors that originate within the jaw and metastatic tumours, predominantly oral cancers and systemic lesions that involve the mandible secondarily. The most common malignant tumor of the mandible is squamous cell carcinoma.<sup>[1]</sup>

Neuroendocrine tumors (NETs) are a rare type of tumor, originating in the cells of the neuroendocrine system and occurs in different locations. NETs arise preferentially in the bronchopulmonary tree (30%) or gastrointestinal tract (50%) while the extra-pulmonary form accounts for only 4% of all cases.<sup>[2,3]</sup> NET in the oral and maxillofacial region are extremely rare.<sup>[4,5]</sup> The tumour is highly anaplastic with poor prognosis. The premolar and molar region is the most common site of localization. Immunohistochemistry is very important and the most significant tool in differentiating this tumour from tumour of other histogenetic origin.<sup>[6]</sup> We present a rare case of neuroendocrine tumour of mandible with clinical, radiological, pathological and immunohistochemical features.

**CASE SYNOPSIS**

A 64-year-old male was referred to our institute with a complaint of painless swelling on the right side of the face from 4 weeks duration. He also complained of inability to chew food however there was no history of fever and weight loss. He was a chronic smoker with 10-20 bidis/day from last 30 years. There was no history of any chronic illness. Extra-oral examination revealed the presence of an expansile swelling in the right mandibular region. There was stretching of the skin on the right side of face over the swelling. On intraoral examination, jaw movement restricted in all plane along with a visible swelling on right side of cheek obliterating the vestibule extended from anterior border of ramus to just short of corner of mouth. Overlying mucosa was healthy and pink in colour, firm to hard on palpation and nontender. Adjacent molar tooth was periodontal compromised a sessile. Systemic examination was within normal limits. (Figure 1).

Magnetic resonance imaging (MRI) scan demonstrated a altered signal intensity showing hyperintensity on T2 and STIR/PDFS and hypointensity on T1W sequence causing lytic destruction of ramus and coronoid process of mandible on right side with large extraosseous component measuring 53 mm × 60 mm × 76 mm with loss of fat plane. Lesion is showing speculated periosteal

reaction, edema and small intraoral extension measuring 18mm × 24 mm. (Figure 2).

An incisional biopsy of soft tissue from ramus and coronoid process of mandible was done. On microscopy, a skin covered soft tissue piece revealing chronic nonspecific inflammatory granulation tissue and tumour cells arranged in solid sheet and clusters. The cells are monotonous having round to oval hyperchromatic nuclei and scanty eosinophilic cytoplasm. The tumor cells were seen infiltrating the fibrocollagenous connective tissue with focal areas of necrosis; the mitotic activity was 1-2/HPF.

Based on Hematoxylin and eosin stained section morphological diagnosis of small round cell tumour was made. Histochemical stain and immunohistochemistry (IHC) were done for further subcategorization of these cells. On Periodic acid Schiff (PAS) stain the cytoplasm of the cells were negative. With primary panel of IHC markers cells were positive for cytokeratin (epithelial marker), negative for vimentin and desmin (mesenchymal markers) and leucocyte common antigen CD45 (lymphoma marker), ruling out the possibility of lymphoma and mesenchymal tumours. Secondary panel of antibodies were applied for further narrow down the

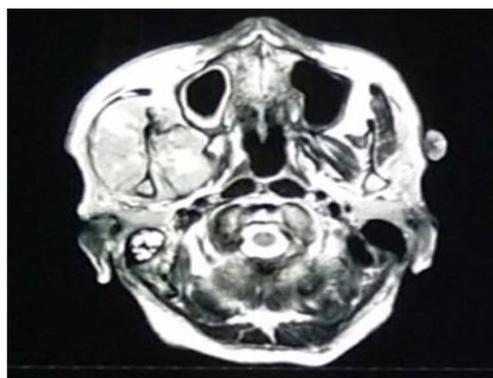
possibilities. Cells were positive for neuron specific enolase, chromogranin, synaptophysin and S-100 (neural differentiation markers), negative for Human Melanoma Black (HMB 45) (marker for melanoma), Thyroid Transcription Factor-1 (TTF1), CD99 and epithelial membrane antigen. (Figure 3).

The final diagnosis was given by correlating the findings of histopathology, PAS and IHC which favored small round cell tumour with neuroendocrine differentiation.

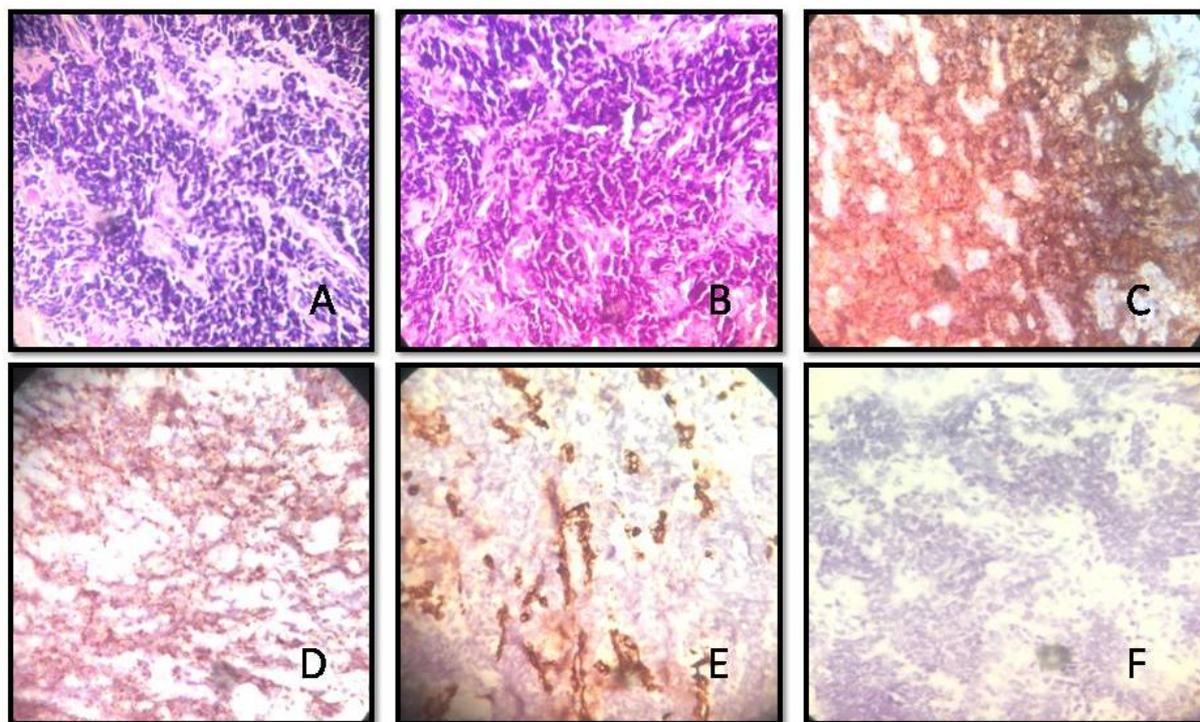
As this is an uncommon site for primary neuronal tumour patient was further investigated. No evidence of primary lesion was detected on CT scan of the brain, thorax, and abdomen. A bone marrow aspiration and biopsy revealed normal study. Surgery was planned but patient refused to give consent for the surgery. So a combination of concurrent chemotherapy and radiotherapy was given. Adjuvant chemotherapy with cisplatin and etoposide six cycles and total 60 Grey external beam radiotherapy was given. Post therapy patient is in regular follow up for last 6 months with no local recurrence or distant metastasis. However; patient is not willing to undergo any further investigations or biopsy to look for any recurrence.



**Fig. 1: Clinical photographs including intraoral view showing swelling on right side of face.**



**Fig. 2: MRI of face showing lytic destruction of ramus and coronoid process on right side of mandible with large extraosseous component.**



**Fig. 3:** (A) Microsection examined show tumour cells arranged in solid sheets and clusters having round to oval hyperchromatic nuclei and scanty eosinophilic cytoplasm (Hematoxylin and Eosin stain, 400X); (B) On Periodic Acid Schiff staining, cells were negative; On Immunohistochemistry, cells were positive for (C) Chromogranin; (D) Cytokeratin; negative for (E) Vimentin and; (F) Leucocyte Common Antigen .

## DISCUSSION

NETs derive from neuro-ectodermal cells that are dispersed throughout the body constitute a heterogeneous group of neoplasms. Common primary sites are lung, gastrointestinal tract that includes esophagus, pancreas, small intestine and large intestine, genitourinary system including uterus, cervix, urinary bladder and prostate, larynx, breast, and lacrimal gland. Extra-pulmonary primary small cell neuroendocrine carcinomas are uncommon malignant neoplasms, most NETs in the head and neck region occur in the larynx and salivary glands. In oral cavity primary NETs are rare most commonly arise from gingiva, tongue, retromolar region, uvula, floor of the mouth, mandible, and buccal mucosa.<sup>[7,8]</sup>

The true histogenesis of oral NETs is not known. There are various hypothesis proposed for their origin that includes origin from neuroendocrine cells located at the basal layer of the oral squamous epithelium, from primitive and pluripotent indifferent cells of either the squamous epithelium or minor salivary gland or from multi-potential stem cells<sup>2,6</sup>. Recently molecular evidence suggest that it is the genetic alteration/ progression in the organ specific carcinoma that give rise to small cell elements later in course.<sup>[2]</sup>

Diagnosis by histological examination is challenging as it is morphologically similar to its pulmonary counterpart. Definitive diagnosis is made by correlation with immunohistochemistry. In our case, it is an uncommon site for the tumour so to categorize the tumor

besides hematoxylin and eosin staining immunohistochemistry was performed to rule out the common tumours. Immunohistochemical analysis of NETs was positive for keratin a epithelial marker and neuroendocrine markers (chromogranin, synaptophysin and NSE), while negative for high molecular weight cytokeratin 34 $\beta$ E12 and p63, lymphoma marker (LCA) and HMB 45 marker for melanocytes. Therefore, the final diagnosis of the present case, according to the histological and immunohistochemical features, was primary NET.

As per literature, 46 cases of NETs of maxillofacial region are reported till date with three histological types that include small cell carcinoma, merkel cell carcinoma and carcinoid tumour. Most of the (80%) patients were treated by surgical resection, (10%) were by radiation alone and (4.3%) with radical neck dissection and radiation while in (4.3%) cases no details were available.<sup>[5]</sup>

Management of oral cavity neuroendocrine tumour is a controversial subject due to rarity of this neoplasm. No specific recommendation for the management guidelines or treatment options. In our case as patient refused for surgery we offered him chemotherapy and radiotherapy to which he responded very well. So, it is important to report single institution experience which may help in forming the consensus guidelines for its treatment and prognosis.

Although NETs are usually aggressive tumours, the prognosis of NETs of oral cavity is obscure and it varies with size, location and histology of the tumour. Both local invasion and distant metastasis are reported. In our case, clinical investigations failed to detect systemic involvement and also tumour was having a low mitotic index the possibility of metastasis is low.

The presentation of a malignant lesion in the orofacial region may be the first indication of the existence of unknown malignancy at distant primary site. Although of uncommon occurrence, it is crucial to distinguish NETs from other tumours of this area in view of therapeutic connotation. As only very few cases reported in the literature; to know the exact origin, their clinical behavior with respect to malignant potential and management more institutional studies are required. This will help in developing a personalized treatment approach for these patients.

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