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Epithelial-myoepithelial carcinoma of floor of mouth: A case report of double clear cell variant with immunohistochemical correlation

Mohamed.H.Ibrahim[1], Hossam Abdel Halim[2], Ihab S. Abd Elhamid[3], Marwa M. Elshafei[4] Shaimaa E. Ghazy[5], Nermeen S. Afifi[6], Ismail M. Shebl[7]

[1]Master's degree in Oral and Maxillofacial Surgery, Faculty of Dentistry, Cairo University, [2]Master's Degree Oral and maxillofacial surgery, Cairo University, Egypt, [3]Professor of Oral Pathology, Faculty of Dentistry, Badr University, Cairo, Egypt, [4]Professor of Oral pathology, Faculty of Oral and Dental Medicine, Misr International University, [5]Lecturer of Oral Pathology, Oral Pathology Department, Faculty of Dentistry, Ain Shams University and Misr International University, Cairo, Egypt, [6]Lecturer of Oral Pathology, Oral Pathology Department, Faculty of Dentistry, Ain Shams University and Misr International University, Cairo, Egypt, [7]Lecturer of Oral Pathology, Faculty of Oral and Dental Medicine, Misr International University

ABSTRACT

Epithelial-myoepithelial carcinoma (EMC) is a rare biphasic low-grade malignancy accounting for only 0.5% of all salivary gland tumors. Commonly, EMC affects parotid gland (70%) and rarely affecting other salivary glands. Clearing of both, epithelial and myoepithelial cell types, is rare and gives an impression of a monocellular neoplasm. Case report: A 42-year-old male reported to Oral and Maxillofacial Surgery Department in Faculty of Oral and Dental Medicine, Misr International University with a painless growth in the floor of mouth since 5 years. The soft tissue window of computerized tomography (CT) revealed a well-circumscribed swelling in the sublingual space. The provisional diagnosis was pleomorphic adenoma. Results: The histopathological examination showed solid sheets of rounded to polyhedral clear cells forming lobes and lobules separated by connective tissue mucoid septa. A thin fibrous capsule, invaded with some tumor cells was also present. The presented pattern of clear cells together with the encapsulation of the tumor provides an impression of clear cell variant of monocellular neoplasm. Conclusion: The presented case relates to an epithelial-myoepithelial carcinoma originating from the sublingual salivary gland, which is a rare site for this lesion. Based on immunohistochemical staining, differentiation between the double clear cell types was confirmed using S-100 protein and SMA for the myoepithelial nature of the outer cells while the epithelial nature of the inner cells was confirmed by CK-19 and EMA. Thus, the diagnosis of double clear cell variant of EMC was given.

Keywords: epithelial-myoepithelial carcinoma, double clear cell, S-100, SMA, EMA, CK-19

***Correspondence to Author:**
Nermeen Sami Afifi
Lecturer of Oral Pathology, Oral Pathology Department, Faculty of Dentistry, Ain Shams University and Misr International University, Cairo, Egypt,

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Introduction

Epithelial-myoepithelial carcinoma (EMC) is a rare biphasic low grade malignancy accounting for only 0.5% of all salivary gland tumors[1]. It was first described by Danath et al. in 1972. Before its truly malignant nature had been recognized, this neoplasm had been illustrated in the 1972 World Health Organization (WHO) classification of salivary gland tumors[2] and the AFIP (Armed Forces Institute of Pathology) Tumor Fascicle[3] as a “clear cell monomorphic adenoma”. Although histologically EMC exhibits a high degree of differentiation, it has been shown to be a low-grade carcinoma because of its infiltrative and destructive growth tendency, the presence of foci of necrosis, frequent recurrences and perineural involvement with distant metastases. Thus, it was classified by the WHO in 1991 as a rare low grade form of malignancy, representing about 1-2% of all primary tumors of salivary glands in that time[4,5]. Commonly, EMC affects parotid gland (70%) and rarely affecting other salivary glands. There have been case reports of other types of malignancies like adenoid cystic carcinoma existing along with EMC in salivary glands[6]. Hamamoto et al. 2019 published a case report of a ductal carcinoma arising from an existing EMC in the parotid gland[7]. In a study conducted by Gore in 2018, 468 patients were identified with EMC during the time period from 1973-2014. The parotid gland accounted for the greatest number of cases with a 57.7% involvement and only 3 cases of EMC were found to have originated from the floor of the mouth and its overlapping tissues. In a case report and a review of literature by Fukuda et al.2016, 44 cases of EMC were diagnosed in the years between 1991 to 2015. Of these, only 1 case of EMC was identified in the floor of the mouth. Based on their knowledge, the authors mentioned that the lesion they diagnosed as EMC arising from the oral floor was the second to be ever reported[8]. Due to the conflicting data available it is hard to know exactly the number of EMCs ever reported from the floor of the mouth and to that being stated it is even harder to rank this lesion in its occurrence. As a result of the few number of cases, a precise prediction of the prognosis of EMC arising from the floor of the mouth cannot be precisely determined. However, EMC has a fairly good prognosis. EMC is a low-grade carcinoma of ductal origin characterized by its dual cell population of ductal epithelial cells and myoepithelial cells. The myoepithelial cells are large, polygonal, with clear-staining cytoplasm and irregularly shaped nuclei while the ductal elements are composed of cuboidal cells with eosinophilic cytoplasm and uniform, round voluminous nuclei. The cells grow in sheets with an organoid pattern. Atypia is mild or absent. Mitotic figure count is very low [1]. Clear cell change of the myoepithelial component is observed in almost 80% of EMC. Apart from this characteristic picture, there are many histological variants such as oncocytic EMC, EMC ex pleomorphic adenoma, high grade or dedifferentiated EMC, EMC with myoepithelial anaplasia etc. These morphologic disparities cause difficulty in diagnosis as the patterns can overlap with those seen in other salivary gland tumors[9].

In 2007, Seethala et al.[9] observed two cases of a rare variant of EMC called double clear variant, in which the columnar or stratified luminal epithelial cells also showed clearing. Clearing of both, epithelial and myoepithelial cell types, gives an impression of a monocellular neoplasm and can be mistaken with many other salivary neoplasms having clear cells.

Immunohistochemistry may be a useful tool in separating EMC from other salivary tumors; however, it is often diagnostically challenging to correctly diagnose EMC with differentiation between the variants. It is still unknown whether the histologic variations of EMC have any clinical implication. In immunohistochemical analysis, myoepithelial cells in the outer layer are positive for calponin, p63 protein, glial fibrillary acidic protein, S-100 protein and SMA. Epithelial cells in the inner layer are positive for cytokeratin-7 and 19 as well as epithelial membrane antigen (EMA)[10].

Hybrid carcinoma, in which co-existence of

another malignancy, like adenoid cystic carcinoma or malignant ductal carcinoma with EMC, in the same tumor have been reported which necessitate careful histological examination of the specimens[4,11]. On the other hand, if EMC develops in a long standing case of pleomorphic adenoma (PA), it is called EMC-ex PA[5].

The purpose of this paper is to report the rare double-clear variant of EMC arising in the floor of the mouth and to highlight the difficulty in identifying this tumor. In addition, we would also like to underline the importance of including this tumor as part of the differential diagnosis of tumors with benign like behavior arising from the salivary glands in the head and neck regions.

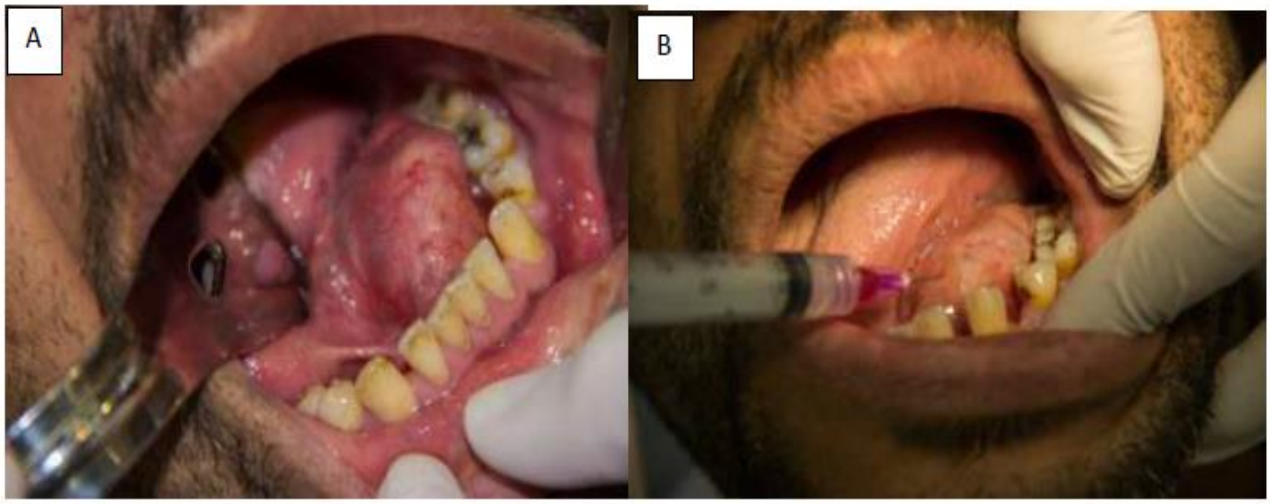

Figure 1: (A) The initial presentation of the lesion. (B) Negative aspiration using 3ml syringe.

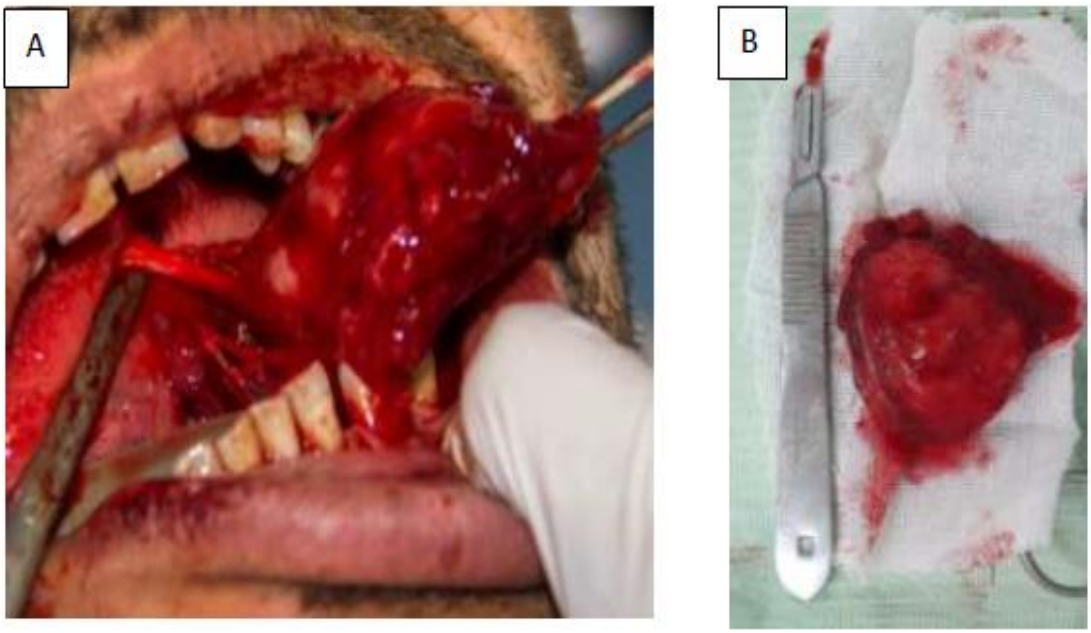

Figure 2: (A) Identification of the submandibular duct. (B) The tumor after excision.

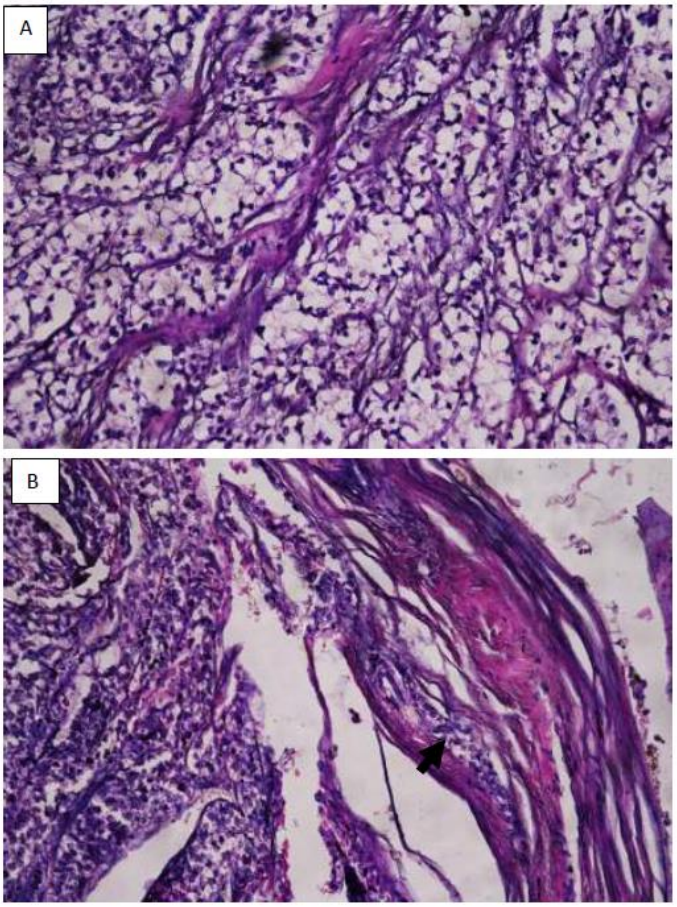

Figure 3: Photomicrographs of H&E stained section from the lesion revealed lobulated sheets of clear cells with small dark nuclei and minimal mitosis (A). The lesion is encapsulated (B) with some tumor cells invading the capsule (arrow). (orig. mag. X40).

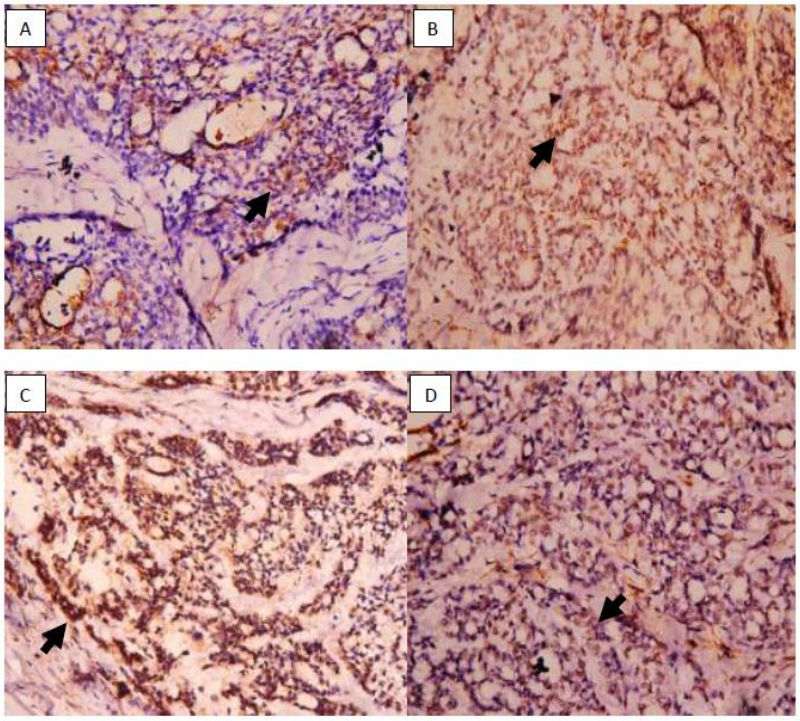

Figure 4: Immunohistochemical staining showing positive reaction of inner cells to CK-19 (A) and EMA (B). The outer cells of theses masses showed positive reaction to S-100 protein (C) and SMA (D) (orig. mag. X20).

Case Report

In April, 2019 a 42-year-old male reported to Oral Surgery Department in Faculty of Oral and Dental Medicine, Misr International University with a growth in the floor of mouth that gradually increased in size and has been constant since the last 5 years, without pain. On examination, a 5 cm × 4 cm ovoid sessile swelling was palpated lingual to the alveolar ridge (figure 1A). It was firm, non-tender swelling with no regional lymph node involvement. The swelling was not fixed to the underlying tissues and salivary secretions were normal. The patient did not report any numbness or dysphagia. There were no pulsations felt on palpation of the lesion. Aspiration was negative with no blood or fluid seen (figure 1B). The teeth in the proximity of the lesion were normal and no radiographic pathology was seen in the mandible. No lump or facial asymmetry was observed in the neck or the face. However, the lesion was bulging more as pressure was applied extra-orally to the submandibular region. The computerized tomography (CT), soft tissue window, revealed well circumscribed swelling in the sublingual space. A provisional diagnosis of a pleomorphic adenoma was established. No medical history was contributory so local excision of the tumor under Local anesthesia was planned. A standard left inferior alveolar nerve and lingual nerve blocks using 1.8ml of 4% articaine with 1:100 000 epinephrine was administered for pain control. Another carpule of the same previously mentioned criteria was infiltrated around and at the base of the lesion for haemostasis and pain control. After ensuring sufficient pain control was established a traction suture was placed at the tip of the tongue and held with an artery forceps retracting the tongue away from the surgical site. A linear incision was made over the most prominent part of the tumor taking care to have sufficient soft tissue cuff at the end of the surgery for the closure of the wound. After some dissection was achieved, the lingual vein branch was identified and ligated to prevent further bleeding. The submandinular duct was also identified inferiomedially to the tumor and was preserved and dissected away from the tumor (figure 2A). The tumor and overlying capsule were excised and removed as a whole unit (figure 2B). The tumor was delivered into a 20% formalin jar and sent to the oral histopathological lab for histopathological examination. Surgical wound was closed with the use of multiple interrupted sutures 4-0 (Polyglactin). The patient was given instructions for the use of cold fomentations and was prescribed with antibiotics and analgesics as appropriate.

The histopathological examination showed solid sheets of rounded and polyhedral cells forming lobes and lobules separated by connective tissue septa. Additionally, eosinophilic mucoid substance was scattered in the lesion (figure 3A). A thin fibrous capsule, invaded with some tumor cells was also present (figure 3B). The majority of tumor cells showed clear cytoplasm and small deeply stained nuclei of variable size and shape. Large number of the nuclei showed prominent vesicular nucleolus. Few mitotic figures were also evident in these cells.

Discussion

Although histopathological diagnosis plays a major role in the diagnosis of salivary neoplasms, very few contributions need special stains, immunohistochemistry and cytogenetic studies[12]. The presented pattern of clear cells in the present case provides an impression of a monocellular neoplasm composed of clear myoepithelial cells. Together with the encapsulation of the tumor mass and the lobular pattern, this case can be diagnosed as a clear cell variant of pleomorphic adenoma or myoepithelioma. Moreover, other tumors that may contain clear cells should be also considered, such as clear cell carcinoma, the clear cell variants of acinic cell carcinoma, oncocytoma, oncocytic carcinoma, mucoepidermoid carcinoma, myoepithelioma or myoepithelial carcinoma. All these lesions in addition to metastatic clear cell renal cell carcinoma are to be considered in the differential diagnosis of the lesion before reaching a definitive diagnosis.

In conjunction with hematoxylin & eosin staining, the gold standard method used for the diagnosis, immunohistochemistry can enhance the accuracy of diagnosis. It is a helpful tool when used to investigate the subjects that cannot be assessed by histological examination, such as the cell nature, differentiation status, cell proliferation and tumor protein expression[12]. In our case, utilizing immunohistochemistry to differentiate this tumor from others with a similar histologic pattern can be of great benefit.

Immunohistochemically, the inner clear cells of the tumor masses were positive for cytokeratin 19 (CK-19) (figure 4A) and epithelial membrane antigen (EMA) (figure 4B). While the clear cells in the outer layer of the masses showed positive immunohistochemical staining for S-100 protein (figure 4C) and smooth muscle actin (SMA) (figure 4D). Only with immunohistochemistry, distinction between the myoepithelial and ductal epithelial cells can be visualized clearly. This was due to clear cell change occurring in both luminal and myoepithelial cells, thus creating a false solid architecture. The solid growth pattern of this particular lesion emphasizes the trouble in differentiating and recognizing the biphasic component that characterizes this entity.

The diagnosis of epithelial-myoepithelial carcinoma double-clear variant was made and the patient is currently put on follow up every 3 months to clear out the possibility of recurrence.

The largest group of age that usually acquires EMC is between 65-69 years[13]. This fact correlates with the age of the patients reported in the two case reports of EMC in the floor of the mouth cited in this article[6, 8]. There is a female predominance with a female to male ratio of 1.6:1. Again, this corresponds to the two other case reports as both patients reported were females. However, in our case the patient was a 42-year old male. During history taking the patient reported the occurrence of the tumor following a visit to the dentist where he received a needle injection in this area. The hypothesis that the tumor was initiated by the trauma caused by the needle is highly disputed. Given the number of patients who receive similar injections on daily basis without developing any pathology makes this assumption greatly disputed. However, this supposition mentioned by the patient cannot be entirely denied. A relatively rare disease, EMC mostly develops in the parotid gland, but some reports claim that it also occurs in the submandibular gland and base of the tongue[1]. Although fine needle aspiration cytology (FNAC) was not performed prior to the surgical excision of this tumor, FNAC has always been inconclusive in detecting this type of tumor. In a study by Arora et al. 2012, 4 cases of EMC from different sites in the head and neck were investigated. Out of the 4 cases, 3 showed cytological features of pleomorphic adenoma and the fourth showing features of EMC. All were suggestive of benign tumors[11]. In another study, 44 EMC cases where investigated, out of them 18 cases under went FNAC but all were not conclusive of EMC[14]. Even though, the lesion was most likely believed to be a pleomorphic adenoma by both the surgical and pathological teams a malignant yet low grade tumor was diagnosed. Prognosis of EMC shows conflicting evidences. In one study the recurrence rate was found to be 36.3% with a 10-year disease-specific survival of 81.8%. The most common predictor of recurrence was margin status[9]. Out of the 44 reports identified in the study by Fukuda et al. 2012, 35 cases showed no evidence of recurrent disease, 4 cases showed local recurrence, 1 case showed nodal metastasis, 2 cases showed distant organ metastasis and 2 cases died from the cause[8]. In another study by Gore et al. 2018 that focused on the prognosis of EMC, the rate of nodal and distant metastasis was found to be low at 5 % with a 20-year-old survival rate of 38.3%[13]. In a case report series by Arora et al. 2012, 3 out of the 4 cases of EMC studied showed evidence of local recurrence. One of them had originally developed in the floor of the mouth region. The study suggested that EMC had a high chance of recurrence and that distant metastasis is not uncommon[11]. Accordingly, our patient is currently put into a follow up period with no evidence of recurrence so far after 30

months of follow up.

Conclusion

The presented case relates to an epithelial-myoepithelial carcinoma originating from the sublingual salivary gland which is a rare site for this lesion. Our provisional diagnosis for the case was pleomorphic adenoma. Based on immunohistochemical staining, differentiation between the double clear cell types was confirmed using s-100 protein and SMA for the myoepithelial nature of the outer cells while the epithelial nature of the inner cells was confirmed by CK-19 and EMA. Although rare in occurrence there have been reported cases of EMC with local recurrence, local and distant metastasis from similar lesions in the floor of the mouth. For these reasons, it is highly recommended to raise the surgeon's suspicions about other low grade malignant tumors that may arise from salivary glands in the head and neck region. We recommend prolonged periods of follow up after initial diagnosis of the tumor.

Conflict of Interest

None to declare

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