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Mucoepidermoid Carcinoma Misdiagnosed as Palatal Odontogenic Infection: An Overview on the Differential Diagnosis of Palatal Lesions

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ABSTRACT

Mucoepidermoid carcinoma (MEC) accounts for approximately 30% of malignant salivary gland tumors and approximately 30% occur in minor salivary glands. The palate is the most frequent localization for those arising in minor glands. A 33-year-old male patient with MEC of the hard palate was treated as an acute odontogenic infection, which was not cured after tooth endodontic treatments, repeated incisions and antibiotics. On the hard palate ovoid, a hard painless mass, which had not extended over the middle palatal line, was observed. Partial maxillectomy was performed. A review of the literature was performed in order to provide a coherent overview on the differential diagnosis of palatal lesions. To the best of authors' knowledge, this is the first report in English literature describing palatal MEC misdiagnosed and treated as odontogenic infection. Considering the extensive list of MEC's differential diagnoses on the hard palate, acute odontogenic infection can now be added to that list.

Key words: oral cancer; salivary gland tumor; mucoepidermoid carcinoma, odontogenic infection, hard palate tumors

Introduction

In 1945, Stewart et al.¹ published the first large series of mucoepidermoid carcinomas (MECs) and suggested the term MEC. They divided these tumors into benign and malignant varieties, however, due to the appearance of metastases, Foote and Franzell considered all MECs malignant², and it is the most common malignant tumor of minor salivary glands (MSGT) in the oral cavity³⁻⁷.

The incidence of salivary gland tumors increased with age⁸. However, it is important to realize that the relative incidence of malignant tumors increases, as the size of the glands in which they develop decrease⁹. MEC accounts for up to 47% of all malignant salivary gland tumors^{10,11} and 21.1% of benign and malignant salivary gland tumors with 30% appearing in the minor salivary glands¹². In studies after 1990, MEC represented 45%, a twofold increase in comparison with studies before 1990

(an average of 27% of all malignant salivary tumors)¹³. These findings are inconsistent and not sufficient to suggest a geographic related appearance¹⁴. Reviewing the English-language literature, Buchner et al.¹⁵ concluded that it was very difficult to make a valid comparison between intra-oral minor salivary gland tumors because many reports were based on outdated classification, the small number of some cases, limited list of tumors, and new entities are not included. Pires et al.¹⁶ concluded that reports from different populations using the same diagnostic criteria are essential to compare and estimate true racial and geographic variations in MSGT. The palate is the most frequent localization for those arising in the minor glands⁸. Some authors^{4-7,17-21} found a higher incidence of palatal involvement by salivary gland tumors, including MEC. Wang et al.²² found that palate was

the most commonly affected site among intraoral minor salivary gland tumors in a Chinese population.

In adults, MEC is most common in the fourth to sixth decades with no established gender predominance²³. Microscopically, MEC is composed of mucous cells, epidermoid cells and intermediate cells¹.

Low-grade carcinomas appear as painless, slowly enlarging ovoid masses, which are greater than 2–3 cm in diameter and rarely larger than 4 cm, may produce metastases and have a 5-year determinate cure rate of approximately 90% with a recurrence rate of 6%²⁴. Oncocytic MEC (OMEC) has been rarely reported with previous cases suggesting they are largely cystic low-grade neoplasms with a favorable prognosis. The differential diagnosis of OMEC includes numerous oncocytic/»oncocytoid« neoplasms. Although recent evidence suggests that, unlike in OMEC, p63 is a reliable marker in the diagnosis of conventional MEC, OMEC behaved as a low-grade tumor, and is diffusely positive for p63, which may aid in its differential diagnosis²⁵. High-grade MECs present as painful, rapidly enlarging masses that tend to be firmer and less moveable, with a 5-year determinate cure rate of 27%. These are associated with a high recurrence rate (78%) and metastases²⁶. Okami et al.²⁷ found a metastatic MEC in the lung 43 years after the initial treatment for the primary tumor.

Intraosseous salivary gland tumors are most commonly MECs, usually asymptomatic,

three-fold more common in the mandible than in the maxilla in the region of the third molar and occur twice as often in women. It is believed that these tumors arise from the odontogenic cysts or salivary glands entrapped during embryological development²⁸.

Differential diagnosis on the hard palate includes all benign and malignant tumors of the hard palate, mostly pleomorphic adenoma, polymorphous low-grade adenocarcinoma, adenoid cystic carcinoma and squamous cell carcinoma. Chronic sialadenitis or mucocoele, which is histologically similar, could be misdiagnosed as a low-grade MEC or necrotizing sialometaplasia. Odontogenic cysts, lymphoma, plasmacytoma, Langerhans cell histiocytosis or metastatic carcinoma could also be included as well as a rare papillary oncocytic cystadenoma²⁹.



Fig. 1. An ortopantomograph reveals semi-ovoid transparency of the left maxillary process above the teeth roots, which lifts the hard palate and floor of the maxillary sinus.

To the best of authors' knowledge, this is the first report in English literature describing palatal MEC misdiagnosed and treated as odontogenic infection.

Case Report

A 33-year-old male patient visited the dentist complaining of upper first molar toothache. On the left side of the hard palate ovoid, a hard painless mass, which had not extended over the middle palatal line, was observed. The dentist, who began the initial endodontic treatment and filled root canals, using iodoform paste (Vitapex) for one week, did not indicate an incision. After 7 days, the dentist performed the palatal incision, no puss was detected and no improvement occurred.

One month later, the patient was referred to the outpatient oral surgeon who performed a re-incision. Seven days later, some improvement had occurred. The oral surgeon advised the endodontic treatment to be continued. Three months later, the patient visited his dentist with the same palatal ovoid mass; however, the patient experienced no toothache. The patient was subsequently admitted to our Department.

An ortopantomograph revealed semiovoid transparency of the left maxillary alveolar process above the teeth roots that lifted the hard palate and floor of the maxillary sinus (Figure 1). An axial CT scan showed a pathological process of the hard palate (diameter, 25 mm) with cystic bone transformation and a small bone infraction (Figure 2). Coronal CT showed the submucous mass near the alveolar ridge and thickening of the Schneider's membrane of the left maxillary sinus without bone destruction (Figure 3). A presumptive diagnosis was pleomorphic adenoma. A cytological diagnosis considered a low-grade MEC or cytologically similar mucocoele. The histopathological diagnosis of a biopsy specimen was MEC, grade 1.

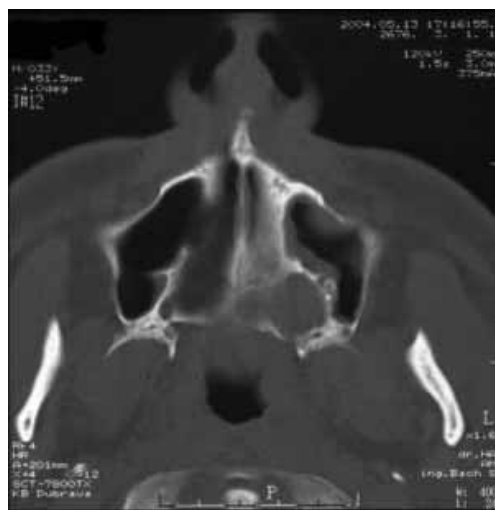


Fig. 2. Axial CT scan shows the pathological process of a hard palate (25 mm in diameter) with a cystic bone transformation and a small bone infraction.



Fig. 3. Coronal CT shows the submucous mass near the alveolar ridge and thickening of the Schneider's membrane of the left maxillary sinus without bone destruction.

A partial maxillectomy was subsequently performed. Figure 4 shows the tumor specimen. The palatal plate was placed immediately following surgery.

Histopathological examination of the excised portion of the hard palate revealed an invagination in the central portion of the bone, occupied by a soft, partially cystic node measuring 2 cm in diameter. The tumor was composed of multiple cystic spaces lined by well-differentiated mucinous cells, intermixed with intercalated and occasionally squamous epithelial cells. One of the larger cystic spaces contained a papillary structure lined by multilayered squamous epithelium with scattered mucinous cells. Pools of mucinous material with occasional multinucleated foreign-body giant cells were present within the fibrous stroma. The tumor tissue was invaginated into the underlying bone with pushing borders showing minute evidence of infiltration. Adjacent salivary glands were normal as well as surgical margins (Figure 5). Figure 6 shows the post surgical defect, 5 years following treatment, with no signs of recurrence.

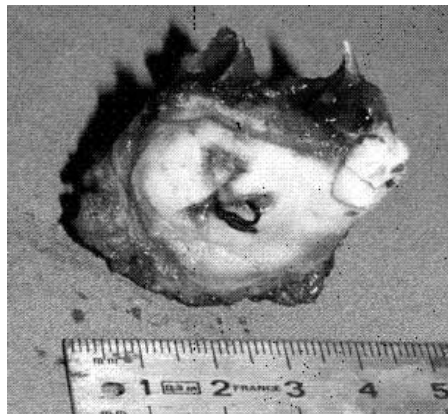


Fig. 4. Tumor specimen with a suture in the center of a palatal mass, at the biopsy site.

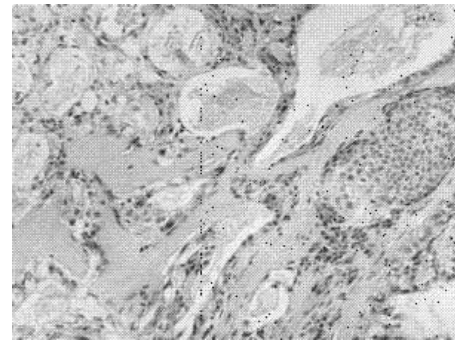


Fig. 5. Histopathological examination of the excised portion of hard palate reveals an invagination in the central portion of the bone, occupied by a soft, partially cystic node measuring 2 cm in diameter. The tumor is composed of multiple cystic spaces lined by well-differentiated mucinous cells, intermixed with intercalated and occasionally squamous epithelial cells (hematoxylin-eosin stain, original magnification x 200).

Discussion and Differential Diagnosis of Palatal Lesions

In our case, the initial diagnosis and long term unsuccessful treatment clearly indicates that the initial diagnosis and the subsequent treatment administered should have been revised. Minor salivary gland tumors are, in fact, uncommon tumors of the oral cavity. They are found mostly on the hard palate, as in our case, but also on the tongue, buccal mucosa, soft palate and other sites³⁰.

The extensive list of differential diagnoses possibilities can result in confusion, as follows.

Pleomorphic adenoma

Pleomorphic adenoma is the most common benign tumor and MEC is the most common malignant tumor of minor salivary glands in the oral cavity³. The pleomorphic adenoma, or benign mixed tumor, is the most common salivary gland tumor. The mean age of occurrence is 45 years, with a male-to-female ratio of 3:2. In minor

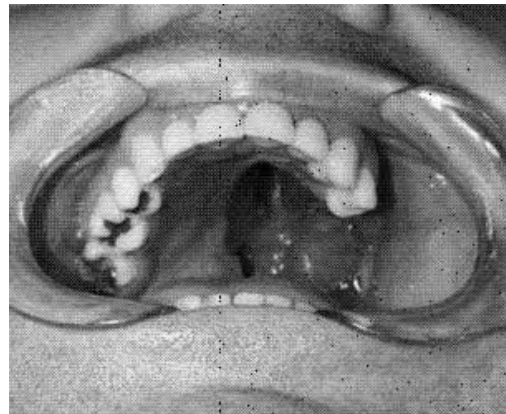


Fig. 6. Postsurgical defect on the left side of the hard palate, with no signs of recurrence, 5 years after surgery.

glands, the most common site is the palate where it usually presents as a slow-growing, painless mass. There is a small risk of recurrence, as well as a small (5%) risk of malignant transformation to a carcinoma-ex pleomorphic adenoma^{12,15,17}. Matsubayashi and Yoshihara³¹ suggested that carcinoma ex pleomorphic adenoma acquired the particular biological behavior in contrast to the other salivary neoplasms in the long-standing process while pleomorphic adenoma undergoes malignant transformation.

Myoepithelioma

Myoepithelioma, in most studies probably included within the group of pleomorphic adenoma, is defined as a tumor composed almost exclusively of myoepithelial cells³². Buchner et al.¹⁵ reported five intraoral lesions, two of them located in the palate. The criteria to distinguish myoepithelioma from pleomorphic adenoma with a predominance of myoepithelial cells are largely subjective³³.

Myoepithelial carcinoma (MC), also known as malignant myoepithelioma, is a rare malignant salivary gland tumor with a predilection for the parotid gland. Yang et al.³⁴ described seven cases of MC of intraoral minor salivary glands and found three cases arose in the hard palate. It is a low-grade malignant tumor with little propensity for regional or distant metastasis and low recurrence. Wide local excision is the treatment of choice. MC with predominantly clear cell morphology is rare³⁵.

Warthin's tumor

The papillary cystadenoma lymphomatosum or Warthin's tumor almost exclusively affects the parotid gland, especially the tail. The peak incidence occurs during the sixth decade of life, with a male-to-female ratio of 7:1. This lesion presents itself as a slow-growing, soft painless mass^{28,36}. Ciapasco et al.³⁷ presented Warthin's tumor of the palate. They presumed that the lymphoid tissue is reactive and a direct origin from the ductal epithelium with secondary lymphocytic infiltration is more likely to occur.

Basal cell adenoma

The basal cell adenoma is an uncommon solitary lesion composed of one cell type, affecting predominantly the upper lip minor glands (canalicular adenoma) and the parotid gland (basal cell adenoma). In a few studies canalicular adenoma involved the palate^{12,15}.

Ductal papilloma

Ductal papillomas (benign papillary lesions) include intraductal papilloma, inverted ductal papilloma, and sialadenoma papilliferum²⁹. The palate is the most common location of sialadenoma papilliferum, although cases of other ductal papillomas involving the palate have been presented^{15,38}. The most important lesion to distinguish from inverted ductal papilloma is MEC, because they both have epidermoid and mucous cells. Unlike in-

verted ductal papillomas, MECs are multicystic or multinodular and infiltrate surrounding tissue³⁹.

Neurilemmoma

Neurilemmoma (schwannoma, neurolemoma, neuroinoma, perineural fibroblastoma, peripheral glioma, and peripheral nerve sheath tumor) is a common, histologically distinctive, benign, usually encapsulated, peripheral nerve tumor originated from Schwann cells that cover myelinated nerve fibers. Intraoral development is uncommon (only 1%). The palate is the second frequent intraoral location^{40–42}.

Lipoma

Lipomas and lipoma variants are relatively uncommon in the oral region. Overall incidence in the oral cavity is between 1% and 4.4% of all benign oral lesions⁴³. Furlong et al.⁴⁴ reported six palatal out of 78 intraoral lipomas. Most patients presented with an asymptomatic, circumscribed mass; the duration of the tumors prior to excision ranged 6 weeks to 15 years. Fanburg-Smith et al.⁴⁵ reported one palatal out of 14 intraoral liposarcomas which are rare in the oral and salivary gland region. They concluded that local excision and careful follow-up, without adjuvant therapy, appears to be the best treatment of salivary gland region liposarcoma.

Polymorphous low-grade adenocarcinoma

The polymorphous low-grade adenocarcinoma is, following MEC, the second most common intraoral salivary gland malignancy. It was first described in 1983 and prior to this, was probably misdiagnosed as an adenoid cystic carcinoma. The most common site is the junction of the hard and soft palate. The male-to-female ratio is 3:1, with a mean age of 56 years. This tumor presents as a slow-growing, asymptomatic mass that may be ulcerated^{28,29,36}.

Adenoid cystic carcinoma

The adenoid cystic carcinoma, the third most common type of the intraoral salivary gland malignancies, affects older individuals, where the mean age of occurrence is 53 years with a male-to-female ratio of 3:2. Fifty percent of these tumors occur in the parotid gland, whereas the other 50% occur in the minor gland of the palate. These present as slow-growing, ulcerated masses, with an associated chronic dull pain²⁹.

Hybrid tumors are very rare salivary gland lesions composed of two or more different tumoral entities in a single neoplasm. In most cases, adenoid cystic carcinoma has been the predominant component in these lesions. Ruiz-Godoy et al.⁴⁶ described two patients with hybrid tumors located in the palate, one involved adenoid cystic carcinoma and MEC.

Clear cells tumor

Clear cells tumors are observed in several malignant salivary gland tumors including MEC³³. Occasionally,

mucin material from structural MEC's cysts leak into the surrounding stroma, resulting in an inflammatory reaction and a nonrepresentative biopsy may mislead the physician to a diagnosis of chronic sialadenitis, which is painful. On some occasions, the inflammatory response may lead to extensive fibrosis, so-called sclerosing MEC⁴⁷. Information concerning calcifications in clear cell MEC of the salivary gland is very scarce. Yang and Chen⁴⁸ concluded that clear cell MEC should be considered in the differential diagnosis of salivary gland tumors with calcification.

Acinic cell carcinoma

Acinic cell carcinoma (ACC) is an infrequent malignant salivary gland tumor. Approximately 16% of all ACCs occur in the mouth; it accounts for 6% of all primary salivary gland neoplasms and 17% of all primary malignant salivary gland tumors. Omlie and Coutlas⁴⁹ found 28.6% out of 21 ACC's cases in the palate. In general, intraoral ACCs are more common in the buccal mucosa, upper lip and palate; more frequent in women; usually asymptomatic and slow-growing, and treated with local excision; much less aggressive in the minor salivary glands, and patients rarely die of disease, and tumors seldom metastasize. Triantafillidou et al.⁵⁰ concluded that ACCs are characterized by an indolent clinical course with the potential for both local recurrence and distant metastases. Histologically, microcystic, papillary cystic, follicular and solid, and combinations of these types characterize the lesions.

Cystadenoma

Papillary oncocytic cystadenoma of palatal minor salivary glands is a very rare lesion but is important in the differential diagnosis on a palate. Cystadenomas of salivary gland origin are benign, well-circumscribed or encapsulated, multicystic neoplasms that can exhibit intracystic papillations. The relative rarity of such lesions is reflected by their exclusion from many principal surgical pathology texts and major review articles⁵¹. Cystadenoma of the minor salivary gland occurs very rarely and presents as a painless mass beneath the mucosa of the hard palate, cheek or posterior tongue. Occurrence of oncocytic carcinoma (or malignant oncocytoma) arising from minor salivary glands of the sinonasal tract is an unusual event⁵². As oncocytic metaplasia and oncocytomas are most often observed in older individuals, the oncocyte was previously regarded as a »functional exhaustion« of a normal cell. Most reported cases were treated by simple excision without recurrence. Recurrences are attributable to incomplete excision or due to the mistaken diagnosis of a low-grade cystadenocarcinoma^{51,53}.

Angiosarcoma

Angiosarcomas of the oral and salivary gland region are extremely rare, often with relatively good outcome. Fanburg-Smith et al.⁵⁴ reported 22 primary and 7 secondary angiosarcomas; one palatal out of 18 intraoral

angiosarcomas. Symptoms included a mass with recent enlargement and bleeding. Histologically all tumors were vasoformative (commonly spindled); most of them had solid rather than distinctive papillary areas; almost one third of oral and salivary gland angiosarcomas are the rare epitheloid angiosarcoma variant.

Metastatic tumors

Metastatic disease of the oral cavity is uncommon, representing 1% of all oral malignancies, however, the mandibular molar and premolar regions are the most frequently (61%) affected sites⁵⁵. The most common primary sites are lungs, prostate, kidney, bone, adrenal glands and breast, colorectal, genital tract and thyroid in females. Lim et al.⁵⁶ found the liver being the most common primary site. The lung was the most common primary site for the jawbone metastases, whereas the liver was for those of oral soft tissue. They concluded this discrepancy might be caused by a relatively high incidence of hepatocellular carcinoma in Koreans. They reported one palatal out of 18 oral soft tissue metastases. Van der Waal et al.⁵⁷ reported three palatal out of 24 intraoral metastatic tumors. Primary sites were kidney (clear cell carcinoma), colon and oesophagus (both adenocarcinoma). The majority of these malignancies are poorly defined radiographically with occasional mixed or radiopaque lesions⁵⁵.

Lymphoma

Lymphoma and plasmacytoma of the jaws usually occurs in older adult patients and presents as an asymptomatic, ill-defined area of radiolucency. Langerhans cell histiocytosis and squamous odontogenic tumor can produce bony destruction that mimics focal periodontal disease. The former condition is often associated with radiographic appearance of »float teeth«; the latter often results in a wedge-shaped radiolucent defect between the teeth⁵⁸. Lymphomas of the palate are rare lesions and those arising from the mucosa-associated lymphoid tissue (MALT) located in the hard palate were first reported in 2006⁵⁹.

Intraosseous tumors

Primary intraosseous squamous cell carcinoma is more common in older adult men than MEC, but both can result from malignant transformation of pre-existing dentigerous cysts, periapical cysts, odontogenic keratocysts and residual cysts^{60,61}.

Primary central mucoepidermoid carcinoma (CMEC) is an uncommon lesion that was first described by Leep in 1939⁶², with a high predilection for a mandibular location with an average age of onset in the mid-30s²⁸. It represents less than 1% of all salivary gland MECs. The fact that 30–50% of CMEC cases are associated with impacted teeth has even led some authors to classify CMEC as odontogenic²⁸. Occasionally, it is difficult to distinguish between central and peripheral salivary gland origin. The criteria for diagnosis of intraosseous MEC are the following: presence of intact cortical plate; radiographic

evidence of bone destruction; histologic conformation; positive mucin staining; absence of primary lesion in the salivary gland and exclusion of an odontogenic tumor⁶³.

Biswas and Crank⁶⁴ presented findings regarding the relative distribution of various conditions causing maxillary swelling and found 20.8% of palatal bulge. Clinically they found 5 infected/carious teeth and 10.4% dental and dentigerous cysts among 48 patients and 45.4% among 11 non-neoplastic lesions.

It has been suggested that residual odontogenic cysts are the most common form of odontogenic cysts to undergo carcinomatous transformation, which is a rare complication⁶¹. It is also not unusual to misdiagnose the non-ulcerative form of necrotizing sialometaplasia as squamous cell carcinoma or MEC. Patients with intra-oral MEC had a reduced survival expectation if they were of a male gender, with regional metastasis, high grade of malignancy, strong expression of PCNA and weak expression of c-erbB-2, which plays an important role in the development, differentiation and mitogenic signalization in normal cells⁶⁵.

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Conclusion

Considering the extensive list of differential diagnoses on the hard palate, unfortunately, acute odontogenic infection, as we previously reported⁶⁶, can now be added to that extensive list. However, the most important factors for presumptive diagnosis of tumorous lesions on the hard palate are time of presence, relation to the middle palatal line, presence of pain and the nature of bone destruction.

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MUKOEPIDERMROIDNI KARCINOM POGREŠNO DIJAGNOSTICIRAN KAO ODONTOGENA UPALA. PREGLED DIFERENCIJALNE DIJAGNOZE NEPČANIH LEZIJA

SAŽETAK

Mucoepidermoidni carcinom (MEC) čini oko 30% malignih tumora žlijezda slinovnica i otprilike isto toliko ih nastaje u malim žlijezdama slinovnicama. Nepce je najčešća lokalizacija onih koji nastaju u malim žlijezdama slinovnicama. Bolesnik star 33 godine s nepčanim MEC-om neuspješno je liječen kao akutna odontogena upala, koja nije reagirala na endodontsko liječenje zuba, višekratne incizije i antibiotike. Na tvrdom nepcu postojala je polukuglasta, tvrda, bezbolna tvorba koja nije prelazila središnju liniju. Učinjena je djelomična maksilektomija. Temeljem pregleda literature prikazujemo diferencijalnu dijagnozu nepčanih lezija. Koliko je autorima poznato ovo je prvi prikaz nepčanoga MEC-a pogrešno dijagnosticiranoga i liječenoga kao odontogena upala. S obzirom da diferencijalno dijagnostički postoje brojne promjene na nepcu, sada u diferencijalnu dijagnozu MEC-a možemo pribrojiti i akutnu odontogenu upalu.