

Polymorphous low-grade adenocarcinoma of the upper lip with metachronous myoepithelioma of the buccal mucosa

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Examples of multiple minor salivary gland tumors, synchronous or metachronous, are uncommon. We report a patient who initially presented with polymorphous low-grade adenocarcinoma (PLGA) and subsequently with myoepithelioma. A 91-year-old white woman presented in 2009 with a 1-cm, firm, nontender, well-circumscribed nodule of the left side of the upper lip extending to the anterior buccal mucosa. Excisional biopsy revealed PLGA. While the margins were positive, further treatment was not recommended due to the patient's age. In 2011, the patient returned with a 1.5-cm, asymptomatic mass of the left buccal vestibule. Excision of the lesion revealed a circumscribed proliferation of epithelioid and plasmacytoid cells arranged in spherical or whorl-like islands and immersed in a mucinous stroma, consistent with myoepithelioma. The PLGA recurred 3 years after initial diagnosis. Excision was again associated with positive margins, and again no further treatment was recommended. A few months later, at a scheduled follow-up appointment, she presented with a painless nodule of the left upper lip, consistent with recurrent PLGA. One month later, the patient died of unrelated causes. We also present a literature review of multiple minor salivary gland tumors. (*Oral Surg Oral Med Oral Pathol Oral Radiol* 2014; 117:e441-e448)

Multiple salivary gland tumors (MSGTs) can be categorized by topographic distribution as unilateral or bilateral and by chronologic appearance as synchronous or metachronous.¹ The histopathologic subtypes of MSGTs may vary. This terminology has occasionally led to misinterpretations and confusion, especially for cases of synchronous unilateral SGTs, as "unilateral" could also imply 2 well-demarcated and histopathologically distinct tumors arising in the parenchyma of the same salivary gland.²

Regarding the histopathologic characteristics of MSGTs, the following combinations have been observed: (1) multifocal benign tumors,³⁻⁵ (2) benign and malignant tumors,⁶ and (3) exclusively malignant examples.^{2,7,8} Regardless of regional distribution and synchronicity or metachronicity, major salivary glands are more frequently affected than the minor glands.² Additionally, a predominant synchronous pattern of appearance has been identified in the majority of reported cases of major-gland MSGTs, with bilateral Warthin tumor and acinic cell carcinoma representing the most frequently encountered benign and malignant histologic subtypes, respectively.²

Intraoral MSGTs are rare, and only a very limited number of them have been reported in the English-language literature.^{2,9-16} These synchronous or metachronous minor MSGTs have been either benign or malignant. To our knowledge, the synchronous or metachronous occurrence of an adenoma and an adenocarcinoma of minor salivary glands has not been reported in the literature.

Herein, we report an unusual example of metachronous myoepithelioma occurring in the left buccal mucosa of a 91-year-old woman with prior upper lip manifestation of a polymorphous low-grade adenocarcinoma (PLGA), and we present their immunohistochemical and histochemical characteristics. In addition, the English-language literature on intraoral MSGTs is reviewed. Cases representing involvement of both major and minor salivary glands, synchronous hybrid or multifocal minor SGTs affecting one gland, and malignancies demonstrating a "collision" pattern were excluded from the present study.

CASE REPORT

A 91-year-old white woman presented in August 2009 for evaluation of a 1-cm, firm, nontender, well-circumscribed nodule of unknown duration, located in the left upper lip and extending to the anterior buccal mucosa. An excisional biopsy was performed. Microscopically, the tumor was composed of aggregates of neoplastic epithelial cells featuring enlarged vesicular nuclei, inconspicuous eosinophilic cytoplasm, and, focally, indistinct cytoplasmic borders and were embedded in a dense fibrous or fibromyxoid connective tissue stroma (*Figure 1, A to C*). A polymorphous architectural pattern was observed, including solid nests, chords, and cribriform formations (see *Figure 1, B and C*). Duct-like structures were occasionally present, containing amorphous basophilic material. In addition, rare psammomatoid intraductal calcifications were identified (see *Figure 1, B, black arrow*), as was focal

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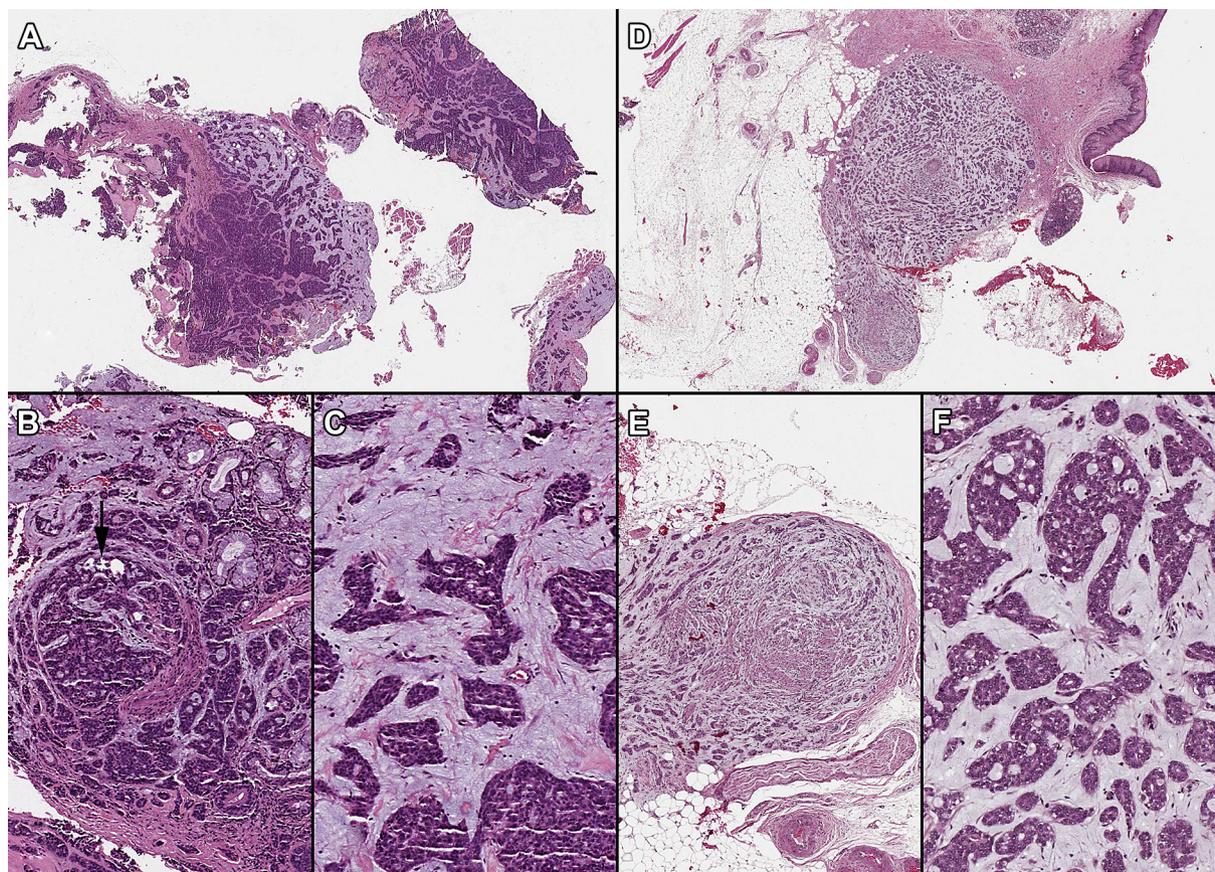


Fig. 1. Histopathologic features of primary (A to C) and recurrent (D to F) polymorphous low-grade adenocarcinoma. Low- and high-power photomicrographs demonstrating aggregates of neoplastic polymorphous low-grade adenocarcinoma cells embedded in a fibromyxoid or exclusively myxoid stroma. The *black arrow* (B) indicates psammomatoid intraductal calcification. In E, diffuse infiltration of a traumatic neuroma is observed (hematoxylin-eosin; original magnification as follows: A and D, $\times 20$; B, $\times 150$; E, $\times 60$; C and F, $\times 200$).

infiltration of mature adipose tissue at the periphery of the lesion. The diagnosis of PLGA was rendered. Surgical margins were positive for tumor. The patient elected follow-up instead of additional surgery.

In March 2011, the patient was referred for evaluation of an asymptomatic, firm, 1.5-cm mass of the left buccal vestibule, opposed to the maxillary second premolar (#13). An excisional biopsy was performed. Histopathologic examination of the specimen revealed the presence of an unencapsulated neoplastic proliferation of epithelioid and plasmacytoid cells, with round to oval uniform nuclei and abundant eosinophilic cytoplasm (Figure 2, A to C). These cells exhibited a predominant arrangement in numerous spherical, whorl-like islands, varying in size, immersed in a mucinous background (see Figure 2, B and C). The initial as well as multiple deeper preparations of the specimen failed to reveal ductal differentiation. Thus, a diagnosis of minor salivary gland myoepithelioma with pronounced mucinous stroma was rendered.

The immunohistochemical profile of the neoplastic cells was investigated with antibodies against pancytokeratin (AE1/AE3), cytokeratins CK5/6, CK7, CK8/18, carcinoembryonic antigen (CEA), CD10, epithelial membrane antigen (EMA), α -smooth muscle actin (α -SMA), S-100 protein, calponin,

glial fibrillary acidic protein (GFAP), and p63. The Ki-67 cell proliferative index was also assessed (Table I). The myoepitheliomatous cells were diffusely and intensely decorated by AE1/AE3, CK7, and S-100 (Figure 3, D and H), whereas they demonstrated sporadic positivity for CK5/6, CK8/18, GFAP, and calponin (see Figure 3, B and J). Rare nuclear immunohistochemical staining was identified with p63 (see Figure 3, F). Finally, absence of immunopositivity was observed for CEA, CD10, EMA, and α -SMA. The Ki-67 index was 0%, verifying the indolent and benign nature of the tumor.

Furthermore, the histochemical characteristics of the lesion were investigated with a panel of special stains including mucicarmine, alcian blue (pH 2.5), colloidal iron with and without hyaluronidase digestion, and periodic acid–Schiff (PAS) stain with and without diastase digestion. The rich mucinous background of the lesion demonstrated positivity for PAS, mucicarmine, alcian blue, and colloidal iron with resistance to hyaluronidase digestion (Figure 4, B, D, and F).

Approximately 3 years after the initial diagnosis of PLGA, a 0.6 \times 0.5-cm, firm, well-demarcated lump was noted in the area of the initial tumor. The clinical differential diagnosis was that of scarring or recurrent PLGA. The lesion was surgically

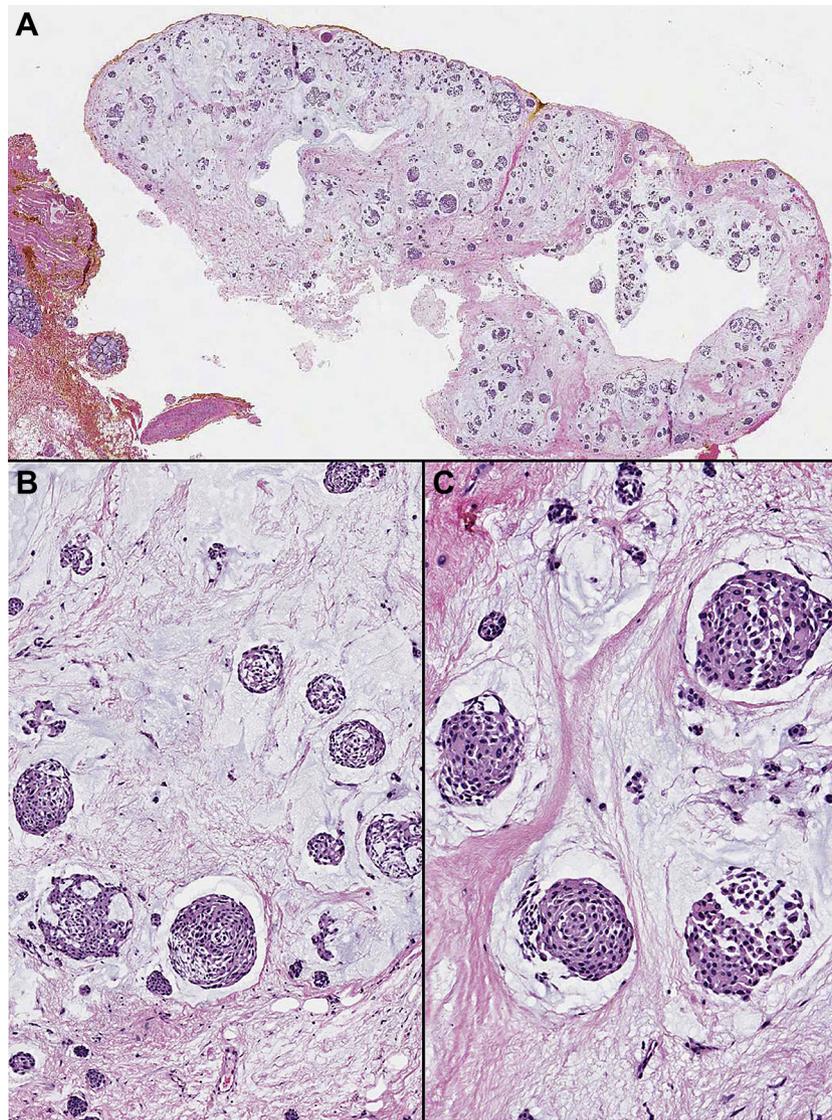


Fig. 2. Histopathologic features of myoepithelioma. Low- and high-power photomicrographs demonstrating whorl-like formations of neoplastic myoepithelial plasmacytoid cells immersed in a mucinous stroma (hematoxylin-eosin; original magnification as follows: **A**, $\times 25$; **B**, $\times 100$; **C**, $\times 200$).

removed along with the surrounding soft tissues. Recurrence was noted and characterized by diffuse infiltration of the connective tissue by PLGA (see [Figure 1, D to F](#)). However, the stroma exhibited pronounced mucinous changes (see [Figure 1, F](#)). Furthermore, neoplastic cells in the form of cords and nests infiltrated the adjacent normal anatomic structures, including the adipocytic tissue, skeletal muscle, perineurium of nerve bundles, and minor salivary glands. Interestingly, a traumatic neuroma infiltrated by neoplastic nests was also identified (see [Figure 1, E](#)). The completeness of the surgical excision could not be assessed, owing to the fragmented nature of the specimen.

Further assessment of the immunohistochemical properties of the recurrent PLGA was performed with the antibodies presented in [Table 1](#). The findings were compared with immunohistochemical results of the primary PLGA. The neoplastic cells

of the recurrence were negative for EMA, GFAP, CEA, CD10, α -SMA, and calponin, and they were uniformly and intensely positive for CK7, p63, and S-100 (see [Figure 3, C, E, G, and I](#)). Pancytokeratin AE1/AE3 was also found diffusely positive with heterogeneous, immunohistochemical staining among different neoplastic lobules. Additionally, selective immunostaining was identified for CK5/6 and CK8/18 (see [Figure 3, A](#)). The initial tumor presented similar immunohistochemical characteristics as the recurrent tumor except for the marker EMA, which was sporadically expressed by the cells of the former but absent in the latter.

Histochemical stains of the recurrent PLGA confirmed the presence of intracytoplasmic glycogen (PAS-positive, diastase-labile) in the form of granules or blobs in a portion of the neoplastic population. Part of the stroma was composed of sialomucin (mucicarmine-positive). Hyaluronic acid labile

Table I. Antibodies and results of immunohistochemistry

Antibody	Source	Clone	PLGA		
			Primary tumor	Recurrent tumor	Myoepithelioma
CK AE1/AE3	Dako	AE1,AE3	+++ (w or s)*	+++ (w or s)*	+++ (s)
CK 5/6	Ventana	D5/16B4	++ (s)	++ (s)	++ (s)
CK 7	Biocare Medical	OV-TL	+++ (s)	+++ (s)	+++ (s)
CK 8/18	Biocare Medical	5D3	++ (s)	++ (s)	++ (s)
CEA	Ventana	TF3H8-1	-	-	-
CD10	Leica	56C6	NA	-	-
EMA	Ventana	E29	+ (w)	-	-
α -SMA	Dako	1A4	NA	-	-
S-100	Ventana	polyclonal	NA	+++ (s)	+++ (s)
Calponin	Dako	CALP	NA	-	++ (s)
GFAP	Dako	polyclonal	-	-	++ (s)
p63	Biocare Medical	BC4A4	+++ (s)	+++ (s)	+ (s)
Ki-67 (%)	Leica	MM1	NA	NA	0%

PLGA, polymorphous low-grade adenocarcinoma; CK, cytokeratin; CEA, carcinoembryonic antigen; EMA, epithelial membrane antigen; α -SMA, α -smooth muscle actin; GFAP, glial fibrillary acidic protein; +, rare positivity; ++, selective positivity; +++, diffuse positivity; w, weak; s, strong; NA, not applicable.

*Heterogeneous immunohistochemical staining among different neoplastic lobules.

after treatment with hyaluronidase was identified as another stromal constituent. The presence of stromal mucopolysaccharides and sialomucin as well as glycogen within tumor cells was verified by colloidal iron, alcian blue (pH, 2.5), and alcian blue–PAS (pH, 2.5) (Figure 4, A, C, and E).

The patient was seen in her last follow-up appointment in July 2012. Clinically, she presented with a 0.5-cm, firm, painless nodule of the left upper lip, consistent with a second PLGA recurrence. However, due to the patient's advanced age, no surgical treatment was administered. One month later, in August 2012, she died of unrelated causes.

LITERATURE REVIEW

A review of the English-language literature revealed a limited number of acceptable cases of MSGTs involving the minor salivary glands proper. In Table II, the demographic data (age and gender) of the patients, as well as the location, histologic subtypes, and chronologic occurrence of tumors, are summarized.^{2,9-16} Ten cases of intraoral MSGTs were identified. Five patients were men and 5 were women, with a mean age of 67.9 years. Six of the cases represented benign synchronous or metachronous tumors histologically diagnosed as canalicular or pleomorphic adenomas.^{10,12-16} The other 4 cases encompassed synchronous or metachronous malignancies, with PLGA being identified as the most commonly encountered malignant lesion.^{9,11} In addition, a case of metachronous mucoepidermoid and adenoid cystic carcinoma has been reported.² Overall, a preponderance for a synchronous pattern of MSGTs in minor salivary glands is observed, with 7 patients demonstrating synchronicity and 3 metachronicity.

As mentioned, all published examples with ambiguous diagnosis or insufficient clinical information were excluded, as were hybrid or multifocal SGTs affecting one gland and collision tumors. Excluded among other

reported cases are the patients presented by Queiroz et al.¹⁷ and Harmse et al.¹⁸ who presented with one tumor, canalicular adenoma of the upper lip, with a multifocal pattern. Excluded also was the article by Shaw¹⁹ that appeared as a short letter to the editor, because of poor documentation. Specifically, the lesion described as metachronous mucoepidermoid carcinoma of the palate represents a recurrence of a primary mucoepidermoid carcinoma that had developed in the same anatomic location approximately 10 years prior. The tumor involving the right mandibular angle was diagnosed as pleomorphic adenoma and treated with superficial parotidectomy. It appears that the second lesion most likely represents a major salivary gland tumor extending to the oral mucosa, thus not fulfilling our criteria for inclusion in the present study. The case presented by Takeda et al.²⁰ was also excluded as an apparently hybrid tumor composed of a pleomorphic adenoma and a "lumen-less trabecular adenoma" arising synchronously in one palatal minor salivary gland.

DISCUSSION

Herein, we presented an example of PLGA of the upper lip combined with a metachronous myoepithelioma of the buccal mucosa. The immunohistochemical characteristics of the PLGA and myoepithelioma and the histochemical stromal properties for each lesion were thoroughly investigated. Regarding the PLGA, the initial and recurrent tumors were both evaluated. Differences in the immunohistochemical profiles of the primary and recurrent PLGAs were not appreciated save for the rare and weak staining for EMA observed in the cells of the primary lesion.

Between the PLGA and the myoepithelioma, differences were observed in the expression of the

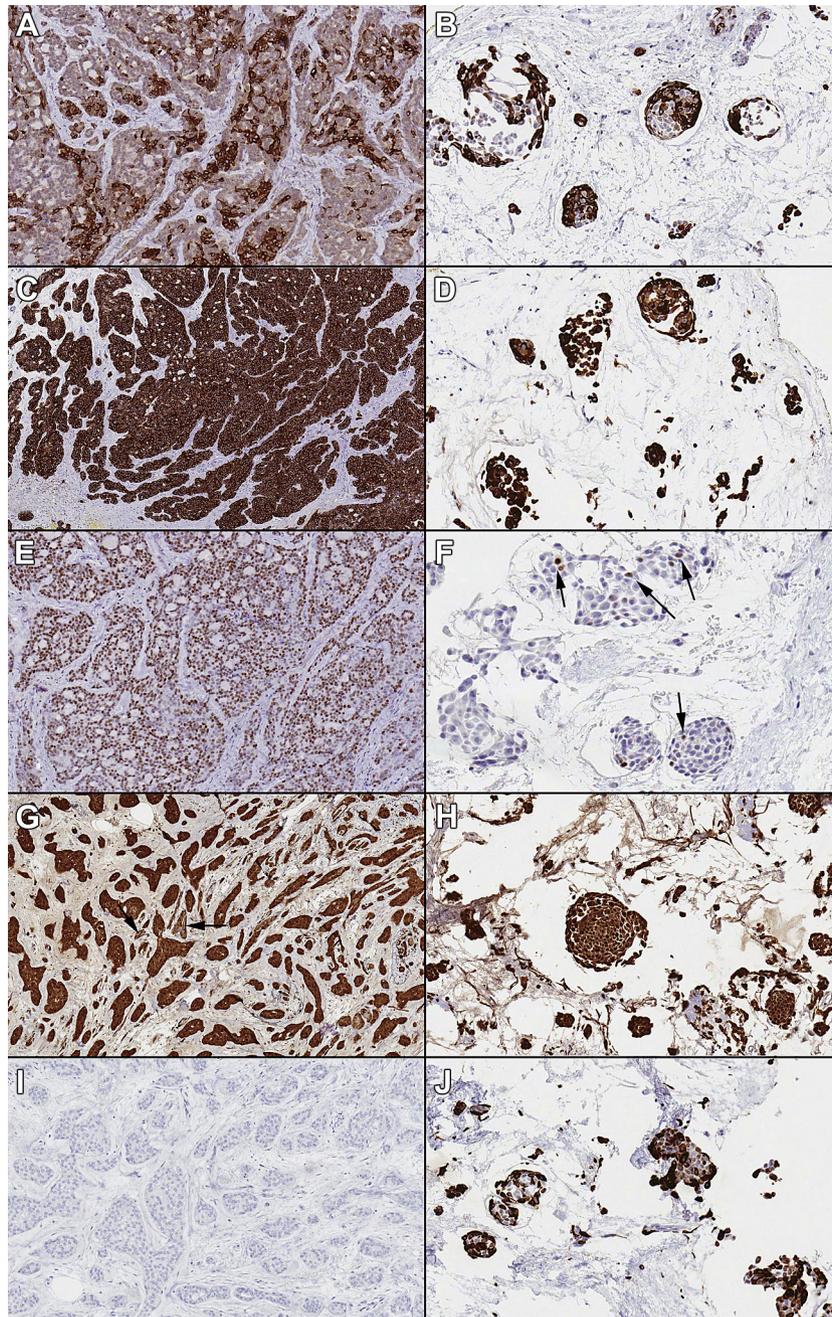


Fig. 3. Immunohistochemical findings. **A, C, E, G, and I** refer to the polymorphous low-grade adenocarcinoma neoplastic population, whereas **B, D, F, H, and J** refer to the myoepithelioma. In **G**, *black arrows* were used to indicate entrapped and infiltrated nerve bundles of the traumatic neuroma. **A and B**, CK 5/6; **C and D**, CK 7; **E and F**, p63; **G and H**, S-100; **I and J**, GFAP. In **F**, the *black arrows* demonstrate positive nuclear immunoreactivity for the marker p63 (immunoperoxidase stain, original magnification $\times 150$ to $\times 200$).

immunohistochemical markers calponin, GFAP, and p63. The first 2 markers were positive only in the myoepithelioma, whereas p63 presented different staining distribution patterns in the 2 tumors. Specifically, it was diffuse in PLGA and selectively positive in the myoepithelioma. The immunoreactivity against cytokeratins (CK5/6, CK7, CK8/18) was essentially similar in both. Calponin,

GFAP, and p63 have been considered together with α -SMA, muscle-specific actin, h-caldesmon, maspin, and CD10 as markers of neoplastic myoepithelium.²¹ GFAP is a low-sensitivity marker usually present in benign salivary gland neoplasms with a prominent myoepitheliomatous component such as pleomorphic adenoma and myoepithelioma.²² Interestingly, it is not

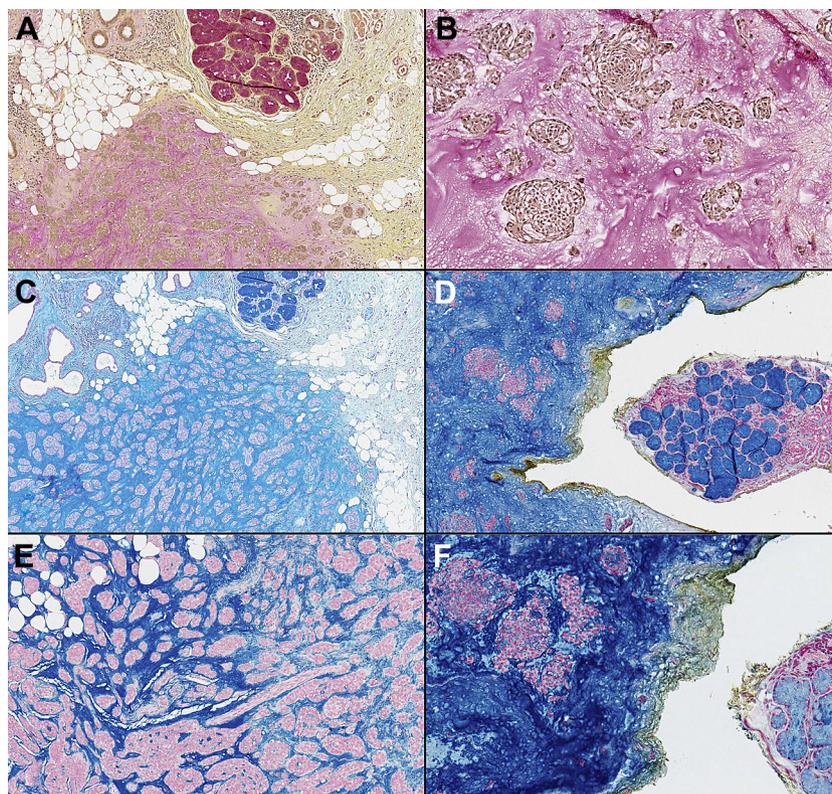


Fig. 4. Histochemical properties of the stroma. A, C, and E are from the polymorphous low-grade adenocarcinoma, whereas B, D, and F represent the myoepithelioma. A and B, mucicarmine; C and D, alcian blue (pH, 2.5); E and F, colloidal iron (original magnification $\times 20$ to $\times 50$).

Table II. Reported cases of synchronous or metachronous MSGTs with intraoral occurrence (present case included)

Author	Age (y)	Gender	Location	Histologic type	Temporality
Appel et al. ⁹	62	female	upper lip/upper lip	PLGA/PLGA*	synchronous
Khullar et al. ¹⁰	59	male	upper lip/anterior buccal mucosa	canalicular adenomas	metachronous
Clayton et al. ¹¹	68	male	buccal mucosa/nasolabial fold	PLGA/PLGA	synchronous
Clayton et al. ¹¹	70	male	upper lip/buccal mucosa	PLGA/PLGA	synchronous
Nelson et al. ¹²	75	female	buccal mucosa/upper buccal sulcus	canalicular adenomas	metachronous
Rousseau et al. ¹³	64	male	upper lip/anterior buccal mucosa	canalicular adenomas	synchronous
Yoon et al. ¹⁴	76	female	upper lip/upper lip	canalicular adenomas	synchronous
Whitt et al. ²	57	male	palate/floor of mouth	MEC/ACC	metachronous
Pelaz et al. ¹⁵	70	female	palate/parapharyngeal space	pleomorphic adenomas	synchronous
Mansueto et al. ¹⁶	78	female	nasolabial wrinkles	canalicular adenomas	synchronous
Present case	91	female	upper lip/buccal mucosa	PLGA/myoepithelioma	metachronous

MSGTs, multiple salivary gland tumors; PLGA, polymorphous low-grade adenocarcinoma; MEC, mucoepidermoid carcinoma; ACC, adenoid cystic carcinoma.

*The authors agree with the interpretation by Whitt et al.² regarding the histopathologic features of the MSGTs presented by Appel et al.⁹

expressed in PLGAs and adenoid cystic carcinomas; hence, GFAP is routinely used for distinguishing between benign and malignant tumors with pronounced myoepithelial participation.²³ In the current case, only the cells of the myoepithelioma were selectively and intensely decorated with GFAP.

The transcriptional factor p63, a member of the p53 family, is known to participate in human salivary gland morphogenesis, maturation of myoepithelial cells, and salivary gland tumorigenesis.²⁴⁻²⁶ As a result, p63 immunostaining has been widely used to discern neoplastic myoepithelial processes, although the p63 nuclear marker

labels cells with basal differentiation as well.^{24,25} In the present case, uniformly diffuse and intense nuclear immunostaining for p63 was noted in the abluminal population of the primary and recurrent PLGA tumors, whereas rare positive staining was observed in the epithelioid and plasmacytoid myoepitheliomatous cells. Furthermore, the latter demonstrated selective positivity against calponin with uniformly absent α -SMA staining. The calponin-positive/ α -SMA-negative immunohistochemical characteristic has been reported in the literature and has been attributed to the absence of microfilaments in the so-called “modified” myoepithelial neoplastic cells.²⁷

Immunohistochemical expression of CD10, a cell surface peptidase, has been identified in a wide variety of normal and neoplastic tissues, including renal cell carcinoma and endometrial stromal sarcoma.²⁸ Regarding SGTs, CD10 has been incorporated in the diagnostic panel of markers for identification of the myoepithelial constituent in benign and malignant lesions including pleomorphic adenomas, myoepitheliomas, and myoepithelial carcinomas.²⁹ Nevertheless, the reported positivity frequency is relatively low, not exceeding 30% in benign and 40% in malignant salivary gland neoplasms.²⁹ Hence, CD10 remains an immunohistochemical marker of limited sensitivity regarding the detection of myoepithelial SGTs, but with a potentially important value in excluding other metastatic neoplasms. The presented myoepithelioma was negative for CD10.

Recent studies have highlighted the role of novel markers in the diagnosis of SGTs with a myoepitheliomatous component, including podoplanin and CD109.³⁰⁻³² In the study by Tsuneki et al.,³⁰ cytoplasmic immunohistochemical staining of variable intensity against podoplanin was identified in all 4 cell phenotypes of myoepitheliomas. In addition, CD109, a glycosylphosphatidylinositol-anchored protein, was reportedly expressed in mammary, lacrimal, and salivary gland neoplasms. Concerning the latter, myoepitheliomatous cells in pleomorphic adenomas as well as basaloid cells in Warthin tumors demonstrated positivity for CD109 with a specificity equivalent to the one reported for the p63 myoepithelial marker.³²

In the present case of PLGA with metachronous myoepithelioma, the constituents of the tumor stroma for both lesions were investigated using PAS with and without diastase digestion, mucicarmine, alcian blue (pH, 2.5) for acidic mucopolysaccharides and glycoproteins, and colloidal iron with and without hyaluronidase digestion for identification of sulfated and carboxylated mucopolysaccharides in general. As previously reported in the histopathologic features of the lesions, the recurrent PLGA demonstrated extensive mucinous change of the fibrous connective tissue stroma, and the whorl-like islands of myoepithelial epithelioid and plasmacytoid cells of the metachronous tumor were embedded in an

exclusively mucinous myxoid stroma. Interestingly, the stromal histochemical properties of both tumors were essentially similar, comprising increased portions of sialomucin, hyaluronic acid, and other sulfated and carboxylated mucopolysaccharides.

In conclusion, we reported a rare example of metachronous intraoral MSGTs and presented the immunohistochemical differences, emphasizing on the myoepithelial component, and the similarities of the 2 tumors, as well as their histochemical stromal properties. The English-language literature concerning synchronous and metachronous minor MSGTs was reviewed, confirming the rarity of these neoplasms.

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