Adherent white plaques in a nonsmoker

Andres Flores-Hidalgo, DDS, MS,[a] and Alice E. Curran, DMD, MS[b]

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CLINICAL PRESENTATION

A 48-year-old native-born Caucasian female, nonsmoker, presented to the Oral and Maxillofacial Pathology Clinic on referral from a local oral surgeon for multiple well-defined white plaques of 6 months' duration. The mandibular anterior attached gingiva and the maxillary and mandibular vestibules at the frenula were involved, with smaller areas of bilateral buccal mucosa and tonsillar pillars. The lesions appeared homogeneous, bright white, and smooth surfaced (Figures 1A to 1D). She denied any history of pain or tenderness, and there was no history of recent dental treatment, any type of trauma, or any recent change in the use of oral health care products. At the time of clinical examination, the patient did not demonstrate restricted mouth opening, nor was there tightening of oral mucosal tissues. There were no lesions of any kind on the skin of the face or arms. Her eyes were asymptomatic and free of any visible lesions, as was the nasal mucosa, and she denied any changes in the anogenital mucosa. Her past medical history was notable for type 2 diabetes mellitus, gastroesophageal reflux disease, and hypercholesterolemia. Her current medications included estradiol, sertraline, fish oil, melatonin, cetirizine (Zytrec), iron, and dicyclomide. Uric acid, C-reactive protein, antinuclear antibodies panel (ANA), rheumatoid factor (RA Qn), and antitreptolysin-O (ASO) values were all negative or within normal limits. She reported that her mother was recently diagnosed with a mucosal disorder affecting the anogenital area.

DIFFERENTIAL DIAGNOSIS

The plaque form of oral lichen planus can present in several forms that may appear alone or in combination.[1] Oral lichen planus is a chronic autoinflammatory disease, characterized by a cell-mediated response to an unknown antigen.[2] The plaque-like variant, with confluent white patches of keratosis, favors the dorsal tongue and is usually seen in smokers.[1] This clinical presentation was inconsistent with that in our patient.

Lichenoid drug reactions (LDRs) are usually accompanied by a history of new drug intake and have been reported to be associated with a number of drug classes, including the sulfonylureas and sulfonamides.[3] LDRs most frequently resemble erosive lichen planus, but reticular and plaque-like forms can be seen, with or without cutaneous manifestations.[3,4] The diagnosis of LDRs is made when the clinical manifestations subside after removal of the offending drug.[5] The patient's drug history, including when therapy with the offending drug was initiated, should be reviewed.

Lichen sclerosus (LS) is an extremely rare condition in the oral cavity, usually associated with genital/or skin manifestations.[6] LS has been described as atrophic, sclerotic, ivory or porcelain-white plaques that can also exhibit erythematous, telangiectatic, erosive, or ulcerated areas, with accompanying symptoms.[7,8]

Scleroderma, or systemic sclerosis (SS), is a chronic connective tissue disease characterized by skin fibrosis and can involve the lungs, heart, kidneys, gastrointestinal tract, and bones.[9] The oral manifestations of SS are mostly seen in females, and the localized form is usually diagnosed before age 18 years.[10] This form is characterized by limitation of mouth opening, widening of the periodontal ligament, mandibular angle resorption, and telangiectasias.[11] Approximately 30% of patients with SS have ASO antibodies in peripheral blood, and many patients with the localized form have ANAs.[12] In our patient, these values were negative.

The reported frequency of oral lesions is approximately 27% in patients with chronic cutaneous lupus erythematosus. Although the clinical presentation varies greatly, the classic oral lesion is characterized by an area of erythema or ulceration surrounded by white, radiating striae.[13] Widespread honeycomb plaques, similar to lichen planus, with nonspecific erythema have also been reported.[14]

Multifocal oral epithelial dysplasia or proliferative verrucous leukoplakia, a potentially malignant disorder of the oral epithelium, presents as multiple lesions of hyperkeratosis with or without dysplasia, eventually leading to malignant transformation.[15] It has mostly been reported in older women (mean age 60 years). This entity is characterized by its multifocal behavior and its predilection for occurrence in the alveolar ridge

[a]Oral and Maxillofacial Pathology, Department of Surgical Sciences, East Carolina University, School of Dental Medicine, Greenville, NC, USA.
[b]Oral and Maxillofacial Pathology, Department of Diagnostic Sciences, University of North Carolina at Chapel Hill, School of Dentistry, Chapel Hill, NC, USA.

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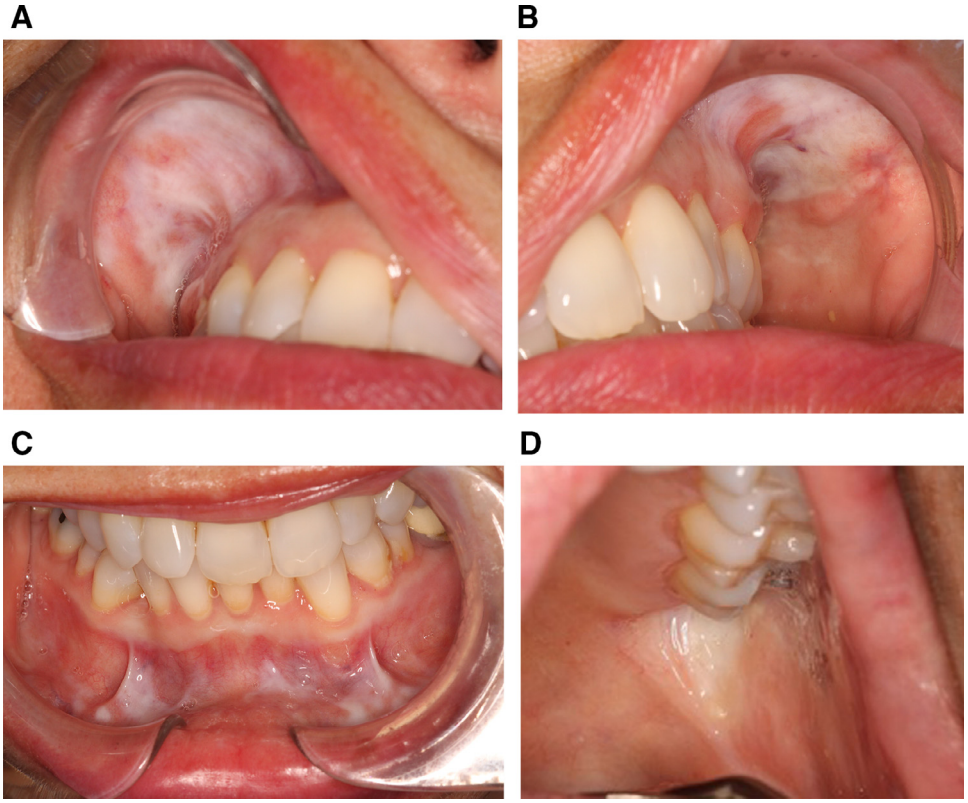

Figure 1. **A-D.** Multiple thick white, well-defined plaques involving: **A, B)** bilateral buccal mucosa **C)** mandibular anterior attached gingiva, **D)** maxillary and mandibular vestibule.

and buccal mucosa.[16] It usually presents in its benign form and then spreads and becomes diffuse within the oral cavity. These lesions are usually elevated plaques that eventually show microscopic features of dysplasia, and later on, it progresses to invasive squamous cell caricinoma.[17]

DIAGNOSIS

We reviewed the mucosal biopsies from the buccal mucosa previously performed by the oral surgeon. Light microscopic examination of the specimens from the buccal mucosa revealed markedly atrophic parakeratotic stratified squamous epithelium about 5 to 6 cells in thickness, with focally hydropic degeneration of the basal layer. The submucosa was very faintly stained and hypocellular, with increased presence of superficial edema. Scattered mast cells and lymphocytes were present in a patchy pattern underlying the altered connective tissue and surrounding vascular channels (Figure 2). Additional tissue was obtained for direct immunofluorescence, which revealed no immunoreactants when specific antihuman IgG, IgM, IgA, C3, and fibrinogen conjugates were used. Because the microscopic features of scleroderma share those of LS, additional laboratory tests were performed to rule it out. Uric acid, C-reactive protein, ANAs, RA Qn, and ASO were all negative or within normal values. On the basis of the clinical, histopathologic, and laboratory findings, the diagnosis of LS was rendered.

MANAGEMENT AND FOLLOW-UP

Our patient was referred to the Rheumatology Department, where rheumatologic evaluation confirmed no evidence of SS. The patient had undergone a recent gynecologic examination, where no anogenital lesions were observed. The patient was able to obtain a report that showed her mother was previously diagnosed with vulvar LS. Treatment of the oral lesions of LS seems to be only necessary when the patient is symptomatic. Treatments reported in the literature range from surgical excision of small lesions to topical and intralesional corticosteroid injections. Because none of these treatments was necessary in our patient, she was placed in long-term follow-up, and the importance of remaining in regular contact with her dermatologist, oral pathologist, and gynecologist was stressed because of the risk of new lesions. Because malignant transformation of vulvar lesions in the oral cavity has not yet been reported, this remains a concern. Therefore, annual follow-up was advised out of an abundance of caution.

At the first 1-year follow-up appointment, the patient reported no significant symptoms or changes related to

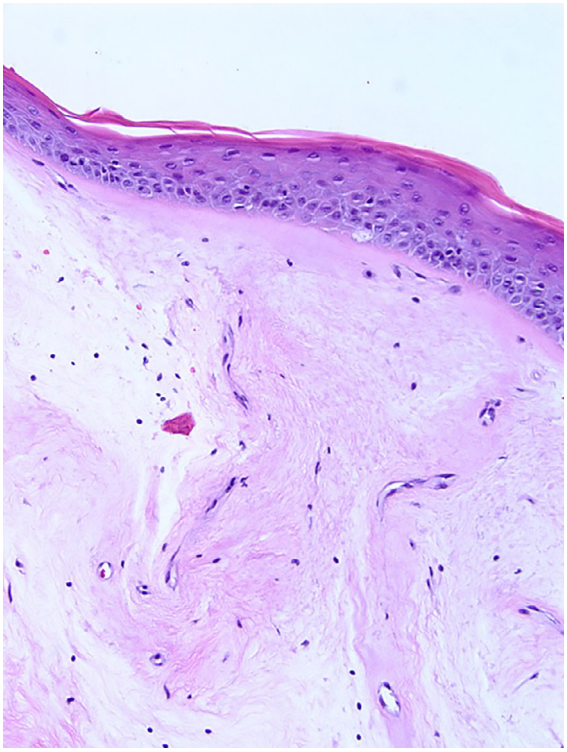

Figure 2. Low power magnification view of fragment of oral mucosa surfaced by parakeratotic squamous epithelium with underlying myxoid stroma (Hematoxylin & Eosin − 100X). A high-resolution version of this slide is available as eSlide VM05477.

her condition. On clinical examination, spread of the previously described leukoplakias toward bilateral anterior tonsillar pillars and anterior facial maxillary gingiva was observed (Figures 3A to 3D). No restriction of mouth opening or induration of mucosal tissues was observed. A recent gynecologic examination did not reveal genital involvement since the initial diagnosis of oral lesions 1 year ago.

DISCUSSION

LS was first described by Montgomery and Hill in 1940 as "lichen sclerosus et atrophicus." It is an extremely rare condition in the oral cavity, with only 35 cases reported in the literature so far.[8,18] The exact etiology is still not clear, although a specific immunologic phenotype of the disease has been previously described.[19] A specific humoral immune response with circulating autoantibodies to the extracellular matrix protein 1 (ECM-1) has been reported, although the mechanism leading to the synthesis of ECM-1 in LS is still not well understood [20]. This autoantibody production may be the result of DNA damage induced by reactive oxygen species, causing changes in structure at molecular level. Sander et al. demonstrated that oxidative DNA damage occurs throughout the LS lesions and that oxidative protein damaged can be detected in the dermal areas of LS and inflammation.[21] It is thought that defects in the control of apoptosis and delayed clearance of apoptotic cells provide a sustained interaction between these oxygen species and apoptotic cell molecules, generating specific antigens that result in autoimmunity.[21] Additionally, an autoimmune phenotype has been observed in vulvar LS, where increased levels of T-helper cell type 1−specific cytokines, dense T-cell infiltration, and enhanced B-cell Integration Cluster/miR-155 expression, as well as autoantibodies against ECM-1 and BP180 antigen, were found.[22] The pathogenic relevance of these observations is still not clear. However, ECM-1 is a plausible target for autoimmunity because antibodies directed to it have been detected in patients with LS. Presumably, there is a genetic predisposition because it seems to be common in some families, and patients with this predisposition may develop symptoms after trauma, injury, or sexual abuse.[23] Thus, cumulative evidence suggests an autoimmune basis for the disease.

LS lesions are extremely rare in the oral cavity and are usually associated with genital/or skin manifestations. LS has been reported as atrophic, sclerotic, ivory or porcelain-white plaques that can also exhibit erythematous, telangiectatic, erosive, or ulcerated areas, with accompanying symptoms.[7,8] In our case, the patient reported no symptoms at the time of consultation.

On direct immunofluorescence microscopy of LS lesions, the presence of antibodies to BP180, similar to bullous pemphigoid, with deposition of immunoglobulin G (IgG) at the basal membrane, has been reported in some cases.[19] This may be associated with an increased risk of LS progressing to vesiculobullous disease.[24] In our case, no specific antihuman immunoreactants (IgG, IgA, IgM, C3) were detected.

SL is a lifelong disease that rarely goes into complete remission. Treatment with topical corticosteroids can help with skin symptoms, such itching and pain. Squamous cell carcinomas have been reported to develop in association with genital involvement but has not been reported in extragenital lesions, such as those in the oral cavity. The risk in genital lesions seems to be decreased by consistent long-term treatment and follow-up. The treatment of oral lesions seems to be only necessary when the patient is symptomatic. Treatments reported in the literature include surgical excision of small lesions to topical and intralesional corticosteroid. Our patient was placed in long-term follow-up, and no treatment was necessary because of the absence of symptoms or any significant aesthetic concerns.

CONCLUSIONS

It is important that patients with oral LS remain in regular contact with the dermatologist, the oral medicine specialist, and the gynecologist because of the risk of

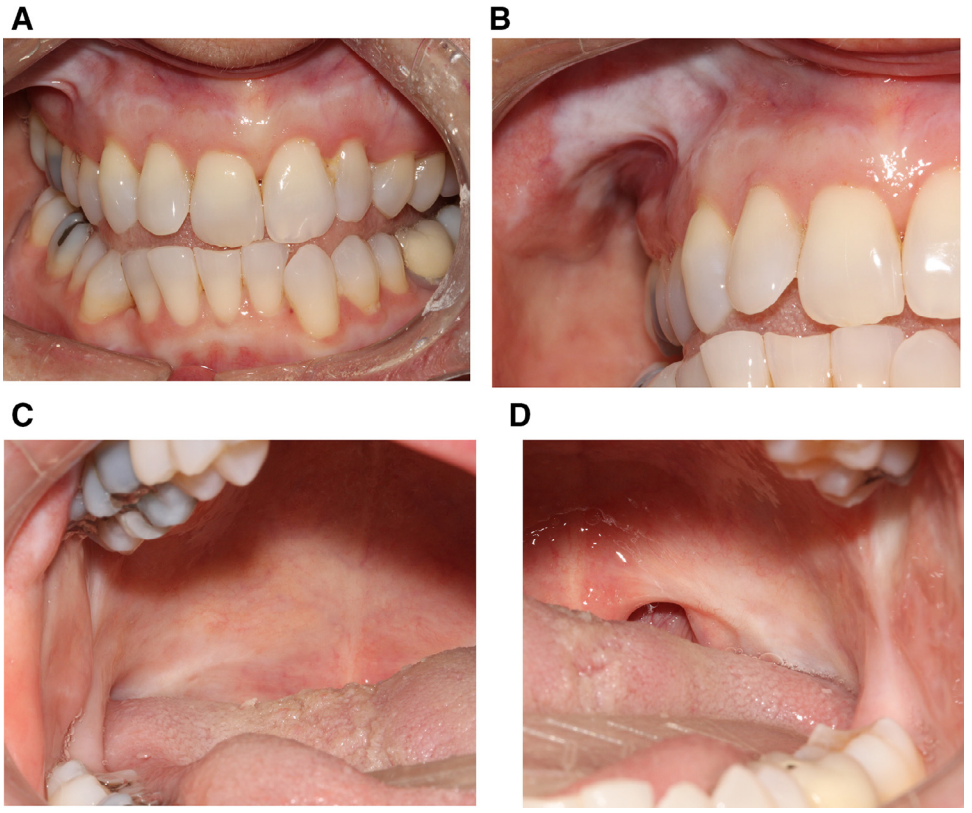

Figure 3. **A-D.** One-year follow-up: **A)** Anterior facial maxillary gingiva **B)** left buccal mucosa **C, D)** bilateral anterior tonsillar pillars.

new lesions and malignancy in the vulvar region. Oral lesions are rare, but the oral cavity should be periodically evaluated. This would help the clinician to identify new lesions, concomitant blistering, atrophic disorders, or stiffness of oral tissues that could potentially result in restriction of mouth opening, alteration in mastication, or other functional or aesthetic issues.[25] Also, it is not known whether a patient with oral LS is predisposed to oral squamous cell carcinoma, so continued life-long monitoring is a prudent approach.

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Reprint requests:

Clinical Assistant Professor,
Oral and Maxillofacial Pathology,
Department of Surgical Sciences,
East Carolina University,
School of Dental Medicine,
1851 MacGregor Downs Road,
Greenville,
NC 27834-4354,
USA.
floresan18@ecu.edu