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# A Rare Presentation of Hyalinizing Clear Cell Carcinoma of Minor Salivary Gland

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**Abstract** **Case Report**

Hyalinizing clear cell carcinoma (HCCC), so-called clear cell carcinoma, not otherwise specified (CCC (NOS)), of the salivary glands is a rare and low-grade malignant tumor. HCCC has a vast differential diagnosis including various clear cell-containing tumors, such as epithelial-myoepithelial carcinoma, mucoepidermoid carcinoma, and myoepithelial carcinoma. HCCC is presently classified as a "clear cell adenocarcinoma" by the AFIP and as "clear cell carcinoma, not otherwise specified (NOS)" by the World Health Organization (WHO). It is considered by the WHO to be a diagnosis of exclusion.We reported a case of HCCC of the minor salivary gland of the buccal mucosa which was clinically diagnosed as pleomorphic adenoma. A 66-year-old woman had presented with a gradually growing and indolent mass in the left buccal mucosa for about two years. The tumor measured approximately 1.5 cm in diameter and was diffuse hard, smooth. Histopathological findings revealed proliferating tumor cells with clear cytoplasm surrounded by hyalinizing stroma with perineural invasion. Immunohistochemical stains revealed these tumor cells to be positive for cytokeratin but negative for myoepithelial ones. These findings confirmed the diagnosis of HCCC.
**Keywords:** Clear cell carcinoma, minor salivary gland, buccal mucosa.


## INTRODUCTION

Hyalinizing clear cell carcinoma (HCCC) was first reported by Milchgrub *et al.* in 1994 as a rare minor salivary gland carcinoma made up of clear cells forming cords and nests in a hyalinized stroma [1]. This tumor was speculated to be previously called or confused with monomorphic variants of epithelial-myoepithelial carcinoma, mucin-depleted mucoepidermoid carcinoma, and myoepithelial carcinoma. It was separated from these entities because of its lack of apparent squamous, mucinous, and myoepithelial differentiation.[1]The tumor showed low-grade morphology and good overall outcome with only occasional metastatic spread. HCCC is presently classified as a "clear cell adenocarcinoma" in the AFIP fascicle [2] and "clear cell carcinoma, not otherwise specified (NOS)" by the World Health Organization (WHO) "blue book" on head and neck tumors [3]. It is considered by the WHO to be a diagnosis of exclusion.

Hyalinizing clear cell carcinoma (HCCC) is a rare entity with distinctive histological features [1]. It predominantly affects the minor salivary gland of the oral cavity in females. Histopathologically, HCCC is composed of proliferating tumour cells with clear cytoplasm, organized in trabeculae, cords, or solid nests surrounded by hyalinizing fibrocollagenous stroma [1, 4]. However, the differential diagnosis can be difficult because the microscopic features of HCCC frequently overlap with those of other salivary gland tumors and metastatic renal cell carcinoma. Immunohistochemical staining is very effective and might differentiate it from tumors with same histopathological features. HCCC cells are positive for epithelial cell markers such as cytokeratin and negative for S-100 protein, mucicarmine, and myoepithelial cell markers such as SMA, MSA, myosin, and calponin [1, 4]. The clear cells show granular PAS positivity and diastase sensitivity, indicative of glycogen in the cytoplasm.

## CASE REPORT

Our case was a 66-year-old female patient presented with a gradually growing and indolent mass at the left buccal mucosa. Clinical diagnosis was pleomorphic adenoma. We received single grey brown soft tissue biopsy measuring 0.7x0.5x0.3cm from Oral maxillo-facial surgery department. Histopathological examination revealed invasive proliferation of tumor cells with clear cytoplasm arranged in trabeculae, cords or solid nests separated by homogenous eosinophilic hyalinizing stroma (Fig.1). The tumor cells demonstrated small nuclei, mild atypia, and no mitosis

(Fig.2).Tumor cells also shows perineural invasion (Fig.3). Mucus-producing cells and acinar cells were not observed. On Immunohistochemistry, the tumor cells were positive for cytokeratin consistent with epithelial cells, but negative for vimentin, S-100. These microscopic features confirmed the diagnosis of HCCC, so-called CCC (NOS).

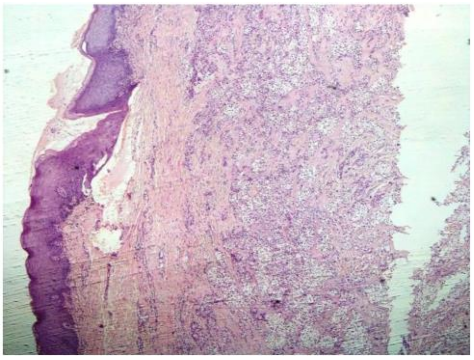

**Fig-1: Tumor cells with clear cytoplasm arranged in trabeculae, cords or solid nests separated by homogenous eosinophilic hyalinizing stroma. H&E (4x)**

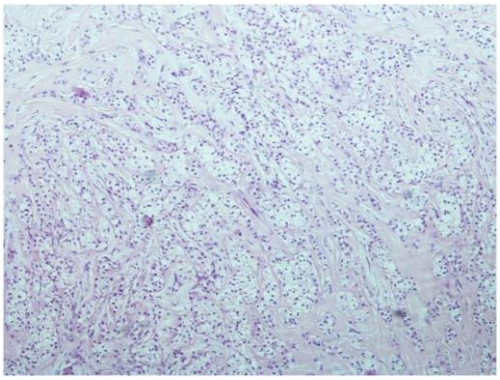

**Fig-2: The tumor cells show small nuclei, mild atypia, and no mitosis. H&E (40x)**

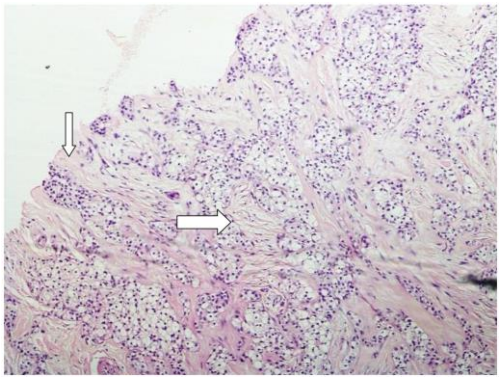

**Fig-3: Perineural invasion of tumor cells seen in this picture. (Arrow marks) H&E (40x)**

## DISCUSSION

HCCC, so-called CCC (NOS), of the salivary gland is a rare and low-grade malignant tumor. It is involved in less than 1% of all malignant tumors in the salivary glands. The most commonly affected sites are the tongue and palate, which constitute almost 50% of the total. The rarity of HCCC in the major salivary glands was already reported. Our case was derived from the minor salivary glands of the buccal mucosa, although the rarity of HCCC of the buccal mucosa was also previously reported [5-8].

It was reported that more than 60% of HCCC occurred in middle-aged women over 50 years old [6]. Our case was also in the same age group and gender. Microscopically, current case was consistent with the characteristic features of HCCC reported. It is composed of trabeculae, cords, islands and nests of glycogen-rich clear cells and eosinophlic cells circumscribed by a hyalinizing stroma. The clear cells are usually due to accumulation of glycogen,which demonstrated by PAS staining but not mucin staining. However, HCCC or CCC (NOS) has been considered a diagnosis of exclusion [3, 5].

Clear cells in salivary gland tumors are found in numerous tumors, such as epithelial myoepithelial carcinoma, mucoepidermoid carcinoma, acinar cell carcinoma, sebaceous carcinoma, and metastases from renal cell carcinoma [8, 9]. Therefore, it is not possible to distinguish HCCC from other tumors by only the presence of clear cells. Each tumor has its own characteristic feature, so both microscopic and immunohistochemical examinations are mandatory for differentiating tissue types of tumors containing clear cells [10]. HCCC is further supported by the expression of cytokeratin and p63 and also lack of expression of S100 and SMA [9].

The differential diagnosis is vast and includes a number of neoplasms with clear cell change.A summary of the potential mimics of HCCC is listed in Table 1. This has long been the source of diagnostic confusion. The usual mimickers of HCCC include clear cell variants of squamous cell carcinoma (SCC), myoepithelial carcinoma, mucoepidermoid carcinoma, clear cell odontogenic carcinoma, calcifying epithelial odontogenic tumor (in bone), epithelial-myoepithelial carcinomaacinic cell carcinoma, oncocytoma, myoepithelioma and metastatic renal cell carcinoma.

In addition, tumors with a cribriform growth pattern and arising in the oral cavity, such as adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma, have to be considered, despite their usual lack of clear cell differentiation. The differential diagnosis also depends somewhat on location. For instance, sinonasal renal cell-like carcinoma would only be on the differential diagnosis for nasal tumors.

**Table-1: Hyalinizing clear cell carcinoma (HCCC) and related mimics**

| **Feature** | **HCCC** | **MEC** | **EMC** | **CCMC** | **CEOT** | **CCOC** | **SCC** |
|---|---|---|---|---|---|---|---|
| Typical location | Predominant oral | 50 % oral 50 % major salivary | Predominant parotid | Predominant parotid | Jaw bone | Jaw bone | Mucosal all sites |
| Ductal structures | Rare (entrapped) in parotid | Rare | Prominent | Rare | Absent | Rare | Absent |
| Cysts | Rare | Common | Rare | Rare | Rare | Rare | Rare |
| Thin cords and small nests | Present | Rare | Rare | Rare | Present | Present | Common |
| Papillary Pattern | Absent | Absent | Focal | Absent | Absent | Absent | Absent |
| Cribriform pattern | Focal | Absent | Common | Common | Absent | Focal | Basaloid variant |
| Stroma | Dual hyalinizing and fibrocellular | Absent or rarely hyalinizing | Absent or hyalinizing | Hyalinizing | Amyloid and hyalinizing | Dual hyalinizing and fibrocellular | Desmoplastic or hyalinizing |
| Spindled pattern | Absent | Absent | Common | Absent | Absent | Absent | Sarcomatoid variant |
| Perineural invasion | Common | Rare | Common | Not described | Rare | Common | Common |
| Mucosal involvement | Common | Common | Absent | Absent | Absent | Common | Common |
| Mucin | Common mostly as single cells | Common goblet type cells lining cysts and forming clusters | Absent | Absent | Absent | Common mostly as single cells | Rare |
| Amyloid (Congo red) | Negative | Negative | Negative | Negative | Present | Negative | Negative |
| P63, HMWK | Positive | Positive | Abluminal cells positive | Positive | Positive | Positive | Positive |
| S100, actin, calponin | Negative | Negative | Abluminal cells positive | Positive | Absent | Absent | Sarcomatoid variant |
| Molecular markers | *EWSR1-ATF1* | *CRTC1-MAML2* | None | None | None | *EWSR1-ATF1* | None |

*HCCC*- hyalinizing clear cell carcinoma, *MEC*- mucoepidermoid carcinoma, *EMC* -epithelial-myoepithelial carcinoma, *CCMC*- clear cell myoepithelial carcinoma, *CEOT* -clear cell calcifying epithelial odontogenic tumor, *CCOC*- clear cell odontogenic carcinoma, *SCC* -squamous cell carcinoma, *HMWK*- high molecular weight cytokeratins

## CONCLUSION

HCCC of the salivary glands is a rare and low-grade malignant tumor. Histopathological and immunohistochemical evaluations are mandatory for its definitive diagnosis. Although it is a low-grade malignant tumor, regular follow-up is needed for further workup and to find new associations with this tumour.

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