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Primary Neuroendocrine Carcinoma of the Palate: A Case Report

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ABSTRACT

Primary neuroendocrine carcinomas (NECs) of the oral cavity represent exceptionally rare malignancies (< 30 reported cases globally), posing significant diagnostic challenges due to histological mimicry of other round cell tumors and nonspecific clinical presentation. This report details a novel case with atypical clinicopathological features and favorable therapeutic outcomes. A 38-year-old male presented with a 3-month history of a right hard palate ulceration. Clinical examination revealed an indurated endophytic lesion. Histopathology and immunohistochemistry confirmed poorly differentiated large cell NEC. Due to unresectable pterygopalatine fossa involvement, chemoradiation was administered. Given the extreme rarity of oral large cell neuroendocrine carcinoma (LCNEC), clinicians must consider this entity even in patients lacking traditional risk factors (e.g., smoking). Its aggressive growth pattern and metastatic propensity necessitate prompt specialist referral for early intervention.

Keywords: Oral pathology; Neuroendocrine carcinoma; Large cell carcinoma.

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Introduction

Neuroendocrine carcinomas (NECs) are a heterogeneous group of malignancies arising from neuroendocrine cells, most frequently occurring in the pulmonary and gastroenteropancreatic systems [1]. However, primary neuroendocrine carcinomas of the head and neck region are exceptionally rare, accounting for less than 1% of all malignancies in this anatomical site [2]. Among these, oral cavity NECs are particularly uncommon, with the palate representing an exceedingly unusual location [3]. Due to their rarity and nonspecific clinical presentation, these tumors often pose significant diagnostic challenges, leading to delays in appropriate management [4]. The World Health Organization (WHO) classifies NECs into well-differentiated neuroendocrine tumors, poorly differentiated neuroendocrine carcinomas (NECs), and mixed neuroendocrine-non-neuroendocrine neoplasms [1].

High-grade NECs, including small cell and large cell variants, are particularly aggressive, with a propensity for early metastasis and poor prognosis [5]. Immunohistochemical markers, such as synaptophysin, chromogranin-A, and CD56, are essential for a definitive diagnosis, as NECs often mimic other round cell tumors [6]. Given their rarity in the oral cavity, NECs resemble diverse neoplasms common in the head and neck region, further complicating clinical management [7]. To date, fewer than 30 cases of oral and maxillofacial NEC have been reported in the literature, underscoring the need for increased awareness among clinicians and pathologists [3]. This case report presents an extremely rare instance of primary high-grade NEC of the palate, highlighting its clinicopathological features, diagnostic challenges, and therapeutic considerations. By contributing to the limited body of evidence, this report aims to enhance recognition of this rare entity and guide optimal multidisciplinary management strategies.

Case Description

A 38-year-old male presented to the Oral and Maxillofacial Surgery Clinic at Ayatollah Kashani Hospital, Isfahan, Iran, with a 3-month history of a persistent ulceration on the right hard palate. Intraoral examination revealed an indurated endophytic lesion measuring 3.5 cm × 2.5 cm, with ulceration, necrotic surface, and ill-defined borders [Figure 1]. The lesion was non-tender, with no bleeding or purulent discharge. The patient reported no systemic diseases, genetic disorders, substance use (tobacco/alcohol), or relevant family history. Hematological investigations were within normal limits.

Diagnostic Imaging

Panoramic radiography demonstrated a radiolucent lesion with poorly defined margins extending from the maxillary left second premolar to the tuberosity, with destruction of the maxillary sinus floor and tuberosity. Contrast-enhanced computed tomography (CT) revealed a soft tissue mass (4.1 cm × 3.2 cm) eroding the ipsilateral maxillary tuberosity, palatine bones, medial pterygoid plate, and sinus floor, with invasion into the oral cavity, maxillary sinus, oropharynx, and masticatory spaces [Figure 2]. Given the higher prevalence in the oral and maxillofacial region, malignant salivary tumors, squamous cell carcinoma (SCC), and osteosarcoma were suggested as clinical differential diagnoses.

Histopathological Analysis

An incisional biopsy yielded two tissue fragments measuring 2.5 cm × 1.5 cm × 0.5 cm, and microscopic examination revealed diffuse sheets of poorly differentiated malignant round and polygonal cells exhibiting the following histopathological features [Figure 3]:

- A high nuclear-to-cytoplasmic ratio.
- Nuclear hyperchromatism and pleomorphism.
- Frequent mitotic figures (≥ 15 per 10 high-power fields). Based on these morphological characteristics, tissue block sections were prepared for immunohistochemical staining to evaluate differential diagnoses, including lymphoma, Ewing sarcoma, neural tumors, and high-grade epithelial malignancies. Immunohistochemical analysis of tumor cells demonstrated the following reactivity profile [Figure 4]:
- Positive staining: Epithelial membrane antigen (EMA), neuron-specific enolase (NSE), Vimentin, and Ki-67 (> 50% nuclear positivity).
- Focal positivity: Pancytokeratin (Pan-CK), S100 protein, and Synaptophysin (SPY).
- Negative staining: Leukocyte common antigen (LCA), CD99, P63, and Chromogranin-A (CgA).

These findings confirmed poorly differentiated large cell neuroendocrine carcinoma (LCNEC).

Treatment & Follow-up

Whole-body PET-CT and brain MRI confirmed no

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distant metastases. Given tumor extension into the pterygopalatine fossa and surgical risks, the multidisciplinary team initiated chemotherapy: cisplatin (80mg/m²) + etoposide (200 mg/m²) for two 21-day cycles. Subsequent radiotherapy (66 Gy/33 fractions over 35 days) achieved significant regression [Figure 1]. At 12-month follow-up, surveillance CT (head/neck/chest) and bone scan showed no recurrence or metastasis.

Ethical Compliance

Informed consent was obtained. The study received ethical approval from Isfahan University of Medical Sciences (IR.MUI.MED.REC.1403.207).

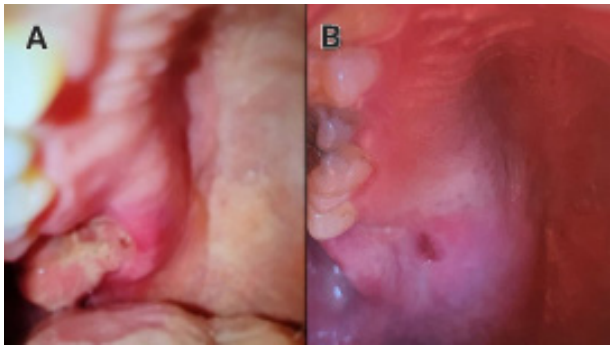

Figure 1. Intraoral view A) Ulceration on the right hard palate B) Remission in 12-month follow-up after receiving chemoradiation.

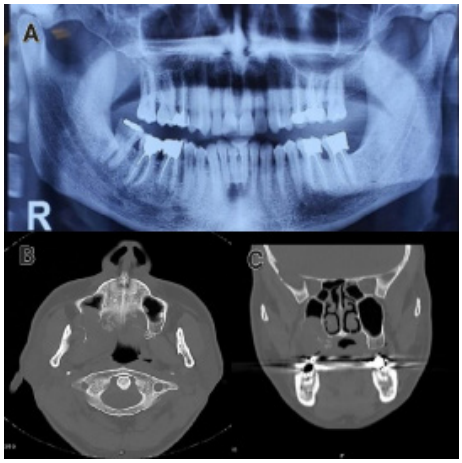

Figure 2. I Radiographs in A) panoramic view demonstrating a radiolucent lesion with poorly defined margins extending from the maxillary left second premolar to the tuberosity, with destruction of the maxillary sinus floor and tuberosity and B) Axial CT-scan and C) Coronal CT-scan revealing a soft tissue mass (4.1 cm × 3.2 cm) eroding the ipsilateral maxillary tuberosity, palatine bones, medial pterygoid plate, and sinus floor, with invasion into the oral cavity, maxillary sinus, oropharynx, and masticatory spaces.

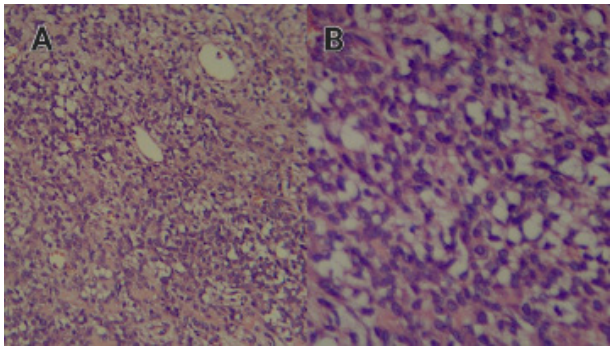

Figure 3. Microscopic view of A) H&E staining (x100) and B) H&E staining (x400) revealing diffuse sheets of poorly differentiated malignant round and polygonal cells.

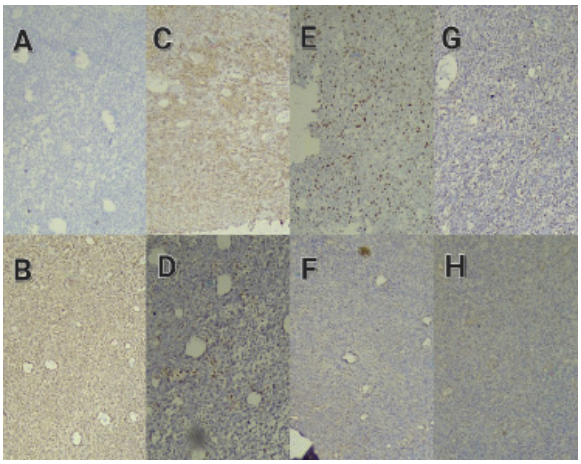

Figure 4. Microscopic view of immunohistochemical staining (x100) for A) LCA -, CD99 -, P63 -, CgA + B) vimentin +, C) EMA +, D) NSE +, E) ki67 > 50%, F) Pan-CK +, G) S100 +, H) SPY+.

Discussion

The initial clinical misdiagnosis of this lesion as a conventional salivary gland malignancy, osteosarcoma, and SCC highlights the diagnostic dilemma posed by NECs in unusual anatomical sites. As emphasized in the WHO classification of head and neck tumors [2], NECs frequently mimic other round cell tumors due to their undifferentiated morphology. Our case demonstrated characteristic features of high-grade NEC, including diffuse proliferation of round and polygonal cells with nuclear hyperchromatism and frequent mitoses (> 15/10 HPF), features consistent with Rindi et al.'s 2018 consensus criteria for poorly differentiated NEC [1]. The immunohistochemical profile proved pivotal for diagnosis; positivity for NSE, EMA, S100, SPY, and Pan-CK confirmed neuroendocrine/epithelial lineage, while negative staining for LCA, CD99, and

p63 excluded lymphoma, Ewing sarcoma, and poorly differentiated SCC, respectively. The absence of CgA, while unusual, has been documented in poorly differentiated variants [6]. This pattern reflects the immunohistochemical heterogeneity noted by Bellizzi [8], where incomplete expression of neuroendocrine markers occurs in 15-25% of cases. We also observed diffuse and strong expression of the Vimentin, which was only observed in Terada's case in 2013 [9].

Comparative Analysis with Literature

This case exhibits three significant divergences from Schuch et al.'s [3] systematic review findings: **(1)** a notably younger presentation age (38 years versus the reported median of 64 years), **(2)** an absence of disease progression following therapy (contrasting with progression in 83% of reviewed LCNECs), and **(3)** no evidence of distant metastasis (compared to a 62% metastatic rate, predominantly pulmonary > hepatic, in the literature). Furthermore, as stated by Perez-Ordonez's study in 2018 [10] , 91% of patients reported being ex or current smokers and/or consuming alcohol; however, our patient denied these kinds of habits.

Therapeutic Strategy and Outcomes

The tumor's extension into the pterygopalatine fossa rendered complete surgical resection prohibitively risky due to potential neurovascular damage. This necessitated a platinum-etoposide-based chemoradiation protocol adapted from guidelines for the treatment of pulmonary NEC [11]. The regimen (cisplatin 80 mg/m² + etoposide 200 mg/m² × 2 cycles ⟶ 66 Gy radiotherapy) achieved complete remission of tumor – an exceptional outcome given Schuch et al.'s [3] systematic review reporting 71% mortality at 24 months in oral NECs. This favorable response may be attributable to early therapeutic intervention (≤ 4 months post-symptom onset), supratherapeutic radiation dosing (66 Gy versus the historically suboptimal 50-60 Gy range), and multimodal sequencing incorporating chemotherapy debulking before radiotherapy.

The favorable outcome aligns more closely with Agea Martínez et al.'s [4] floor-of-mouth LCNEC, suggesting that non-sinonasal NECs may have better treatment responsiveness than previously assumed. In addition, nearly 80% of the 493 head and neck NEC patients in Yan et al.'s study had distant metastases [12]. This suggests that oral and maxillofacial NEC may have a lower potential rate of metastasis compared to other anatomical sites. However, patients with oral and maxillofacial NEC typically have a poor prognosis [3]. Such tumors usually exhibit rapid growth within months, and the occurrence of cervical nodal metastases is frequently observed with extremely poor prognosis [3,4]. The present case study of oral and maxillofacial NEC is exceptionally unique because there was no evidence of nodal metastasis, even after an extensive MRI workup for the patient. A bone scan and computed tomography imaging of the head, neck, and chest at a 12-month follow-up also showed no metastases or local recurrence.

Conclusion

Given the exceptional rarity of LCNEC in the oral mucosa, clinicians should maintain a high index of suspicion for this entity irrespective of patient smoking or alcohol consumption history. The aggressive biological behavior of LCNEC—characterized by rapid local progression and high propensity for regional/distant metastasis—necessitates early histopathological diagnosis and prompt referral to specialized oncology services. Definitive diagnosis requires immunohistochemical confirmation, with neuroendocrine markers (e.g., SPY, CgA, CD56) constituting an essential diagnostic component. While surgical resection historically represented the primary therapeutic modality, contemporary management increasingly employs combined-modality therapy incorporating chemoradiation, which has demonstrated significant survival benefit in select cases (including the present report). This manuscript provides clinicopathological insights to enhance diagnostic acuity and therapeutic decision-making for oral/maxillofacial pathologists and oncologists encountering this uncommon malignancy.

Conflict of Interest

There is no conflict of interest to declare.

References

[1] Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol. 2018; 31(12):1770–86

[2] El-Naggar, Chan AK, Grandis J, Takata JR, Slootweg T. World Health Organization classification of head and neck tumours. 4. IARC Press; 2017.

[3] Schuch LF, Schmidt TR, de Oliveira Zigmundo G,

 DOI: 10.18502/jcr.v12i3.20628

Kirschnick LB, Silveira FM, Martins MAT, et al. Oral and maxillofacial neuroendocrine carcinoma: A systematic review. Head Neck Pathol. 2021; 16(2):525–37

[4] Agea Martínez M, Navarro Cuéllar I, Sada Urmeneta A, Alijo Serrano F, Navarro Cuéllar C. Large cell neuroendocrine carcinoma on the floor of the mouth: a rare entity in an unusual location. Int J Oral Maxillofac Surg. 2022; 51(6):742–5

[5] Benzerdjeb N, Traverse-Glehen A, Philouze P, Bishop J, Devouassoux-Shisheboran M. Poorly differentiated neuroendocrine carcinoma of the head and neck: human papillomavirus tumour status/p16 status and impact on overall survival. Histopathology. 2020; 76(4):581–91

[6] Vanoli A. The spectrum of neuroendocrine neoplasia: A practical approach to diagnosis, classification and therapy by Sylvia L. Asa, Stefano La Rosa, Ozgur Mete. Endocr Pathol. 2023; 34:361–2

[7] Bal M, Mittal N, Rane S, Rabade K, Patil A. Primary neuroendocrine carcinoma in oral and maxillofacial region: a comprehensive study of twelve rare cases including mixed neuroendocrine non-neuroendocrine carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol. 2024; 138(2):e43

[8] Bellizzi AM. Immunohistochemistry in the diagnosis and classification of neuroendocrine neoplasms: What can brown do for you? Hum Pathol. 2020; 96:8–33

[9] Terada T. Pathologic diagnosis of large cell neuroendocrine carcinoma of the lung in an axillary lymph node: a case report with immunohistochemical and molecular genetic studies. Int J Clin Exp Pathol. 2013 May 15; 6(6):1177-9

[10] Perez-Ordoñez B. Neuroendocrine carcinomas of the larynx and head and neck: Challenges in classification and grading. Head Neck Pathol 2018; 12(1):1–8

[11] Gadducci A, Carinelli S, Aletti G. Neuroendrocrine tumors of the uterine cervix: A therapeutic challenge for gynecologic oncologists. Gynecol Oncol. 2017; 144(3):637–46

[12] Yan O, Xie W, Teng H, Fu S, Chen Y, Liu F. Nomograms forecasting long-term overall and cancer specific survival of patients with head and neck neuroendocrine carcinoma. Front Oncol. 2021; 11:619599.