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Case Report

Papillary Cyst Adenocarcinoma Arising in a Papillary Cyst Adenoma: A Rare Entity in the Sublingual Gland

Ilana Kaplan[1*], Vadim Raiser[2], Gal Frenkel[3], Benjamin Shlomi[4]

[1]*Director of The Oral Pathology Service, Tel-Aviv Sourasky Medical Center, Goldschleger School of Dental medicine and Sackler School of Medicine, Tel-Aviv University, Israel*

[2]*Senior Surgeon, Department of Oral and Maxillofacial Surgery, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

[3]*Resident, Department of Oral and Maxillofacial Surgery, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

[4]*Head of Oral and Maxillofacial Surgery Unit, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

**Corresponding author: Dr. Ilana Kaplan, 1Director of The Oral Pathology Service, Tel-Aviv Sourasky Medical Center, Goldschleger School of Dental medicine and Sackler School of Medicine, Tel-Aviv University, Israel, Tel: 972-523390330; Email: dr.ilanakaplan@gmail.com*

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Abstract

Papillary cystadenocarcinoma of salivary glands is an extremely rare low-grade malignant tumor, with which has considerable overlap in microscopic characteristics with the benign papillary cystadenoma Case report: a 78 years old female presented with a long standing multi-lobulated mass in the floor of mouth, which had recently increase in size. MRI identified a well-circumscribed multicystic mass above the mylohyoid. Biopsy showed multicystic architecture, thin cuboidal epithelium creating small intra-luminal papillary projections, with a uniform and bland cytology, diagnosis papillary cystadenoma. In the resection specimen, a focal invasion pattern was observed, reversing the diagnosis from benign to malignant papillary cystadenocarcinoma. Conclusion: A history of long duration, recent increase in size, encapsulation of the tumor periphery with a localized front of invasion suggested the possibility of papillary cystadenocarcinoma arising in papillary cystadenoma , a phenomenon which had never been documented before.

Keywords: Cystadenoma; Cystadenoacrcinoma; Papillary; Salivary Glands

Introduction

Papillary cyst adenocarcinoma (PCAC) of salivary glands is an extremely rare, usually low-grade tumor, with a papillary - cystic architecture, first classified as a distinct neoplasm in 1991 by the World Health Organization (WHO)[1], and Ellis and Auclair [2]. It accounts for less than 0.2% of all salivary gland tumors according to some studies. [3-5] Only a single lesion of PCAC of the parotid was described within a series of 834 salivary glands tumors.[5] The sublingual gland is an uncommon location for this lesion .[6] PCAC has considerable overlap in microscopic characteristics with the benign counterpart papillary cyst adenoma (PCA); the main difference between the two is the presence of frank invasion into surrounding tissues in PCAC.

In the following report we present a case diagnosed as papillary cystadenoma of the sublingual gland in an incisional biopsy, which following resection, turned out to have an area of invasion and the final diagnosis was PCAC. The diagnostic

challenges in differentiating the benign from the malignant variants are discussed. Transformation from PCA to PCAP has never been reported before.

Case Report

A 78-year-old woman presented with an asymptomatic mass of the floor of the mouth, left side. The patient was aware of a lesion in that area which was constant in size for a long duration. Some increase in size had been observed within 4 months prior to her examination.

Clinical examination revealed a multi-lobulated submucosal mass of 4 cm diameter. It was bluish, firm and the overlying mucosa was intact. (Figure.1)

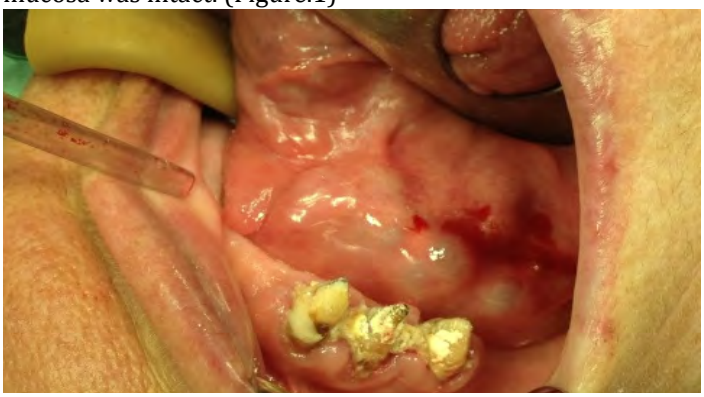

Figure 1. The clinical presentation was of a bluish, multilobulated mass on the floor of the mouth, left.

An incisional biopsy was performed, with provisional differential diagnoses of pleomorphic adenoma, adenoid cystic carcinoma or mucoepidermoid carcinoma.

Microscopic examination exhibited a multicystic architecture, lined by a thin cuboidal epithelium, creating small and delicate intra-luminal papillary projections. The cells were uniform, with a bland cytology, lacking atypia, prominent mitotic activity or necrosis.Thus malignancy had not been suspected and thediagnosis was PCA. (Figure 2, a-d)

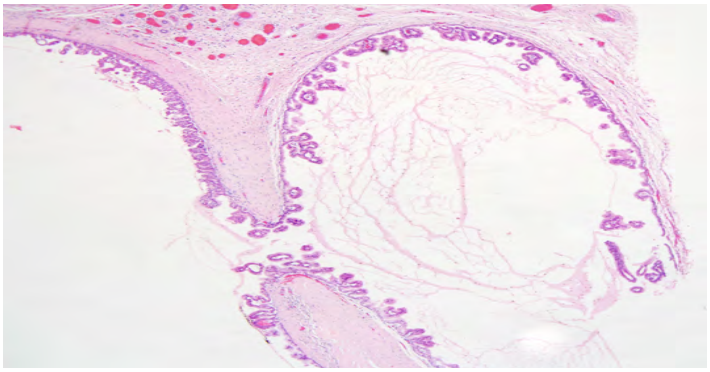

Figure 2A. Exhibits a cystic structure with intra-luminal papillary projections and micro-papillary architecture of the lining epithelium .The cells are small and cuboidal. (H&E, original magnification x40)

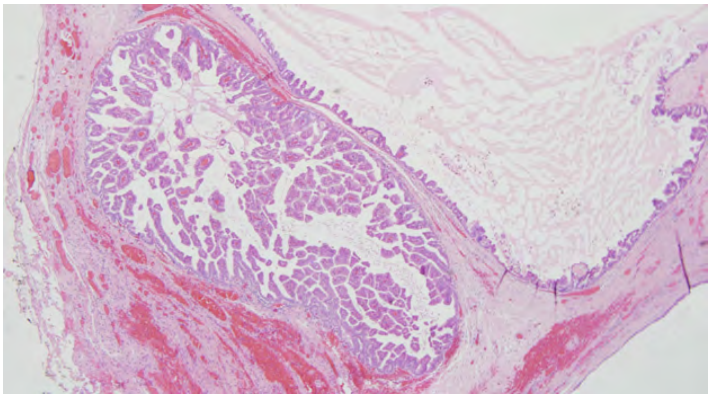

Figure 2 B: Islands exhibiting prominent papillary hyperplasia, which almost obliterates the cystic lumen. (H&E, original magnification x40)

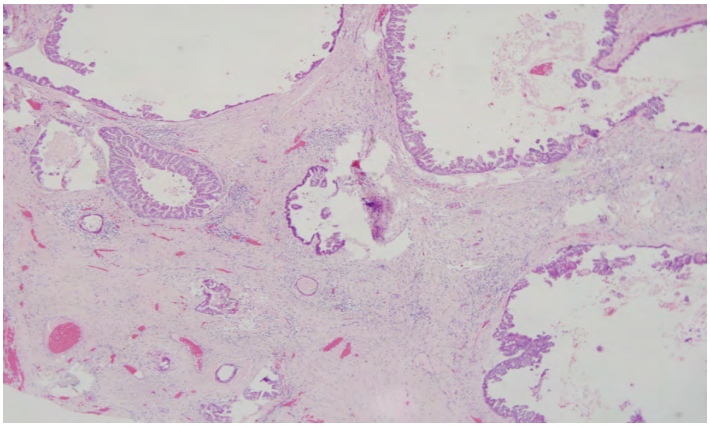

Figure 2C. The tumor exhibits an invasive pattern close to the surgical margin, with multiple small cystic structures invading the connective tissue and muscle. (H&E, original magnification x40)

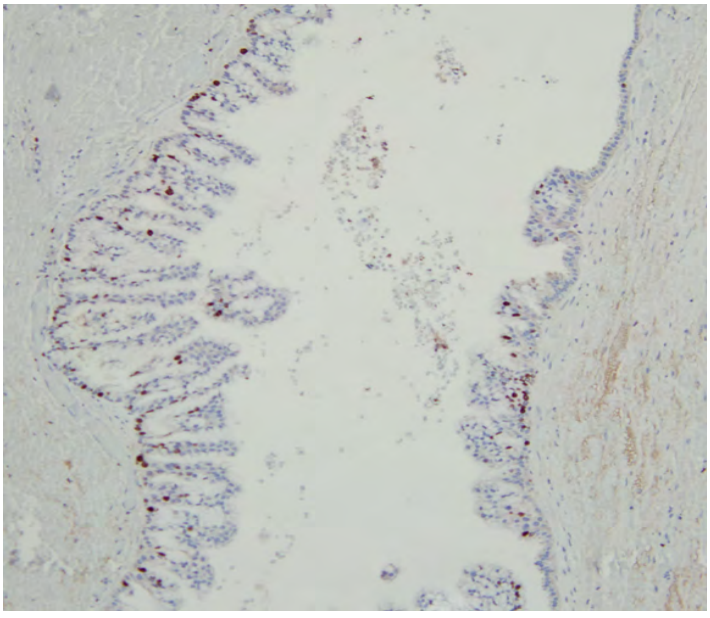

Figure 2D. Ki67 Demonstrates a low proliferation index, below 5%. (Ki67, original magnification x40)

MRI performed to define the extent and nature of the lesion revealed a multicystic mass measuring 2 X 3.2 X 4.5 cm in the left sublingual space, above the mylohyoid. It was well circumscribed, did not involve the mandible, and lymph node enlargement was not observed. The left sub- lingual gland could not be demonstrated in the MRI. (Figure.3)

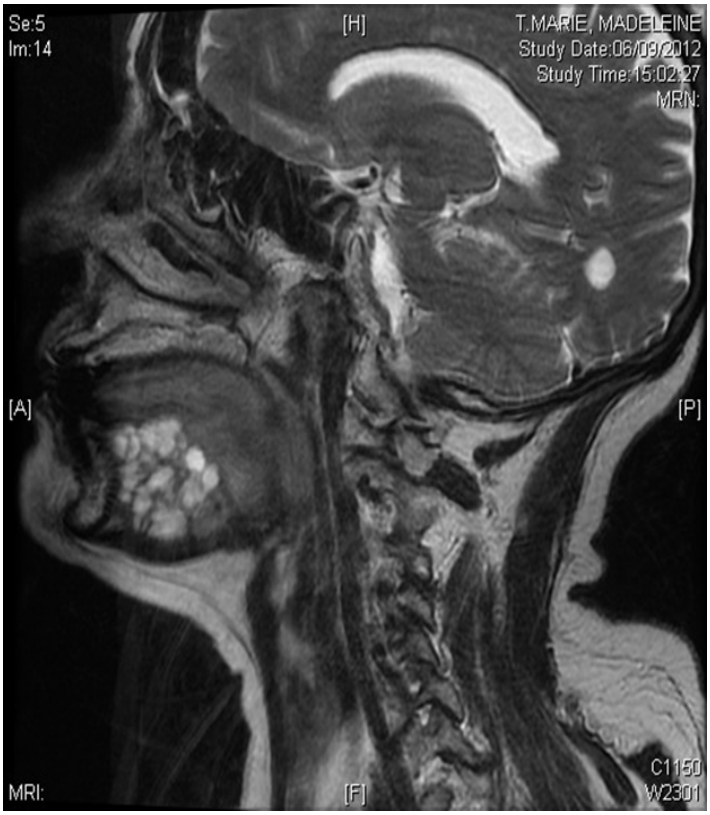

Figure 3. Sagittal T2 weighted MRI depicts multiple hyperintense cyst- like lesions in the floor of the mouth, above the mylohyoid muscle.

Under general anesthesia, a mucosal incision was preformed. The lesion seemed to present a distinct capsule, thus an extracapsular dissection was carried out, easily separating the tumor from surrounding tissues. In the posterior aspect, a firm attachment to the submandibular salivary gland was observed, with no clear demarcation in that area. The surgical specimen seemed macroscopically to be multi-lobulated, well-circumscribed and encapsulated.

Multiple microscopic sections exhibited essentially the same features described in the initial biopsy, with multiple cystic structures, lined by thin bland cuboidal epithelium with intra-luminal papillary projections. However, while examining the margins it became evident that although a fibrous capsule was present in the majority of the tumor periphery, at least in one area (which corresponded with the posterior aspect), the tumor had an invasive pattern rather than a capsule, with multiple small tumoral cysts and islands invading into adjacent tissues. With this finding, the diagnosis was reversed from benign to malignant, and signed-out as PCAC.

Follow Up

Radiotherapy as an adjuvant therapy had been advised, but was refused by the patient. She has now been under follow up for 30 months with no evidence for recurrence.

Discussion

Cystadenoma is characterized by a mass composed of epithelium-lined cystic spaces that contain serous or mucinous secretion material. When the tumor presents both papillary and cystic features it is classified as PCA. This tumor type is found in the ovaries, pancreas and salivary glands. In salivary glands it is most frequently found in the parotid, with decreasing frequency in submandibular , minor salivary glands and the sublingual gland.[1]

The World Health Organization (WHO) described PCA of the salivary glands as a tumor that closely resembles Warthin's tumor, but without the lymphoid elements, constituting multiple papillary projections arising from undifferentiated epithelium of intercalated ducts of the glands.[1,7] In this variant, the epithelial cells are typically tall and present abundant eosinophilic cytoplasm, similar to those found in Warthin's tumor. However, some cases present cystic papillary architecture, but the cells tend to be small and cuboidal.

Salivary gland PCAC is an extremely rare malignant neoplasm, with a peak of incidence in the 7^{th} - 8^{th} decades. A single case of PCAC was described in a child.[8] The sublingual gland is an uncommon location for this lesion. Foss et al. described only 2 PCAC in the sublingual glands in a series of 57 PCAC. [5] In the past 15 years only 3 cases involving sublingual and submandibular glands have been reported, with only one of these in the sublingual gland[,4,11,14]. (Table 1)

Due to similar architecture and cytology, it may be difficult to distinguish the benign variant (PCA) form PCAC, especially in a biopsy specimen.[9] Both lesions lack overt atypia, necrosis or prominent mitotic figures. In fact, the only definitive feature separating PCA from PCAC is the presence of frank invasion in PCAC, as opposed to complete encapsulation and absence of invasion in PCA.

In the present case, the majority of the surgical specimen was encapsulated clinically, with only one area in which the tumor seemed to be inseparable from the surrounding tissues during surgery. This area corresponded with the microscopic finding of local invasion into the peri-tumoral tissue. This fact, coupled with the information the patient was aware of a mass in that area, which was constant in size for a long duration, and presented some growth only 4 months prior to her

Author	Gender /Age	Location	Diameter (cm)	Duration	Dg & Grade	Treatment	FU
Harimaya 2006	M,54	submandibular	4.0	2 yrs	PCAC, grade not reported	Submand. gland excision	FOD 6 yrs
Yamada 2007	M,67	Sublingual gland	3.0	10 yrs	PCAP, grade no reported	Enucleation, repeated surgery, chemo & radiotherapy after recurrence	Recurrence with metastasis In 3 months after first surgery.
Koc. 2010	M, 74	Submand. gland	9	1 yr	PCAC, lntermediate grade	NA	NA

Table 1. Literature survey of Papillary Cystadenocarcinoma (PCAC) of submandibular/sublingual gland, 2000-2016.

examination, raises the possibility of malignant transformation to PCAC in a long-standing benign PCA.

Similar processes are well recognized in other salivary gland tumors, such as transformation to carcinoma- in- situ in long standing pleomorphic adenoma, however, it has not been described in the constellation of PCA to PCAC. [10].

Hence, once an incisional biopsy of PCA is signed out, especially in long standing large lesions, both the surgeon and the pathologist should keep in mind there is a possibility of the lesion exhibiting invasive features in the final surgical specimen, which would than require re-classification from benign (PCA) to malignant (PCAC). High-grade variants may present cervical lymph node metastases.[6,11]

Occasional cases of low grade PCAC with cervical lymph nodes metastases have also been reported.[12] Local recurrence can occur at an average of 76 months after initial treatment. [6] The recommended treatment for PCA is surgical excision. In most reported cases of PCAC additional wider excision or postoperative radiotherapy has been suggested and annual revisions for a minimum period of five years. [4, 5, 12, 13]

Conclusions

A history of long standing lesion, a recent increase in size and encapsulation of the tumor periphery with only a localized front of invasion suggested the possibility of papillary cystadenocarcinoma arising in papillary cystadenoma , a phenomenon which had never been documented before.

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