A PIGMENTED NODULE IN THE BUCCAL MUCOSA

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CLINICAL PRESENTATION

A 59-year-old woman presented with a chief complaint of a 1-year history of a slow-growing painless nodule in the left buccal mucosa. She had no past or familial history of head and neck diseases, although she reported regular tobacco and alcohol consumption. She denied taking any medication at the time of the consultation. Physical examination was unremarkable, but intraoral examination revealed a submucous nodule located in close relation to the occlusal line of the left buccal mucosa near the mandibular residual roots. The lesion was mobile and firm but slightly compressible on palpation. Clinically, the lesion presented as a well-defined asymptomatic pigmented nodule covered by intact mucosa, measuring approximately 8 mm (Fig. 1).

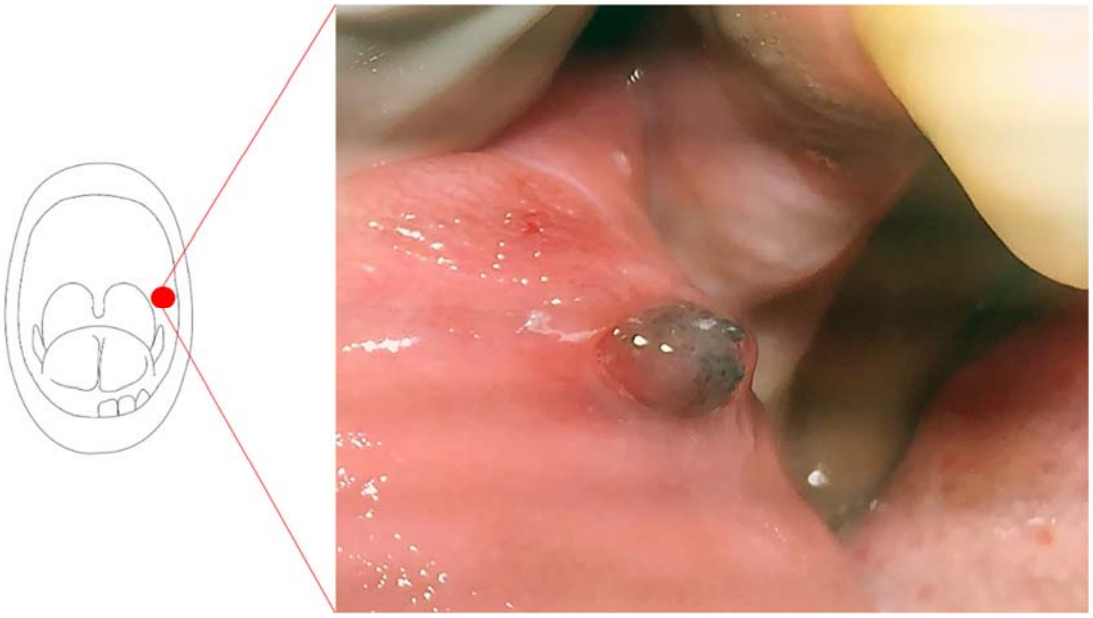

Figure 1. Clinical presentation evidencing a well-defined asymptomatic pigmented nodule in the buccal mucosa.

DIFFERENTIAL DIAGNOSIS

Melanocytic nevi are generally the main differential diagnosis for pigmented lesions of the buccal mucosa. Clinically, they are often found in the skin as macular, papular, or

nodular forms composed of hyperchromatic nevus cells, and when presented in the oral mucosa, they are usually discovered during routine dental examinations.[1] The hard palate is the most common subsite affected by these lesions, followed by buccal mucosa and gingiva.[1,2] In addition, oral melanocytic nevi are mainly biopsied in females with the peak incidence in the fourth and fifth decades of life.[2] In addition, malignant pigmented lesions (i.e. melanoma) were excluded due to the slow growth history.[1,2]

Reactive conditions may also be considered since the patient showed a lesion in the occlusal line near the mandibular residual roots. Mucoceles represent the most common disease of minor salivary glands.[3,4] They may be clinically presented as single or multiple soft and painless nodules, with varied colors, ranging from blue to pink.[4] The lesions may affect both genders with the highest frequency in the second and third decades of life.[3] However, their features did not match the characteristics of the lesion since they did not show any association of rupture of the minor salivary gland duct associated with trauma. The possibility of this being a pyogenic granuloma was considered. Pyogenic granuloma is a reactive lesion characterized by blood vessel proliferation, commonly associated with low-intensity trauma, poor hygiene, and hormonal factors[5]. Clinically, they present as smooth or lobulated exophytic lesions with small, red, erythematous, and hemorrhagic aspects.[5,6] In the present case, the patient showed a residual tooth root in the occlusal line, which may have caused pyogenic granuloma development.

Vascular lesions are usually included in the differential diagnosis of pigmented lesions of the buccal mucosa, including vascular malformation. Vascular malformations represent a structural vascular abnormality commonly diagnosed after birth.[7] They are relatively static in nature and change in size when they sustain trauma, infection, or endocrine changes. True involution never occurs in vascular malformations.[7,8] In our case report, the patient demonstrated a 1-year history, and no regression was seen.

DIAGNOSIS

Due to the clinical presentation, slow-growing behavior, and main differential diagnoses, the possibility of a benign lesion was favored, and an excisional biopsy under local anesthesia was performed. Gross examination revealed two irregular fragments of soft tissue with a brownish surface, measuring 8 mm in aggregate (Fig. 2A). Microscopically, an unencapsulated invasive neoplasm was noted, revealing cystic and solid areas composed of variable admixtures of mucous, epidermoid, and intermediate cells infiltrating the underlying connective tissue (Fig. 2B–C). Prominent subepithelial clusters of epidermoid cells presenting intracytoplasmic heavily pigmented granules were observed (Fig. 2D–E). Periodic acid-Schiff with diastase (PAS-D) staining was performed, highlighting the mucin confined within the mucous cells and cystic structures (Fig. 3A), and Fontana–Masson staining revealed melanin pigment in the epidermoid cells (Fig. 3B). The pigment could be associated with hemosiderin; however, analysis of Perls Prussian blue was negative for hemosiderin (Fig. 3C). Tumor cells showed diffuse cytoplasmic immunoreactivity for cytokeratin 7 (CK7) (Fig. 3D) and 14 (CK14) (Fig. 3E) and strong nuclear staining for p63 (Fig. 3F). Tumor cells were also negative for S100 (Fig. 3G), melan-A (Fig. 3H), and HMB45 (Fig. 3I). The Ki-67 labeling index was considered low (Fig. 3J). The histopathological and immunohistochemical features supported a final diagnosis of pigmented mucoepidermoid carcinoma (MEC). Due to the final diagnosis of a pigmented salivary gland tumor, no laboratorial exam was requested to evaluate the immunosuppression condition of the patient.

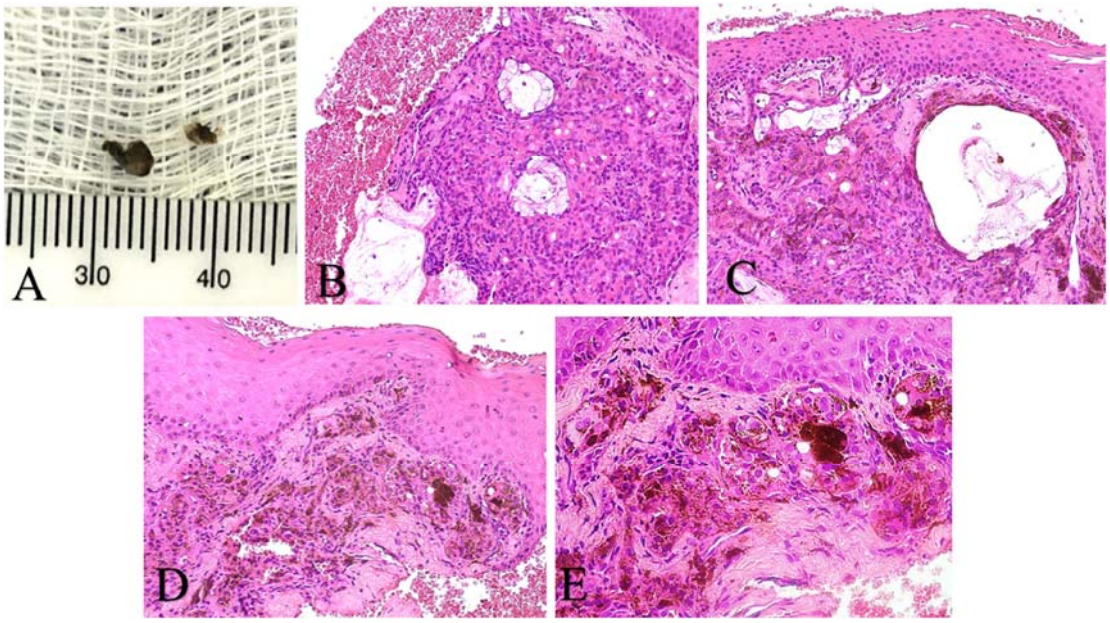

Figure 2. Macroscopic and microscopic features of the neoplasm. A) Gross appearance of the tumor. Two irregularly-shaped black-brown soft tissue fragments measuring 0.8cm in aggregate. B) Photomicrograph reveals mucin-producing cells, mucin in cystic spaces, and surrounding intermediate cells. (H&E, 20x). C) The neoplastic cells surround pseudocystic spaces of different sizes (H&E, 20x). D) Dark pigmented intracytoplasmic inclusions were observed in the intermediate cells (H&E, 20x). E) Pigment contained in cells associated with duct-like structures (H&E, 20x). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM06665.*

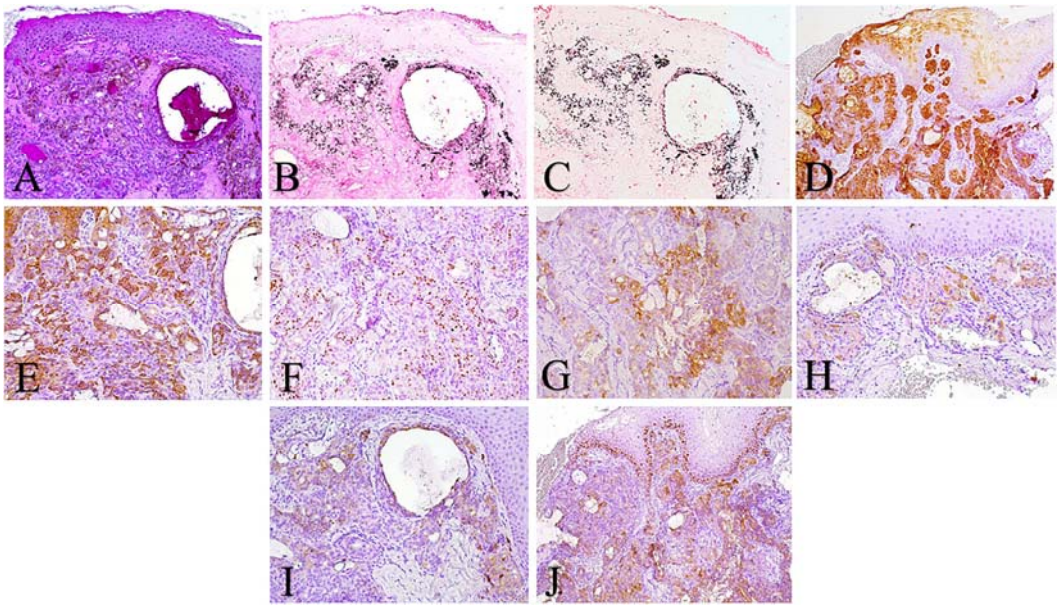

Figure 3. Histochemical and immunohistochemistry aspects. A) Periodic acid-Schiff with diastase (PAS-D) staining evidencing mucin confined within the mucous cells and cystic structures (PAS-D, 20x). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM06670.* B) Fontana Masson staining revealed melanin pigment in the epidermoid cells (Fontana Masson, 20x). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM06671.* C) Perls Prussian blue staining revealed negative staining (Perls Prussian blue, 20x). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM06672.* D) Cytoplasmic immunohistochemical positivity for cytokeratin 7 (CK7) (DAB, 20x). E) Cytoplasmic immunohistochemical positivity for cytokeratin 14 (CK14) (DAB, 20x). F) Nuclear staining for p63 (DAB, 20x). G) Negative staining for S-100 in the tumour cells (DAB, 20x). H) Negative immunolabeling for melan-A in the neoplasm cells (DAB, 20x). I) Negative staining for HMB45 (DAB, 20x). J) Low proliferation index of Ki-67 (DAB, 20x).

MANAGEMENT

Given the diagnosis, the patient was subsequently referred to an oncology department where wide surgical resection with margins was performed. The surgical specimen

evidenced margins free of disease, and the diagnosis of pigmented mucoepidermoid carcinoma was reconfirmed. The patient was under regular follow-up for 16 months, with no sign of recurrence (Fig. 4).

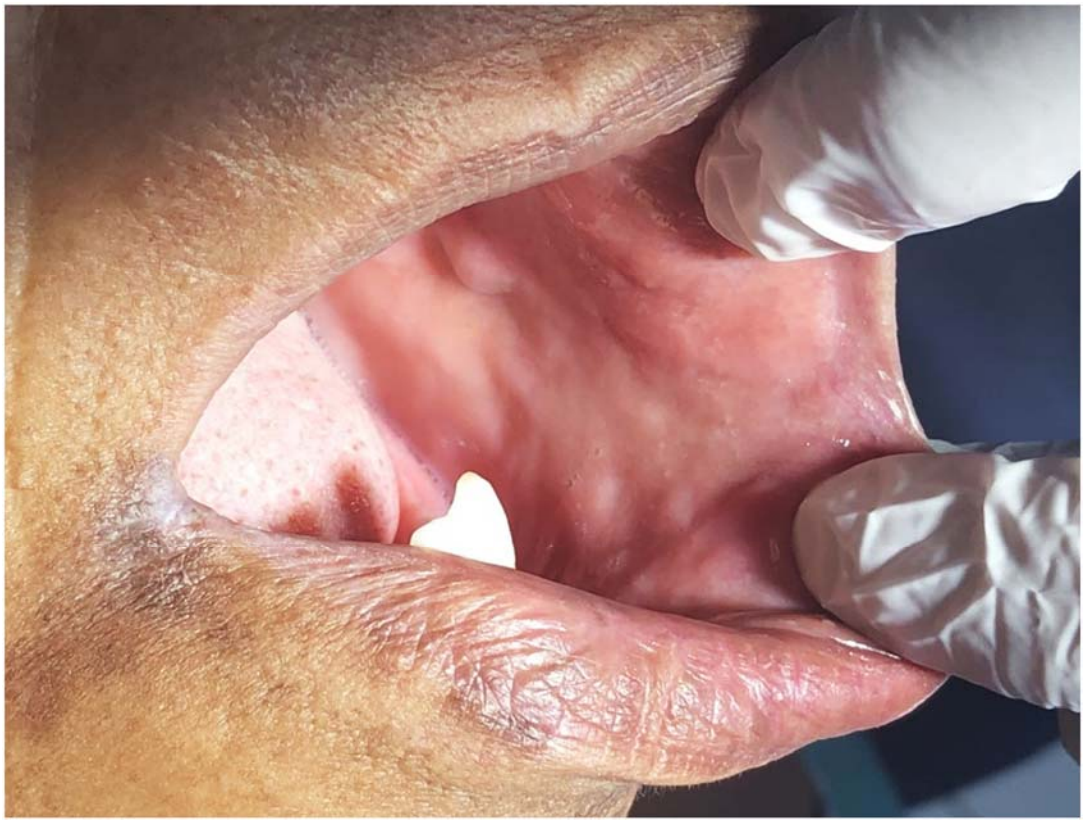

Figure 4. Clinical aspect after 16 months of treatment with no sign of recurrence.

DISCUSSION

MEC represents the most common malignant salivary gland tumor in adults and children and comprises 15% of all salivary gland neoplasms.[9,10] It was first described by Stewart in 1945 as a "mucoepidermoid tumor," presenting benign characteristics due to its low-grade profile. The World Health Organization Classification of Head and Neck Tumors incorporated it in the second edition published in 1991, under the term mucoepidermoid carcinoma, recognizing its malignant behavior and metastatic potential.[11] Since then, attempts have been made to understand its [mucoepidermoid carcinoma's] clinical-

pathological characteristics, in order to improve the approach to its diagnosis. We therefore wanted to report our patient's uncommon presentation of pigmented MEC of minor salivary gland origin.

The MEC has a strong predilection for the major salivary glands, particularly the parotid glands. Intraorally, MEC most frequently occurs in the palate and buccal mucosa.[12] Patients are commonly diagnosed in the third to sixth decades of life.[11,12] This entity does not present gender predilection, although some studies have shown a slight predilection for females.[12] The lesions that may present as painless, fixed, rubbery, and soft tissue swellings, showing a blue-red tinged appearance, are similarly seen in mucoceles and vascular lesions.[12,13] In addition, it is recognized that color alteration and pain are suggestive of malignant disorders in the salivary gland neoplasms of the palate.[13] The current case report occurred in a female patient who developed a painless pigmented nodule in the buccal mucosa, reducing the possibility of a malignant salivary gland tumor. MEC diagnosis is currently rendered on its morphological features without immunohistochemistry or molecular confirmation.[10] The neoplasm is comprised of three cell types: mucus, intermediate and squamoid ("epidermoid") cells.[11,14] In addition to the heterogenicity of cell types, varied architectural growth patterns are considered a hallmark of MEC. Architecturally, MECs range from predominantly cystic, in which the cystic spaces can be lined by any of the cell types and frequently show intraluminal growth, to completely solid tumors.[14] Although numerous histologic subtypes and patterns have been described in the literature, including spindle cells, clear cells, sclerosis, and calcifications[11,14], limited reports have identified the presence of melanin pigmentation (Supplement 1).

Pigmented MEC diagnosis may be assisted by histochemistry and immunohistochemistry techniques. Cases are commonly stained by periodic acid-Schiff (PAS), diastase

resistance, and evidence of the mucous origin of the lesions.[12,15] The occurrence of intracytoplasmic pigment may be indicated by Fontana–Masson staining.[16,17] In addition, immunohistochemistry in MEC has been extensively investigated, although it is not commonly employed in routine diagnostic practice. As an epithelial neoplasm, the neoplastic cells, except for the mucous and some clear cells, are reactive to low- and high-molecular weight cytokeratin and p63 (mostly basal cells).[11] However, in the current case, the presence of melanin made the diagnosis even more challenging since it was necessary to evaluate if the neoplastic cells presented melanocytic origin. The S-100, HMB-45, and Melan-A markers were used to rule out the diagnosis of melanocytic origin.[11,14,16,18] In our case report, the melanocytic-associated immunomarkers were completely negative in the neoplastic cells. PERLS staining was also negative, excluding the presence of hemosiderin.

MEC grading is still being discussed worldwide. There are a varied number of classifications following the histopathologic aspects, which makes it difficult to create a reproducible and standardized pattern in diagnostic routines.[10,11,14] In general, mitotic rate, invasion of the adjacent tissues, necrosis, neural and/or vascular invasion, and the proportion of cell types may be used as criteria to classify MEC as low-, intermediate-, or high-grade tumors.[10,19] More recently, CRTC1-MAML2 translocation has been described in MEC and has assisted in the diagnosis of lesions with uncommon histological presentation, including cases of pigmented MEC.[14] In addition, the presence of CRTC1-MAML2 translocation may be associated with lower age, male gender, less advanced clinical stage, lower histologic grade, smaller tumor size, absence of lymph node metastases, recurrence, or distant metastasis; a higher survival rate is also observed when this genetic alteration is presented.[10,14]

Regarding treatment, wide surgical excision is usually the treatment of choice for most patients. In the presence of high-grade tumors, positive margins and lymph node metastasis are seen, and adjuvant radiotherapy and chemotherapy are recommended.[11,15,20] Lymph node dissection is also proposed in patients with an increased risk of nodal metastasis. The survival rate of patients with MEC is related to the stage of the disease, but even more so to the histological grade and primary site of the lesions; major salivary glands, except the submandibular gland, have a better prognosis because they tend to recur or metastasize.[11,21]

In conclusion, pigmented MEC is a malignant neoplasm with an apparently favorable course and a good prognosis. Because of its histomorphological features, often mimicking benign and low-grade malignant neoplasms, this tumor can be misdiagnosed, adding to the fact that pigmented MEC cases are rarely reported in the English literature. To the best of our knowledge, the presence of melanin in these tumors has no impact on the patient's prognosis.

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CONFLICT OF INTEREST

None.

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