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CLINICAL PATHOLOGIC CONFERENCE CASE 4: MALIGNANCY MIMICKING A REACTIVE PROCESS: MULTIFOCAL LEUKOPLAKIAS AND PIGMENTED LESIONS ON THE BUCCAL MUCOSA

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Clinical Presentation: The patient was a 50-year-old male with a social history significant for heavy smoking of many years' duration. On intraoral exam, the right buccal mucosa displayed multiple scattered areas of pigmentation that vary in size, shape, and intensity of color with 2 areas of overlying leukoplakia that were relatively well defined (Figure 1). There was also a solitary oval pigmented lesion that was heterogeneous in color on the left soft palate (Figure 2). Because of the patient's social history, the clinician was concerned about the leukoplakias on the right buccal mucosa, which prompted an incisional biopsy of the anterior and posterior leukoplakic areas. The patient was relatively light-skinned with dark hair and medical history was stated to be unremarkable.

Differential Diagnosis: Because the patient presented with leukoplakias overlying areas of pigmentation, the differential diagnosis is broad. Leukoplakias in the oral cavity can represent many histologic diagnoses, including hyperkeratosis, epithelial dysplasia, and squamous cell carcinoma, among others.[1] The differential diagnosis for pigmented lesions in the oral cavity is also extensive and can include physiologic pigmentation, exogenous sources of pigmentation, melanocytic pigmentation, and systemic diseases that cause oral pigmentation.[2,3]

Hyperkeratosis is a benign diagnosis in the oral cavity with the characteristic histologic feature being a thickened surface keratin layer. Epithelial dysplasia can appear clinically similar to hyperkeratosis but with atypical changes to the keratinocytes that

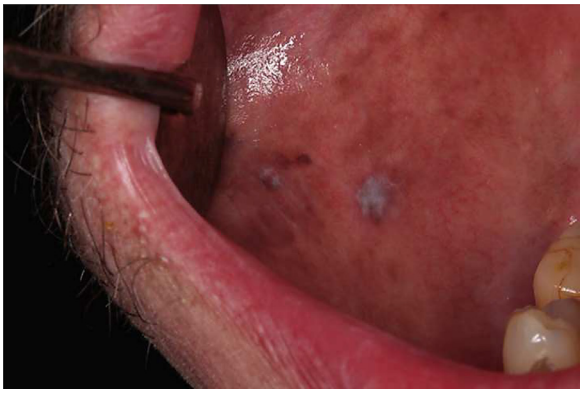

Fig. 1. Irregular scattered areas of pigmentation are seen on the left buccal mucosa. Two areas of pigmentation also have associated overlying relatively well-defined leukoplakias.

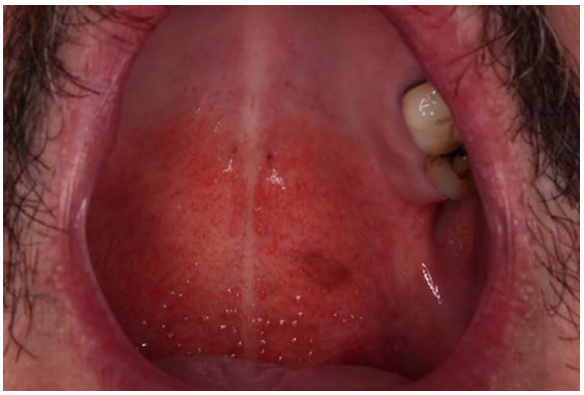

Fig. 2. Solitary pigmented lesion of the right soft palate.

include enlarged and hyperchromatic nuclei, prominent nucleoli, loss of polarity, and pleomorphism.[1] These histologic changes can also be seen in squamous cell carcinoma, in addition to invasion of at least the superficial lamina propria.[1] A biopsy is needed to determine the etiology of oral leukoplakias, and treatment is based on the histopathologic diagnosis.

Smoker's melanosis is a postinflammatory tissue response caused by melanin deposition in the connective tissue stroma of the oral cavity. With a long history of heavy smoking, smoker's melanosis is high on the differential diagnosis. About 21.5% of people who smoke exhibit some degree of oral pigmentation, with a correlation between the number of cigarettes used per day and frequency of oral pigmentation.[1] The most common location for the pigmentation is the anterior facial gingiva in cigarette users and the buccal mucosa or commissure in pipe smokers. There are a few reports of localized pigmentation of the soft palate in patients with underlying chronic lung disease or lung cancer.[4] Again, because of this patient's heavy smoking history, it is possible that he could have an underlying chronic lung disease or malignancy that has not yet been diagnosed.

Without additional medical history, systemic diseases that can cause pigmentation without other underlying symptoms or with a slow disease course should be considered in the differential diagnosis for oral pigmentation. Two systemic diseases that could cause oral pigmentation without many other symptoms include Addison's disease and Laugier-Hunziker syndrome.[1]

Addison's disease is defined as primary hypoadrenocorticism that is caused by autoimmune destruction, infections, malignancy, and other systemic conditions.[5] Symptoms are nonspecific, including fatigue, irritability, depression, weakness, and hypotension, and occur over many months. Generalized bronzing of the skin occurs due to high levels of adrenocorticotropic hormone. Oral manifestations include diffuse or patchy brown, macular pigmentation of the oral mucosa caused by excess melanin production. Oral pigmentation can precede other symptoms by up to 10 years and may be the first sign of disease.[1]

Laugier-Hunziker syndrome is a rare acquired mucocutaneous disorder with an unknown etiology. Oral manifestations include multiple brown, black, or gray macules involving the lips, hard palate, tongue, gingiva, and buccal mucosa.[6] These pigmented areas may have an irregular shape and tend to be less than 5 mm in diameter. Acral pigmentation and longitudinal nail

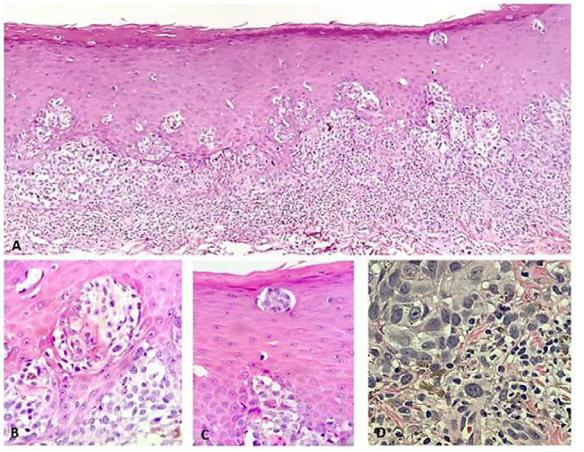

Fig. 3. Hematoxylin and eosin−stained sections on light microscopy reveal **(A)** a junctional proliferation of atylipcal melanocytes showing confluence (10 ×); **(B)** nests of epithelioid melanocytes with amphiphilic cytoplasm, enlarged nuclei, and prominent nucleoli (20 ×); **(C)** small islands of the epithelioid melanocytes demonstrating pagetoid spread into the superficial epithelium (20 ×); and **(D)** individual cells infiltrating the superficial connective tissue (40 ×).

streaks can also be seen. There are no other associated systemic symptoms.[1,7]

In the oral cavity, oral melanotic macules are common and consideration should also be given to biopsy of pigmented lesions to rule out the possibility of oral mucosal melanoma, especially those located in high-risk areas.[8]

Diagnosis and Management: Two biopsy specimens were obtained, one of the posterior leukoplakia and underlying pigmentation and another of the anterior leukoplakia and underlying pigmentation. On microscopic examination, the posterior specimen consisted of invasive lobules of enlarged epithelioid cells with prominent amphiphilic nuclei and intracytoplasmic melanin pigment (Figure 3). The overlying intact squamous epithelium demonstrated an increased population of atypical melanocytes (Figure 3). This biopsy was interpreted as "invasive mucosal melanoma arising from lentiginous melanoma in situ." The anterior biopsy was interpreted as "lentiginous melanoma in situ." Immunohistochemical stains for Melan-A (Figure 4) and SOX-10 (Figure 5) were both strongly and diffusely positive in the malignant melanocytes. A third biopsy of the palate was subsequently interpreted as "mildly acanthotic and inflamed squamous epithelium with pigment incontinence."

The *AJCC Cancer Staging Manual*, 8th edition separates mucosal melanoma of the head and neck from melanoma of the skin.[9] On surgical resection, the primary tumor staging starts at T3, which includes tumors limited to the mucosa and immediately underlying soft tissue, regardless of depth. T4 is defined as moderately (T4a) or very advanced disease (T4b).[9] Depending on the overall stage, treatment options include radical surgery with or without radiation therapy for patients in stage III.[1] Patients in stage IV may be eligible to enroll in clinical trials that include the kit inhibitor imatinib and the tyrosine kinase inhibitor ponatinib.[10-12] A trial for imatinib showed a median overall survival of 46.3 weeks with 2 complete responses at 94 weeks.[10]

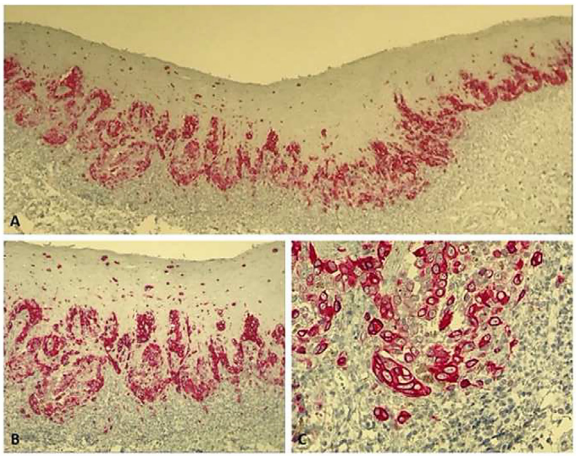

Fig. 4. **(A)** Low-power (10 ×) view of Melan-A immunohistochemical stain. **(B)** Atypical melanocytes are strongly and diffusely positive (20 ×). **(C)** Melan-A cytoplasmic staining highlighting individual cell infiltration (40 ×).

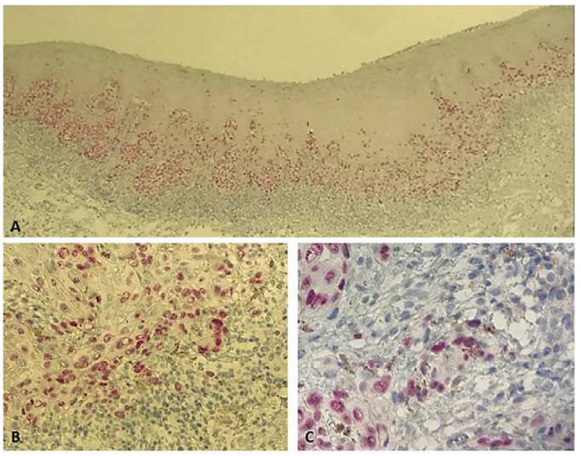

Fig. 5. **(A)** Low-power (10 ×) view of SOX10 immunohistochemical stain. **(B)** Atypical melanocytes show strong and diffuse nuclear staining (20 ×). **(C)** SOX10 highlighting individual cell infiltration (40 ×).

Primary mucosal melanomas are more aggressive than their cutaneous counterparts, with an extremely poor overall survival.[12] The 5-year survival is about 10% to 25%. Independent predictors of outcomes include clinical stage, surgical margin status, tumor thickness of greater than 5 mm, and vascular invasion on light microscopy.[12]

On excision, this patient had negative margins and his pathologic stage was T3N0M0, which corresponded to overall stage III. He underwent a resection and radial forearm flap reconstruction and received 60 Gy radiation treatment. At 6-month follow-up, he was free of disease and doing well.

Discussion: Primary oral mucosal melanoma is rare and accounts for less than 1% of all melanomas.[1] Most lesions present as nodular black to brown pigmented areas with irregular borders and show a predilection for the maxillary or palatal gingiva.[1,11] Ten percent to 33% of cases present with an associated ulceration and many can clinically appear red or amelanotic.[1,11] The initial concern in our case was the leukoplakias of the buccal mucosa because of the patient's smoking history. Our case is unusual in that the patient presented with many seemingly discrete flat areas of pigmentation on the buccal mucosa with no associated area of ulceration, which mimics a reactive process. This clinical presentation serves as a reminder that it is important to address all areas of clinically abnormal tissue in the oral cavity. Though the majority of oral melanomas arise on the hard palate and maxillary gingivae, a diagnosis of melanoma should also be considered in non-high-risk sites and early melanoma can mimic both benign pigmented lesions and reactive processes.

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CLINICAL PATHOLOGIC CONFERENCE CASE 5: A NONHEALING GINGIVAL ULCER

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