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Case Challenge
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A "Speckled" Lesion

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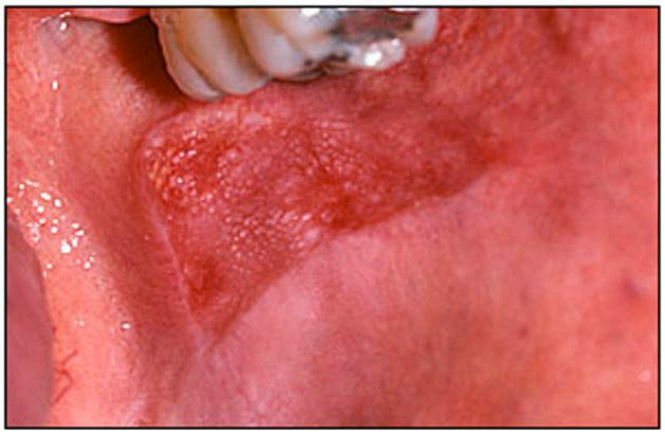


The following Case Challenge is provided in conjunction with the American Academy of Oral and Maxillofacial Pathology.

Case Summary

This 61-year old Caucasian male presented with a chief complaint of sensitivity of the left buccal mucosa for approximately eight to nine months. The patient noted discomfort when eating spicy or acidic foods.

After you have finished reviewing the available diagnostic information, make the diagnosis.

Diagnostic Information

Additional Clinical History

Four months prior to presentation the patient's general dentist obtained a brush specimen from the lesion, which was reported as "negative for epithelial abnormality." Since then the patient stated he had experienced periodic sensitivity of the area.

The patient's past medical history included gastroesophageal reflux disease and mild osteoarthritis affecting his back. His medications included esomeprazole magnesium (Nexium) and rofecoxib (Vioxx). The patient reported a ten-year history of smoking as a young adult. He denied alcohol use or exposure to toxic chemicals.

Clinical Findings

This patient was a well-nourished, 61-year old white male. Examination of the oral cavity revealed a slightly raised, 2 x 2 cm, indurated, red and white speckled plaque with a granular surface on the left posterior buccal mucosa (Figure 1). Attempts at wiping away the lesion were unsuccessful. There were no skin lesions, and examination of the neck was negative for lymphadenopathy.

Incisional Biopsy and Photomicrograph

An incisional biopsy was performed. Microscopic examination revealed a strip of mucosa surfaced by a thinly parakeratinized stratified squamous epithelium exhibiting cellular and nuclear pleomorphism, nuclear enlargement, prominent nucleoli, increased mitotic activity, and dyskeratosis. Islands and nests of atypical epithelial cells were seen extending into the underlying lamina propria. A moderately intense chronic inflammatory cell infiltrate also was present. (Figures 2 and 3)

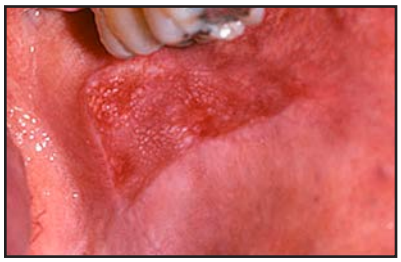


Figure 1. Slightly raised, red and white speckled plaque on the left posterior buccal mucosa.

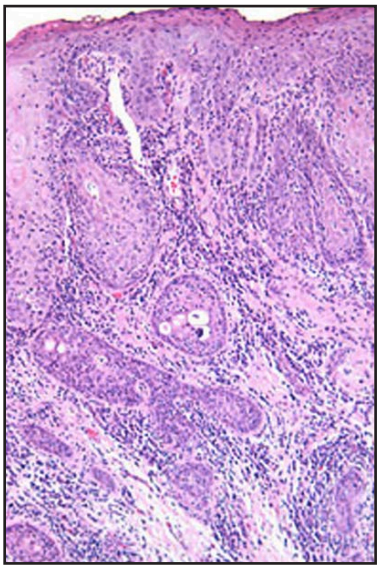


Figure 2. A low-power photomicrograph shows mucosa surfaced by parakeratotic stratified squamous surface epithelium with infiltrating islands of epithelial cells and a moderately intense inflammatory cell infiltrate. (Magnification 100x. Hematoxylin and eosin stain.)

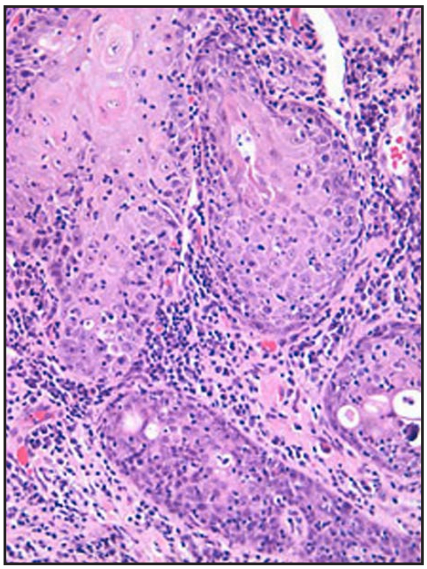
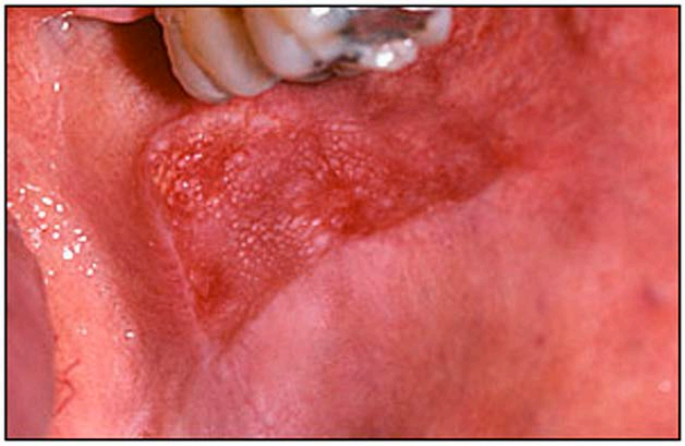


Figure 3. A medium-power photomicrograph shows cellular and nuclear pleomorphism, nuclear enlargement, prominent nucleoli, increased mitotic activity, and dyskeratosis. (Magnification 200x. Hematoxylin and eosin stain.

Can you make the diagnosis?

This 61-year old Caucasian male presented with a chief complaint of sensitivity of the left buccal mucosa for approximately eight to nine months. The patient noted discomfort when eating spicy or acidic foods.



Select the Correct Diagnosis

A. Erosive Lichen Planus
B. Candidiasis
C. Squamous Cell Carcinoma
   Presenting as Erythroleukoplakia
D. Mucosal Cinnamon Reaction

Erosive Lichen Planus

Choice A. Sorry, this is not the correct diagnosis.

Although erosive lichen planus commonly affects the buccal mucosa and presents as red and white lesions associated with pain or sensitivity, it would be unusual for this condition to occur unilaterally as a solitary lesion. Bilaterally symmetric involvement is more typical of this condition. Also, the clinical appearance of a plaque with a rough, granular surface would be somewhat unusual for erosive lichen planus, which typically presents as atrophic, erythematous lesions with central ulceration and, at times, peripheral radiating, keratotic striae.[1]

Lichen planus is a chronic inflammatory condition of unknown pathogenesis affecting approximately 1-2% of the adult population. Current evidence suggests an immune-mediated mechanism possibly via a T-cell-mediated autocytotoxic response.[2] Most patients are middle-aged adults, and there is an approximately 3:2 female-to-male ratio.[1] Sites of involvement include the oral cavity, skin, nails, and genitals as well as other sites.[3] The two major forms of oral lichen planus are the reticular and erosive forms. The more common reticular form classically presents as an interlacing network of white lines referred to as “Wickham’s striae” and is usually asymptomatic. In contrast the erosive form is frequently symptomatic and presents as atrophic, erythematous areas with central ulceration and, occasionally, peripheral radiating white striae.[1]

Histopathologic features include varying degrees of orthokeratosis and parakeratosis, thickening of the spinous cell layer, “saw-toothed” rete ridges, hydropic degeneration of the basal cell layer, apoptotic keratinocytes (termed “Civatte bodies”), and a bandlike lymphocytic infiltrate in the superficial lamina propria. In the erosive form an irregular separation of the epithelium from the underlying connective tissue may be seen.[1]

Please re-evaluate the information about this case.

Candidiasis

Choice B. Sorry, this is not the correct diagnosis.

Although pseudomembranous candidiasis may present as white plaques on an erythematous base and may produce a burning sensation, these plaques are soft and may be wiped off with a gauze or tongue blade. Another consideration might be a form of candidiasis known as hyperplastic candidiasis, which presents as a white patch not removable by scraping. However, this condition is most commonly found on the anterior—rather than posterior — buccal mucosa.[4] Some of the microscopic features observed, including parakeratosis, elongated rete ridges, and a chronic inflammatory cell infiltrate in the subjacent connective tissue may be seen in candidiasis. However, neutrophilic microabscesses (small collections of neutrophils) were not present in the parakeratin layer and fungal hyphae were not demonstrated on microscopic examination. Moreover, the severe epithelial atypia observed in this case is not characteristic of candidiasis.

Please re-evaluate the information about this case.

Squamous Cell Carcinoma Presenting as Erythroleukoplakia

Choice C. Congratulations! You are correct.

This case represents a classic example of erythroleukoplakia or "speckled leukoplakia" — a clinical pattern that frequently reveals advanced dysplasia or carcinoma upon microscopic examination.

Leukoplakia, *erythroplakia*, and *erythroleukoplakia* are purely clinical terms whose definitions unfortunately are somewhat confusing and even controversial. As defined by the World Health Organization, leukoplakia is "a white patch or plaque that cannot be characterized clinically or pathologically as any other disease."[7] Hence, leukoplakia is a clinical diagnosis of exclusion—conditions such as candidiasis, lichen planus, and leukoedema should not be considered examples of leukoplakia. Similarly, erythroplakia is defined as a red patch that cannot be characterized clinically or pathologically as any other condition and, thus, inflammatory conditions that may result in a red clinical appearance are excluded by this definition. Finally, some lesions may demonstrate intermixed red and white areas—hence the term erythroleukoplakia. Note these three terms have no specific histopathologic connotations and, thus, do not constitute microscopic diagnoses.[8]

Compared to leukoplakia, erythroplakia and erythroleukoplakia are much more likely to demonstrate dysplasia or carcinoma upon microscopic examination. The frequency of dysplasia or carcinoma in leukoplakia ranges anywhere from 15.6% to 39.2%, reflecting differences in clinical definitions of leukoplakia used among various investigators.[8] In contrast in a study by Pindborg et al., 65% of erythroleukoplakias showed dysplasia or carcinoma.[9] Even more alarmingly, in a study by Shafer and Waldron, 100% of cases of erythroplakia showed dysplasia or carcinoma.[10] Since it is the red component that seems particularly likely to demonstrate dysplastic or carcinomatous changes, when faced with an erythroleukoplakia, the clinician must always be sure to include the red component in submitted biopsy specimens. This is not to discount the importance of sampling purely leukoplakic lesions, however, since even small, subtle leukoplakias can manifest significant dysplasia or even carcinoma.[11]

In this particular case, the initial brush specimen was reported as "negative for epithelial abnormality." Two recent papers have described patients with oral squamous cell carcinoma or epithelial dyplasia, which were previously sampled by brush biopsy and reported with negative results.[12,13] In a retrospective review of all cases of oral squamous cell carcinoma diagnosed by the Indiana University Oral Pathology Service during a 22-month period, Potter et al. identified four cases of brush biopsy-negative squamous cell carcinoma.[13] Recently Poate et al. reported one squamous cell carcinoma and five epithelial dysplasias among a group of 75 patients with negative brush biopsy results. These investigators concluded not all potentially malignant disease is detected with the brush biopsy procedure.[12]

If a lesion persists despite an initial negative biopsy, then one must evaluate the clinical situation and consider rebiopsy.[14] In the present case, the clinical presentation of a persistent, symptomatic, erythroleukoplakic lesion in an older male with a history of smoking was highly suspicious for carcinoma or epithelial dysplasia. Thus, an incisional biopsy was performed and the diagnosis of squamous cell carcinoma was made.

Squamous cell carcinoma accounts for over 90% of malignancies of the oral cavity.[8] In the United States cancers of the oral cavity and oropharynx comprise approximately 3% of all malignancies in men and 2% of all malignancies in women. The American Cancer Society estimates that in the year 2004 there will be approximately 28,260 new cases of oral cancer.[15] The highest incidence is seen among white males over the age of 65 years, and the overall male-to-female ratio is 3:1. The most common sites for intraoral carcinomas are the posterior lateral tongue, ventral tongue, and floor of mouth. Other sites in descending order of frequency include the soft palate, gingiva, buccal mucosa, labial mucosa, and hard palate.[16]

There is a strong association between oral cancer and tobacco smoking; the risk of developing oral cancer is five to nine times greater for

smokers than nonsmokers. Alcohol also has been identified as a major risk factor and appears to have a synergistic effect when combined with smoking. In addition chronic use of betel quid (paan) is strongly associated with an increased risk of oral cancer, although this habit is more frequently encountered in India and Southeast Asia than in the United States. Other possible risk factors with less definite associations include marijuana use, snuff and chewing tobacco use, human papillomavirus infection, iron deficiency anemia, diets low in fresh fruits and vegetables, and immunosuppression.[8]

Microscopic examination of oral squamous cell carcinoma shows invasive islands and cords of malignant squamous epithelial cells arising from dysplastic surface epithelium. Histopathologic features that may be observed include nuclear and cellular enlargement, prominent nucleoli, increased nuclear-to-cytoplasmic ratio, nuclear hyperchromatism (dark staining), nuclear and cellular pleomorphism (variation in shape), increased mitotic activity, abnormal mitotic figures, and individual cell keratinization or keratin pearl formation (round collections of concentrically layered keratinized cells).[16]

Individual lesions of squamous cell carcinoma may be graded based upon the degree to which the tumor resembles its parent tissue (squamous epithelium), the degree of nuclear and cellular pleomorphism, and the presence or absence of keratinization.[16,17] A three-tier grading system may be used which includes well differentiated, moderately differentiated, and poorly differentiated categories. Lesions with abundant keratinization and a more modest degree of pleomorphism are classified as well differentiated or low grade, whereas lesions without keratinization and with marked pleomorphism are classified as poorly differentiated or high grade.[17] Note that histologic grading is somewhat subjective and does not always correlate with clinical staging and patient prognosis. Clinical staging is based upon the size of the primary tumor, involvement of regional lymph nodes, and the presence or absence of distant metastasis.[16]

The patient elected to seek treatment for his tumor at an outside institution. Treatment of oral squamous cell carcinoma is guided by clinical staging and usually consists of wide surgical excision and/or radiation therapy. Adjuvant chemotherapy may be included in the management of advanced tumors. With suspected lymph node metastasis, a neck dissection may be performed.[16] A patient with oral squamous cell carcinoma is best managed by a multidisciplinary team, including a head and neck surgeon, oral and maxillofacial pathologist, general pathologist, radiation oncologist, medical oncologist, neuroradiologist, general dentist, oral and maxillofacial surgeon, maxillofacial prosthodontist, speech pathologist, nutritionist, dental hygienist, nurse specialist, and tobacco cessation counselor.[18] The overall five-year disease-free survival rate is approximately 76% if metastasis has not occurred by the time of diagnosis (stage I and II), 41% when regional lymph nodes are involved (stage III), and 9% when distant metastasis has occurred.[16] The overall 5-year survival rate for oral cancer is approximately 50 to 55% and, unfortunately, this survival rate has not improved significantly over the past several decades despite advances in treatment.[8] Long-term follow-up is extremely important due to frequent recurrence and multifocal involvement.[16]

Mucosal Cinnamon Reaction

Choice D. Sorry, this is not the correct diagnosis.

Certainly, an oral mucosal cinnamon reaction may cause symptoms of pain and burning with variably red, white, and/or ulcerated mucosal lesions. A variety of clinical presentations are possible depending upon the source of cinnamon exposure. Although a more diffuse pattern of gingival, buccal mucosal, and lingual erythematous mucositis associated with cinnamon toothpaste usage is not seen here, in this case one might consider a more localized reaction from cinnamon chewing gum or candy. However, the buccal mucosal lesions of a localized cinnamon reaction are usually more oblong and exhibit a more ragged or shaggy area of hyperkeratosis and erythema compared to the present lesion.[5] Moreover, the patient denied using any cinnamon-oil containing products, including toothpaste, mouthwash, dental floss, gum, candy, breath fresheners, or ice cream.

Histopathologic features of cinnamon stomatitis include hyperkeratosis, psoriasiform acanthosis, neutrophilic microabscesses in the spinous cell layer, a chronic lichenoid mucositis (with a lymphoplasmacytic infiltrate obscuring the epithelial-connective tissue interface), and a deeper perivascular infiltrate comprised of lymphocytes with occasional plasma cells and rare eosinophils.[5,6]

Please re-evaluate the information about this case.

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Note: Bio information was provided at the time the case challenge was developed.

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