Smokeless tobacco keratosis

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Abstract

Smokeless tobacco keratosis is a benign lesion characterized by the formation of white, gray, or pale macules or papules with wrinkling or rugae. It forms in the oral mucosa in response to the use of smokeless tobacco products. We present a 50-year-old man with an extensive history of smokeless tobacco use and development of the characteristic lesion. Shave biopsy showed typical changes of this benign condition and tobacco cessation was recommended.

Keywords: chronic irritation, keratosis, oral mucosa, smokeless tobacco, white plaques

Introduction

Smokeless tobacco keratosis, or snuff dipper's keratosis, is a benign lesion characterized by the formation of white, gray, or pale macules or papules in the oral mucosa, often accompanied by wrinkling or rugae in response to use of smokeless tobacco products. In 2018, it was estimated that 2.4% of adults over age 18 in the United States use smokeless tobacco products, equating to 5.9 million Americans [1]. Smokeless tobacco products include chewing tobacco, moist snuff, and dry snuff.

The product's composition influences the risk of oral malignancy. The primary chemical carcinogen in smokeless tobacco products is tobacco-specific N-nitrosamine (TSNA). Products vary in the number of carcinogenic agents, cancer inhibiting properties, and processing mechanisms. Dry snuff is associated with an increased risk of oral cancer and higher concentrations of TSNA. Dry snuff comes in a powder formulation commonly inhaled through the nostrils or used orally. Chewing tobacco and moist snuff classify as having a very low risk [2]. Chewing tobacco consists of cured, shredded, and flavored tobacco leaves. This form was traditionally favored by men for years but is now waning in popularity. The most popular smokeless tobacco product is wet snuff which consists of finely cut, flavored tobacco that is often sold in pre-portioned pouches. Users place the pouches in the lower buccal vestibule and less often in the maxillary sulcus for desired effects. The risk of smokeless tobacco keratosis is higher among snuff users than chewing tobacco. Moist snuff has a higher alkalinity than dry snuff, leading to greater mucosal penetration and higher likelihood to cause formation of smokeless tobacco keratosis [3,4]. It has been demonstrated that smokeless tobacco keratosis can develop in 60% of smokeless tobacco users within 6 months to three years of usage [5].

Case Synopsis

A 50-year-old man with a past medical history of hypertension, hypercholesterolemia, and reflux esophagitis was seen in our clinic for a complaint of a "wrinkly spot" on his lower inner lip for over 20 years. He admitted to using smokeless tobacco for the past 34 years. When he first began using, he placed the tobacco on the sides of his mouth. Then, he switched the position so that the tobacco was in front of his front bottom teeth. He noticed the lesion develop soon after he switched the tobacco to this

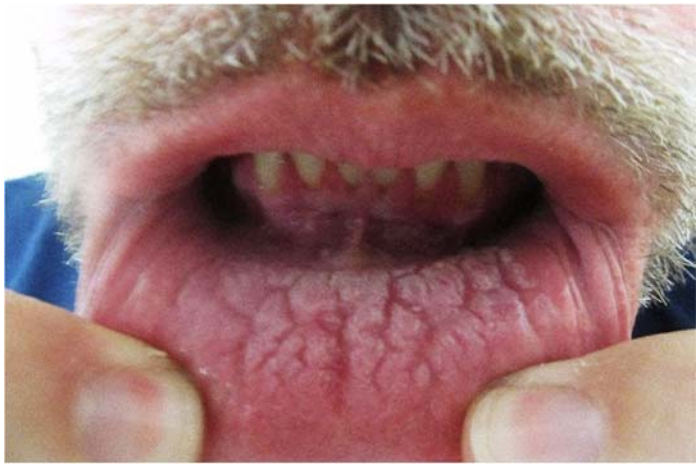

Figure 1. *Whitish discoloration of inner lip with rugae.*

position. The lesion was painful when tobacco was placed in the area. He denied any other mucocutaneous changes and felt otherwise well. His current medications included omeprazole, lisinopril, simvastatin, and hydrochlorothiazide.

Physical examination of the skin and oral mucosa revealed whitish discoloration with rugae located from the lower central lip extending all the way toward the lower vestibule of the lip to the gum (**Figure 1**). There was no cervical lymphadenopathy and the rest of the examination was normal.

Tangential shave biopsy of the lip lesion showed irregular acanthosis with marked pallor and edema along the granular layer as well as tiers of parakeratosis noted within the pale superficial zone (**Figure 2**). There was no marked atypia and periodic acid-Schiff stain was negative for fungal elements. These findings are typical of smokeless tobacco keratosis.

Case Discussion

The presentation of smokeless tobacco keratosis is dependent on the frequency, amount, and length of tobacco use. There may also be considerable variation in color and texture in presentation. Color may range from white to brown and texture from mild wrinkles to deep leathery furrows. Early lesions may present with pallor and wrinkling of oral mucosa. Advanced lesions resulting from years of tobacco use can present with well demarcated white plaques with fissures [6]. Greer and Poulson developed a three-degree classification system based on the clinical features of the lesion that was applicable across the age spectrum [5,7]. Degree I lesions feature superficial keratosis with mild paleness and mostly normal surrounding mucosa. Degree II lesions feature superficial keratosis with whiteness, surrounding erythema, and moderate wrinkling. Degree III lesions feature white keratotic lesions with significant mucosal thickening and intense wrinkling. Sialadenitis of minor glands and reduction of intraepithelial Langerhans cells have also been observed in patients with smokeless tobacco keratosis [8,9].

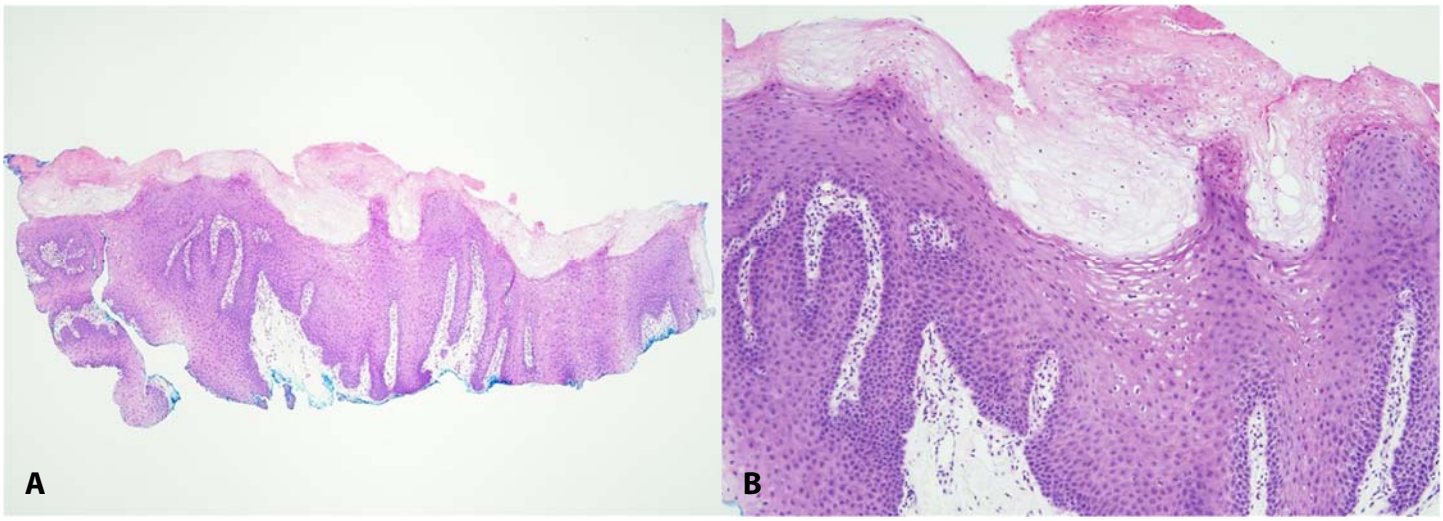

Figure 2. *H&E histopathology of have biopsy from central inner lip,* ***A)*** *4×;* ***B)*** *demonstrates irregular acanthosis, parakeratosis, pallor, and edema along the stratum granulosum, 20×.*

Pathogenesis involves chronic irritation from the placement of smokeless tobacco products directly onto the oral mucosa, resulting in thickening of keratin at the affected area. Altered keratin differentiation and mutations to TP53 gene may play a role in the development of these lesions [10,11]. The gross white appearance of these lesions is believed to be caused by edema of superficial keratinocytes from direct contact injury [6].

Diagnosis can be made by patient history and examination of the oral mucosa. Clinicians should suspect smokeless tobacco keratosis if a wrinkled, white, mucosal lesion correlates with placement of tobacco products. Smokeless tobacco keratosis normally resolves with cessation of smokeless tobacco products. Larsson et al. demonstrated both clinical and histological resolution of smokeless tobacco keratosis lesions within six months of cessation in the majority of patients [13]. If the lesions do not resolve on their own within several weeks of cessation, the lesion should be biopsied. If the patient is not agreeable to stopping smokeless tobacco altogether, then recommendations can be made to switch the location of the tobacco use within the mouth. This can provide time for present oral lesions to heal. Patient education should be provided on the risks of the continuation of smokeless tobacco products. The lesion will not resolve with continued use and changes in color from white to red, ulceration, or an enlarging mass should prompt biopsy to rule out malignancy. Providers can closely monitor the lesion for changes in appearance or remove the lesion entirely with excision. Surgical excision of oral lesions with malignant potential is preferred over destructive therapies, such as laser ablation or cryosurgery, to preserve the specimen for pathologic evaluation [14]. Smokeless tobacco keratosis with dysplasia is at a greater risk of developing cancer [15]. The degree of dysplasia on biopsy can guide clinical decisions of surgical intervention or monitoring.

Histology can help support diagnosis and rule out more worrisome pathologies. Microscopically, these lesions present with non-specific histological findings. There is a characteristic pattern of keratinization involving parakeratosis that forms wavy "chevron" peaks which sit upon a layer of pale edematous keratinocytes. Cellular atypia is normally absent. Other histological findings may include acanthosis, basal layer hyperplasia, non-amyloid hyaline deposition in the lamina propria, and dark cell keratinocytes in basal or parabasal layers [6,12].

There are several conditions that may present with similar features to smokeless tobacco keratosis. The clinical differential diagnosis includes frictional keratosis, oral leukoplakia, and oral squamous cell carcinoma. Frictional keratosis results from constant irritation of the oral mucosa from activities such as chewing or rubbing. Buccal mucosa, tongue, and lips are sites where frictional keratoses typically form. Although clinical appearance may vary, there may be formation of a distinguishing white keratotic linea alba along the occlusal plane. Other presentations range from poorly defined white or gray papules, ulceration, or maceration with fissures [15]. Clinical history and examination are usually sufficient to make this diagnosis. Biopsy may be performed if there is high clinical suspicion for malignancy. Histology will show hyperparakeratosis, epithelial hyperplasia, intracellular edema of cells in the spinous layer, and no cytologic dysplasia. These lesions typically resolve upon cessation of the irritative behavior and have not been reported to have malignant potential [14].

Oral leukoplakia is characterized by the presence of a white patch or plaque that cannot be scraped off or explained by another disease. There is a male predominance and the peak incidence is in adults over the age of 50. The patches or plaques may be entirely white or have intralesional red speckles. Common sites include the soft palate, lateral and ventral tongue, or the floor of the mouth. Oral leukoplakia is a clinical diagnosis and should prompt biopsy when suspected. It is the most common premalignant oral mucosal lesion and is associated with alcohol and tobacco use. They usually demonstrate hyperkeratosis and benign features. However, dysplasia may be present and can be graded from mild to severe. Dysplastic lesions may be treated with surgical excision or cryotherapy. If there is no dysplasia present, periodic monitoring may be appropriate if the lesion is located in a low-

risk area such as the buccal mucosa, labial mucosa, or hard palate [16].

Oral squamous cell carcinoma is the most common malignancy of the oral cavity. Risk factors include alcohol, tobacco, and high-risk HPV strains 16 and 18. It is most commonly seen in middle aged and elderly men. The most common sites of oral squamous cell carcinoma include the floor of the mouth, lateral and ventral surfaces of the tongue, and the soft palate [16]. This lesion may present as an irregular or rough ulcer, white and/or red plaque, or mass. Induration on examination should raise concern for squamous cell carcinoma. The patient may be otherwise asymptomatic or present with dysphagia, dysphonia, and regional lymphadenopathy depending on the location and staging of the tumor. If a lesion is present in a high-risk area with suspicious clinical presentation, a biopsy should be performed to rule out malignancy. Histology will demonstrate findings typical of squamous cell carcinoma including nuclear atypia, prominent nucleoli, keratin pearls, intercellular bridges, and varying degrees of differentiation [17]. Treatment involves combinations of surgical excision, radiotherapy, and chemotherapy.

Conclusion

Smokeless tobacco keratosis is a benign lesion that forms in the oral mucosa in response to smokeless tobacco use that should be differentiated from malignancy. It may resemble clinical features of other pathologies, including frictional keratosis, oral leukoplakia, and oral squamous cell carcinoma. Oral lesions may be difficult to distinguish clinically, therefore a biopsy can be performed to rule out malignancy. Smokeless tobacco keratosis typically resolves with cessation of tobacco products. If the lesion persists despite cessation of products or dysplasia is present on histology, it may be monitored with periodic observation or removed with surgical excision.

Potential conflicts of interest

The authors declare no conflicts of interest.

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