

**Case Report** 

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# Mucinous Adenocarcinoma of Minor Salivary Gland: Case Report and Literature Review

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## Abstract

Mucinous adenocarcinoma (MAC) is a glandular tumor characterized by large pools of extracellular mucin. The tumor can arise as a primary tumor of the major salivary glands. However, its occurrence is exceedingly rare and has only recently been recognized. Only few cases in the major salivary glands have been reported. This report is an additional case of MAC with origin in minor salivary gland at the oral floor. Immunohistochemical analysis of the tumor for cytokeratins 7, 8, 10, 13, 14, 18 e 20, vimentin, SMA, CEA, EMA, p53, ki-67 e histochemical analysis for PAS, Alcian blue e mucicarmin was performed. Predominantly, the tumor expressed cytokeratins 7, 18 and 20 that are commonly found in simple epithelia. Therefore, was observed positivity to PAS, Alcian blue and mucicarmin. No other cancer has been detected. The tumor is considered to be a primary mucinous adenocarcinoma, being the twenty-third case in minor salivary gland reported in the literature and the fourth MAC located in the mouth floor.

Keywords: Mucinous adenocarcinoma; Salivary gland; Oral

## Introduction

The mucinous adenocarcinoma (MAC) is a rare malignant tumor composed of epithelial clusters within large amounts of extracellular mucin. The mucinous component usually occupies the bulk of the tumor mass [1]. This lesion was included in the classification of salivary gland tumors by the World Health Organization, however there are controversies by some authors about its definition as a distinct neoplasm [2].

The real frequency of MAC remains unknown; it comprises less than 0.1% of epithelial salivary gland tumors in the AFIP files [3]. In Chinese population, MAC represented 0.1% (7 of 5.416) of all salivary gland tumors and 0.4% (7 of 1.994) of carcinomas [4,5]. Its incidence was also estimated to be 0.07% (1 of 1.392) of malignant salivary tumors in West China [6]. Recent study of minor salivary gland tumors from the United States indicated that MAC accounted for 0.2% (1 of 546) of all tumors and 0.4% (1 of 241) of malignancies [7].

We describe the clinicopathologic and immunohistochemical findings in one case of MAC with origin in minor salivary gland at the oral floor. Our goal is to compare these data with those of 22 cases from the literature to comprehend the profile of MAC in the intraoral minor salivary glands.



**Figure 1:** (a,b) Extra and intra oral clinical appearance of the tumor, (c,d) Postsurgical extra and intra oral appearance.

## **Case Report**

A 52-year-old male non-smoker over 10 years having a tender, firm, swelling at the oral floor, smooth appearance and color of the mucosa for three months duration (Figures 1a and1b). The clinical history and computerized tomography scan discarded systemic involvement. Computerized tomography scan revealed a large, well-defined, soft tissue mass with dimensions of 5 x 4 cm in its largest diameter showing multiple internal cystic spaces, suggesting diagnosis of ranula, dermoid cyst or thyroglossal duct cyst. The parapharyngeal space, pterygopalatine and infratemporal fossae were well preserved, without osteolytic or osteoblastic images. Aspirative punction was performed in the lesion with negative result. An incisional biopsy was taken, macroscopically the tumor measured 3.5 x 3 x 2 cm and was soft on palpation. The margins appeared bosselated and the cut surface was gelatinous and glistening. The surgical specimen was fixed in 10% neutral buffered formalin and following embedded in paraffin. Histomorphological analysis of sections stained with hematoxilin & eosin showed a well-defined lesion, with connective fibrous strands separating variably sized mucusfilled cystic spaces (Figure 2a), many containing suspended irregularshaped neoplastic epithelial cell nests, clusters and atypical ductal epithelial cells (Figure 2b), separated from the tumor mass by uninvolved salivary gland tissue. The neoplastic cells had atypical large nuclei, and some cells contained small amounts of intracellular mucus (Figure 2c). Mitotic figures were rarely observed. Immunostains using the avidinbiotin technique were performed on the tumor, including stains for cytokeratins (CK) (Table 1). Few of the tumor cells stained positively for

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Figure 2: (a) Fibrous strands separating variably sized mucus-filled cystic cavities and cords of tumoral cells, H & E, 100x, (b) Irregular-shaped neoplastic epithelial cell nests, clusters and atypical ductal epithelial cells, H & E, 200x, (c) Tumoral cells with atypical large nuclei, and some cells contained small amounts of intracellular mucus, H & E, 400x, (d) Few tumoral cells immunopositives for CK 7, SABC, 400x.

Antibody	Source	Dilution	Antigen retrieval	Result	Localization
CK 7	DAKO	1:50	Citrate	+	Cytoplasmic
CK8	Novocastra	1:50	Citrate	-	-
CK 10	Novocastra	1:25	Tripsin 0.1%	-	-
CK 13	Novocastra	1:100	Citrate	-	-
CK 14	Novocastra	1:20	Citrate	-	-
CK 18	Novocastra	1:20	Citrate	++	Cytoplasmic
CK 20	Novocastra	1:20	Citrate	+	Cytoplasmic
Vimentin	DAKO	1:50	Citrate	-	-
α-SMA	Novocastra	1:50	Citrate	++	Nuclear
CEA	DAKO	1:30	No treat- ment	+	Cytoplasmic
EMA	DAKO	1:40	No treat- ment	+	Cytoplas- mic, luminal cells
Ki-67	DAKO	1:100	Citrate	-	-
p53	DAKO	1:50	Citrate	-	-

(-) No immunostaining; (+) weak immunostaining; (++) strong immunostaining

Table 1: Antibody sources, dilutions, antigen retrieval and immunostaining results

CK 7 (Figure 2d). Prominent staining was found for CK 18 (Figure 3a). Only a few cells were CK 20 positives (Figure 3b), there was observed variably immunostaining for smooth muscle actin ( $\alpha$ -SMA), epithelial membrane antigen (EMA) and CEA principally in glandular structures with tubular formation (Figures 3c, 3d and 4a). Tumor cells were negatives for vimentin, ki-67 and p53. There was observed positivity for Alcian blue, mucicarmine and periodic acid-Schiff (PAS) (Figures 4b, 4c and 4d) (Table 2). On basis of the clinic, histomorphological and immunohistochemical features a diagnosis of mucinous adenocarcinoma (MAC) was made. The tumor was surgically removed with margins involved and neck dissection was done with cervical lymphadenectomy. Before therapeutic surgery, radiotherapy was performed and the patient remains free of locoregional and distant disease after eleven months. The result postoperative is showed regarding to patient clinic condition (Figures 1c and1d).

#### Discussion

The mucinous adenocarcinoma (MAC) was included in the clas-

sification of salivary gland tumors by the World Health Organization, however some authors argue that information provided in the World Health Organization classification is, therefore, insufficient to define MAC as a distinct neoplasm [2].

Twenty-two intraoral MAC was previously described in the literature with minor salivary gland origin [5,8]. These authors observed that MAC is a tumor of older adults (average 64.6 years). Usually, the MAC arises in patients over 50 years of age. Males are affected more frequently than females [1,5]. Approximately 10% of these are located in the submandibular and the sublingual gland [9]. These findings are consistent with the case reported here. According to Barnes et al. [1], the most frequently affected sites are the palate and the sublingual gland, followed by the submandibular gland and the upper lip. Just three cases of MAC were reported in floor of mouth, this is the fourth.

Histologically, mucinous adenocarcinoma is so characteristic that it rules out any other salivary gland carcinoma as a differential diagnostic possibility. Some authors argue that mucinous appearance itself is not pathognomonic of MAC and many salivary gland carcinomas may exhibit this trait [3,10,11]. In this sense, the histologic diagnosis of MAC is usually by exclusion [3]. The differential diagnostic consid-



**Figure 3:** (a) Prominent immunostaining for CKs 18, SABC, 400x, (b) Few cells positives for CK 20, SABC, 400x, (c) Positivity for  $\alpha$ -SMA in glandular structures with tubular formation, SABC, 400x, (d) Immunostaining for EMA in glandular structures with tubular formation, SABC, 400x.



**Figure 4:** (a) Immunostaining for CEA in glandular structures with tubular formation, SABC, 400x, (b) Positivity for Alcian blue in stromal tumoral component, (c) Positivity for Mucicarmim, (d) Mucous material PAS positive.

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Histochemical	Result	
Alcian-blue	++	
PAS	++	
Mucicarmin	++	

(++) strong staining

#### Table 2: Histochemical results

erations in the realm of MAC are cystadenocarcinoma [12], mucoepidermoid carcinoma [13], mucin-rich salivary duct carcinoma [14] and signet-ring cell adenocarcinoma [15]. The primary differential diagnosis seemed to be a metastatic tumor, since there is a definite structural resemblance to mucinous adenocarcinomas of the gastrointestinal tract or the breast and to sweat gland carcinoma of the skin. Metastatic tumors in the salivary glands are uncommon. Forty-seven cases out of 10,944 tumors were collected during a twenty-year period in the files of the Hamburg salivary gland tumor register [16]. The metastatic tumors were localized in the parenchyma of the parotid or the submandibular gland. The sublingual gland was free from metastatic tumors [9]. Due to their homologies, distinction of primary MAC from metastatic mucinous carcinoma is impossible on histologic grounds alone [3,5].

Immunohistochemistry has been show to be useful in the supportive diagnosis of salivary gland tumor [17], mainly myoepithelial cell markers such as cytokeratins,  $\alpha$ -SMA, vimentin and S-100 protein. The immunotyping of CK7/CK20 may aid in substantiating a tumor origin. It is mentioned that the CK7(+)/CK20(–) phenotype may be a rationale for a salivary primary [9,17-20], whereas a immunoprofile CK7(–)/ CK20(+) may serve as a clue to an intestinal origin [5,21]. Metastasis from a primary tumor of the gastrointestinal tract or pancreas is not very likely if the tumor shows a pronounced expression of CK 7 and only single cell positivity of CK 20 [9]. In this case, the tumor presented expression for CK 7, but a few isolated cells were weak positives for CK 20, suggesting a primary MAC.

It is known, however, that CK pattern of MAC and its cutaneous and mammary counterparts are comparable [5,21], making a discrimination between them untenable. The cytokeratin profile of the present tumor showed a mixed pattern dominated by the strong expression of CK 18, which are found in simple epithelia.

Other immunomarkers show differential potential, but prove to be less discriminating. It was reported that by immunostaining for CEA in oral mucinous adenocarcinoma and in intestinal carcinomas, variably staining had been observed in skin and breast tumors [5,22]. The biologic behavior of MAC was evaluated through Ki-67 and p53 immunomarkers and was found negatives to this tumor. Association has been reported in cell proliferative index, by immunohistochemical expression of Ki67 with a poor prognosis in many salivary gland tumors [23]. Ide et al. [5] found an average percentile to Ki-67 of 38% in mucinous adenocarcinoma. A high Ki-67 index (>30%) has been found to correlate well with poor overall survival in salivary carcinomas [24]. However, there has been no association between p53 expression with survival in patients with these tumors [25].

Based on this information, the case reported here has analyzed the expression of these proteins in order to infer information about the biological behavior of the lesion, however, both were negative, it can be inferred that this case probably would have a biological behavior and prognosis more favorable, which can be corroborated by clinical follow-up of the patient, who did not show tumor recurrence, no sign of secondary tumor.

Based in the immunohistochemical profile and the negative scan

for any other primary malignancy, we are convinced that this case represents an example of a primary mucinous adenocarcinoma of the minor salivary gland. The patient had been followed-up for ten months without recurrence or disseminated disease. Treatment included total enucleation of the lesion, part of the tongue and, an upper neck dissection. From these cases it is difficult to compare the behavior of mucinous adenocarcinomas of the major salivary glands to a similar tumor in a different location. Tumors of the breast and stomach are associated with a better prognosis, whereas those of the colorectal tract have a more sinister one. In this case the patient had a local tumor confined to the buccal floor region without any metastases. The prognosis of salivary gland tumors varies with location, histological type and grade. The clinical stage of the disease is considered the single most important prognostic factor [25].

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