Case Report

Large cell neuroendocrine carcinoma of oral cavity: A rare case report with review of literature

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Abstract

Neuroendocrine tumours (NETs) primarily affect the lungs and larynx. Primary neuroendocrine carcinomas (NECs) rarely occur in the oral cavity. The classification of these tumours is ambiguous; however, the literature acknowledges their aggressiveness. Merkel cell carcinoma (MCC) is rare and more common in the skin but could occur intraorally. MCC and NECs are aggressive neoplasms and recommend intensive treatment. In this case report, a 22-year-old female presented with an ulceroinfiltrative lesion in the left buccal mucosa of the cheek, which was diagnosed as primary NEC in the oral cavity. This patient underwent wide local lesion excision of oral cavity mass, ipsilateral selective neck node dissection of levels 1–4 and postoperative chemotherapy. This aggressive tumour type requires large local excisions with margins like Merkel cell skin carcinomas. To our knowledge, this is the youngest oral cavity primary neuroendocrine cancer patient to date in the literature.

Keywords: Buccal mucosa, neuroendocrine tumours, oral cavity

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INTRODUCTION

Neuroectodermal neoplasms are classified into two distinct groups. Group I comprises neoplasms that exhibit principally epithelial differentiation, including NECs. On the other hand, Group II encompasses neoplasms that do not exhibit epithelial differentiation, such as olfactory neuroblastoma, malignant melanoma, paraganglioma, neurofibroma and peripheral neuroectodermal tumours.[1] Neuroendocrine carcinomas (NECs) constitute a diverse group of tumours that exhibit variations in terms of their anatomical sites, clinical presentations, histological characteristics, cellular origins, levels of differentiation, biological behaviours and prognostic outcomes.[2] The larynx is the primary site of origin for the majority of NECs in the region of the neck and head. According to the available literature, the salivary glands have been identified as the second most frequently occurring site.[3] There are only 31 cases of NECs reported in the oral and maxillofacial cavities, to the best of our knowledge.[4-6]

This case report describes a rare case of primary NEC in the oral cavity of a 22-year-old young girl. The classification, clinical manifestation, differential diagnosis, histomorphology with immunohistochemistry findings, treatment and prognosis are also discussed in the present case report.

CASE REPORT

A 22-year-old young girl was presented to the Department of Oral and Maxillofacial Surgery of our institute in August

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2021 with a rapidly growing ulceroinfiltrative painless lump in the buccal mucosa of the left cheek. The mass was observed by her in April 2021. She had a history of chronic smoking and tobacco chewing for the last 5 years. The intraoral examination revealed the presence of a pale greyish white, non-tender, indurated lump, which was elliptical in shape, extending from the first premolar to the last molar and had indistinct borders. The dimensions of the lump were approximately 3.5 × 1.5 × 1.0 cm. It was observed to adhere to the overlying ulcerated mucosa [Figure 1]. No organomegaly or lymphadenopathy was noted on examination. Rhinoscopy, otoscopy and nasoscope were used to examine the entire nose, ear and throat. No significant abnormalities were identified. She exhibited no clinical manifestations of carcinoid syndrome, including flushing, diarrhoea, wheezing and other hormonal imbalances. Based on clinical examination, a differential diagnosis of squamous cell carcinoma (SCC), rhabdomyosarcoma and Merkel cell carcinoma (MCC) was considered. A fine needle aspiration cytology was requested from the lesion, which revealed cellular smears displaying pleomorphic cells with enlarged eccentric nuclei, fine to coarse chromatin and a moderate amount of cytoplasm on a haemorrhagic background [Figure 2a and b]. The fine needle aspiration findings suggest a differential diagnosis comprising of poorly differentiated SCC (PDSCC), MCC, rhabdomyosarcoma, neuroendocrine neoplasm, malignant melanoma, plasmablastic lymphoma and Ewing sarcoma. An incisional diagnostic biopsy of the mass was performed. Microscopically, the section showed a tumour infiltrated under the oral squamous epithelium and composed of round to oval cells that are disposed in nests and clusters lying in the oedematous stroma [Figure 2c and d]. These tumour cells are enlarged and have anisokaryotic nuclei, irregularly distributed chromatin and a scant amount of cytoplasm. Immunohistochemical staining was performed to resolve the diagnostic dilemma and showed that the tumour cells were positive for synaptophysin, chromogranin A and neuron-specific enolase, with focal positivity for cytokeratin (CK; AE1/AE3). The Ki-67 proliferation index was ~90% among tumour cells. The tumour cells were negative for vimentin, HMB-45, leucocyte common antigen (LCA), CK-5/6, 34bE12, CK-7, CK-20 and CD99 [Figure 3a-d]. Further investigations included magnetic resonance imaging (MRI) of the head and neck, computerized tomography (CT) scans of the thorax and abdomen and routine blood investigations. There was no significant finding noted. The positron emission tomography (PET) scan revealed a specific area of enhanced uptake exclusively in the main lesion and the adjacent soft tissues. Throughout the entire body, no active uptake was seen elsewhere. Based on the aforementioned findings, a diagnosis of primary large cell NEC of the oral cavity was established.

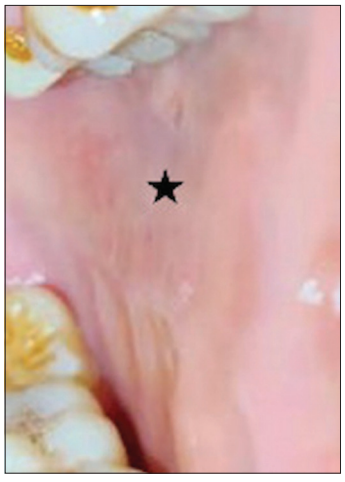

Figure 1: Clinical photograph displayed intraoral lump adhered with overlying ulcerated mucosa

Surgery and post-op treatment were planned after the tumour board meeting. General anaesthesia was used for extensive local excision of the primary lesion and ipsilateral selective neck dissection (levels 1–4). Resected regional lymph nodes showed no metastasis, and recovery following surgery was uncomplicated. The patient tolerated six cycles of adjuvant treatment with cisplatin (80 mg/m^2) and etoposide (100 mg/m^2) on days 1–3 of a 21-day

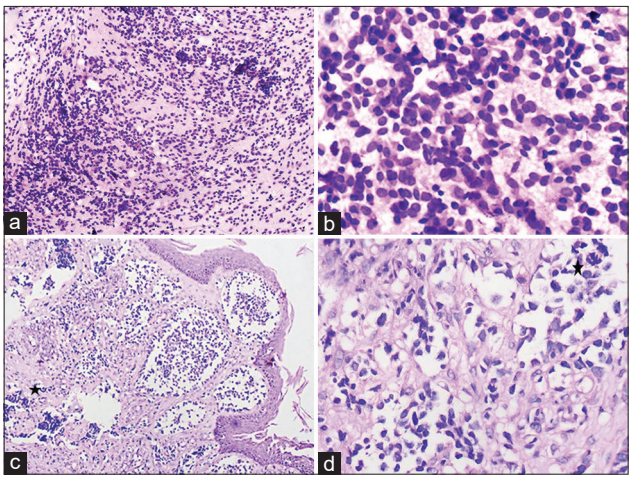

Figure 2: (a) Fine needle aspiration smear revealed cellular smears displaying small clusters and singly scattered pleomorphic cells on a haemorrhagic background (Giemsa stain, x100), (b) high power view displayed enlarged eccentric nuclei, fine to coarse chromatin and a moderate amount of cytoplasm (Giemsa stain, x400), (c) section showed a tumour infiltrated under the stratified squamous epithelium and disposed in nests and clusters lying in the oedematous stroma (Haematoxylin and Eosin stain, x100), (d) high power view revealed enlarged round to oval tumour cells, anisokaryotic nuclei, irregularly distributed chromatin and a scant amount of cytoplasm (Haematoxylin and Eosin stain, x400)

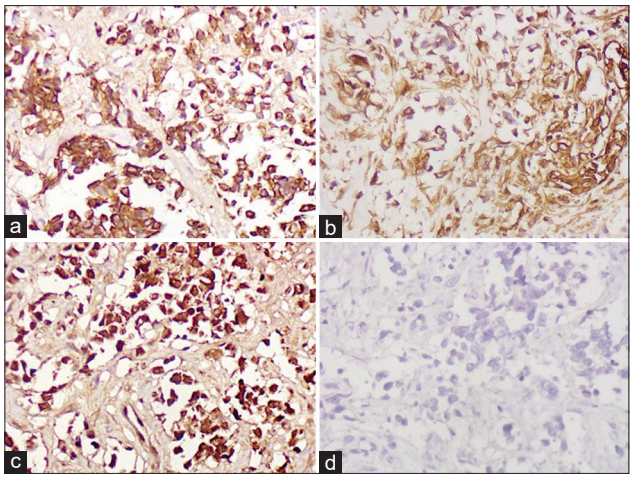

Figure 3: Immunohistochemical staining showed (a) positive expression for synaptophysin (x40), (b) chromogranin A (x40), (c) Ki-67 proliferation index ~ 90% (x40), (d) no expression for CK-20 (x40)

cycle. A bone scan and computed tomography imaging of the head, neck and chest showed no local recurrence or metastasis 24 months after surgery.

DISCUSSION

NECs are heterogeneous neoplasms with diverse tissue origins, clinical behaviours and histomorphology.[4] The 2022 WHO classification of head and neck tumours limits NEC to poorly differentiated epithelial neuroendocrine neoplasms. Neuroendocrine tumours (NET) are well-differentiated epithelial neoplasms classified as G1 (no necrosis, <2 mitoses per 2 mm^2, Ki67 <20%), G2 (necrosis or 2–10 mitoses per 2 mm^2, Ki67 <20%) and G3 (>10 mitoses per 2 mm^2, Ki67 >20%, absence of poorly differentiated morphology). Cytomorphological parameters distinguish NECs (>10 mitoses per 2 mm^2, Ki67 >20% and typically linked with Ki67 >55%) into small and large cell subtypes.[7] The adrenal medulla, pituitary gland and pancreatic islets have numerous agminated neuroendocrine cells. In other places, neuroendocrine cells are scattered across the mucosa, forming a diffuse system. Oral NEC histogenesis is unknown.[8,9] Both MCC and rhabdomyosarcoma are rare tumours that may be considered in the differential diagnosis of NEC of the oral cavity. Primarily, MCC, rhabdomyosarcoma and NEC of the oral cavity can present with overlapping clinical features such as a rapidly growing mass and ulceration of buccal mucosa. As, Merkel cells preferentially scatter in the basal layer of the buccal mucosa epithelium, making them the origin in the oral cavity. Rhabdomyosarcoma is a rare soft tissue malignancy that is more common in young adults and may originate from the sub-epithelial connective tissue of the oral cavity.[9,10] Additionally, MCC, rhabdomyosarcoma and NEC can exhibit overlapping histomorphology features, such as small blue round cell morphology in a set of cases. Due to the rarity of these tumours in the oral cavity, there is limited experience among clinicians and pathologists in diagnosing and differentiating them accurately. This can lead to a consideration of multiple differential diagnoses until a definitive diagnosis is reached with the assimilation of immunohistochemistry study.[10,11] CK-20 positivity with neuroendocrine differentiation identifies MCC. A few previous studies observed that oral cavity NECs can be MCC with CK-20 positivity or NECs with CK-20 negativity. NECs show positive immunohistochemical staining for one or more neuroendocrine markers such as neuron-specific enolase, chromogranin A, synaptophysin, CD56 and neurofilament.[11] The present case of NEC showed positive expression of NSE, chromogranin, synaptophysin and focal cytokeratin (CK/AE1/3). No CK-20 and vimentin expression were noted.

NEC is most common in the lung, although it has been additionally reported in the gastrointestinal tract, larynx, female genital tract and lymph node.[11,12] Oral cavity NEC is rare. To the best of our knowledge, only 31 cases of NECs have been documented in the oral and maxillofacial cavities. This occurred in the retromolar region, mandible, maxilla, gingiva, uvula, mouth floor, tongue and buccal mucosa.[4-6]

Routine histomorphology studies are insufficient to establish a definite diagnosis of NEC in the oral cavity due to its extreme rarity. The utilization of immunohistochemistry is crucial in establishing an accurate diagnosis of a tumour. The conclusive diagnosis of NECs necessitates the utilization of a specific set of markers, including neuroendocrine markers, epithelial markers, lymphoid markers and markers specific to malignant melanoma. Neuron-specific enolase, chromogranin and synaptophysin are commonly employed as neuroendocrine indicators.[13] To rule out a metastatic tumour, a systemic whole-body evaluation is required after an NEC diagnosis. In the present case, despite a careful and detailed dermatological examination, no skin abnormalities were found. The CT thorax, abdomen and head-neck MRIs also revealed no notable abnormalities. An examination of the blood revealed normal results for neuron-specific enolase, 5-hydroxyindoleacetic acid and chromogranin A.[14] NECs must be differentiated from other malignancies such as MCC, Ewing sarcoma, melanoma, lymphoma, paraganglioma, PDSCC and solid-type adenoid cystic carcinoma (ACC). The morphological features of NEC bear a resemblance to those of PDSCC, but it exhibits a lack of neuroendocrine markers. High-molecular-weight cytokeratin, such as CK-5/6 and 34bE12, have the potential to act as discriminatory markers for distinguishing between

NEC and PDSCC, as well as solid-type ACC. In PDSCC and solid-type ACC, they are typically positive, but in NEC, they are negative. Melan-A, HMB-45 and S100 can be used to rule out a diagnosis of malignant melanoma. Lymphoma can be ruled out by a LCA immunohistochemical stain.[15] Surgery has been established to considerably increase overall survival over other single-modality treatments and is the cornerstone of treatment for primary non-metastatic NECs at all locations. The mean age of patients with oral NECs is 56.3 (±17.5) years, with a little male predominance (1.1:1) These patients typically exhibit painless ulcerated masses. Tumours exhibit rapid growth within months, and the occurrence of cervical nodal metastases is very common with very poor prognosis.[4,5] This case study is extremely unique because it involved a young female in her third decade of life. The patient exhibited a rapidly growing, painless ulcerated tumour in her cheek, with no evidence of nodal metastasis even after extensive radiological work-up.

NECs are known for their aggressive nature, and in order to minimize the risk of local recurrence, a recommended approach is to do a wide excision with a margin of up to 3 cm.[9-11] According to previous studies, it is noted that patients who got chemotherapy had a median survival rate of 19 months, while patients who did not get any chemotherapy had a median survival rate of 11 months.[13-15] The primary tumour site may potentially have prognostic significance. It has been observed that salivary gland-derived NECs have a more favourable outcome in comparison with NECs originating from other regions in the head and neck.[14] After excision, the patient in this case had an excellent prognosis with no signs of disease for up to 24 months.

CONCLUSION

NECs in the oral cavity are extremely rare neoplasms. These aggressive tumours need an early and accurate diagnosis. Clinical and morphological characteristics made it difficult to diagnose these oral carcinomas due to their rarity. Oral cavity tumours can be diagnosed by integrating clinical, morphological and immunophenotyping findings. Additionally, more cases are needed to understand clinical behaviour, prognosis and best treatment protocols for oral cavity NEC.

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.

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Conflicts of interest

There are no conflicts of interest.

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