**Background:** Certain mucocutaneous diseases present with painful, ulcerative, or erosive oral manifestations. Chronic ulcerative stomatitis is a newly recognized disease of unknown origin which presents clinically with features of desquamative gingivitis. This report marks only the thirteenth case reported in the world literature. A review of previous reports and studies is presented along with a review of immunofluorescence techniques critical to proper diagnosis. These diseases are difficult to diagnose without the use of immunofluorescence techniques. A 54-year-old Caucasian woman presented with a 2- to 3-year history of stomatitis and dry mouth.

**Methods:** Direct immunofluorescence revealed a speckled pattern of IgG deposits in the basal one-third of the epithelium, while indirect immunofluorescence confirmed the presence of stratified epithelium-specific antinuclear antigen (SES-ANA), both pathognomonic for chronic ulcerative stomatitis.

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**KEY WORDS**
Gingivitis, necrotizing ulcerative/diagnosis; gingivitis, necrotizing ulcerative/drug therapy; gingivitis, desquamative/diagnosis; gingivitis, desquamative/drug therapy; immunofluorescence techniques.

Many skin diseases may present with painful, ulcerative, or erosive oral manifestations. These diseases often share similar oral features and definitive diagnosis is sometimes difficult. Diseases such as lichen planus, cicatricial pemphigoid, and pemphigus vulgaris are mucocutaneous disorders of unknown origin in which host antibodies are directed towards the epithelium and/or its junction with the underlying connective tissue. The presence of these antigen-antibody complexes may induce the epithelial desquamation or erosion observed intraorally. Histopathological differentiation of these conditions is very important since clinical features may be similar, but histologic findings are also often inconclusive. This may be especially true in early lesions or in lesions in which the epithelium has desquamated.

In the last few years, immunohistochemistry techniques, especially direct and indirect immunofluorescence, have been used to clarify diagnosis. Direct immunofluorescence (DIF) is performed by exposing excised lesional tissue to antibodies of various immunoglobulins, complement, and tissue breakdown products. In indirect immunofluorescence (IIF), normal stratified squamous epithelium such as goat or monkey esophagus tissue is exposed to labeled circulating serum antibodies obtained from the patient. A positive result is indicated if the labeled antibody binds with a tissue antigen. To date, distinct DIF features have been identified for lichen planus, pemphigoid, and the various forms of pemphigus. Although only pemphigus is associated with consistent positive IIF findings, a limited number of reports have described a lichen planus specific antigen (LPSA) which, in one study, was found in 80% of patients with lichen planus. Others have reported the “string of pearls” phenomenon using IIF which has been linked with lichenoid reactions to certain medications.

Recently, a distinct new disease entity, chronic ulcerative stomatitis (CUS), has been described in a limited number of case reports. CUS resembles erosive lichen planus or oral discoid lupus erythematosus in its clinical and histologic manifestations. Therefore, it is best diagnosed via immunofluorescence in conjunction with routine histopathology. DIF may reveal nuclear deposits of immunoglobulin G (IgG) in a speckled pattern mainly in the basal one-third of the epithelium, while IIF may demonstrate a speckled pattern of IgG deposits. CUS is a newly recognized disease of unknown origin which presents clinically with features of desquamative gingivitis. This report marks only the thirteenth case reported in the world literature. A review of previous reports and studies is presented along with a review of immunofluorescence techniques critical to proper diagnosis. These diseases are difficult to diagnose without the use of immunofluorescence techniques. A 54-year-old Caucasian woman presented with a 2- to 3-year history of stomatitis and dry mouth.

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third of the epithelium. This may be coupled with deposits of fibrinogen in the basement membrane zone.\textsuperscript{13} This unique pattern of antinuclear antibody (ANA) has been referred to as stratified epithelium-specific antinuclear antibody (SES-ANA).\textsuperscript{11} It is not, however, known whether this DIF pattern is present only in this disease since similar features have been described by some in the presence of lichenoid drug reactions or lupus erythematosus (LE).\textsuperscript{1,7}

Autoimmune diseases such as systemic lupus erythematosus (LE), Sjögren’s syndrome, scleroderma, and rheumatoid arthritis have been associated with circulating serum antinuclear antibodies and the presence of specific subsets of serum ANA may be diagnostic for those diseases. CUS, however, will often go unnoticed on conventional serum ANA testing since its detection requires the use of a unique substrate. Of the systemic autoimmune so-called connective tissue disorders, LE is the most likely to induce localized or generalized oral lesions. Oral LE may mimic lichen planus in clinical, histologic, and immunofluorescence features, and a lupus/lichen planus overlap has been described.\textsuperscript{14}

Due to the clinical, histologic, and DIF diagnostic similarities between LE, lichen planus, lichenoid drug reactions, and CUS, the final diagnosis may sometimes be difficult unless specific IIF tests are used. If more intense or severe desquamative oral lesions are present, conditions such as pemphigus vulgaris, cicatricial pemphigoid, and erythema multiforme may be added to the differential diagnosis.

This paper reviews the literature regarding CUS and presents a newly diagnosed case in which successful treatment was rendered using topical corticosteroids.

**CASE REPORT**

A 54-year-old Caucasian woman presented with a 2- to 3-year history of stomatitis and dry mouth. She stated that she was unable to eat anything spicy and fruit exacerbated her condition. A review of her medical history revealed a hysterectomy 10 months earlier, estrogen replacement therapy, and vitamin B supplements. She believed her condition to be associated with stress since she had just changed jobs and her daughter had just married. A copy of her blood studies was obtained from her physician which revealed a slightly elevated cholesterol level but otherwise, no significant findings.

Clinical examination revealed diffuse erythema along the right and left buccal mucosa, the facial attached gingiva in both arches (Fig. 1), and over the incisive papilla of the palate. Plaque-like white lesions were also present bilaterally on the facial gingiva of the mandibular molars. The patient complained of pain and sensitivity associated with her lesions. A clinical diagnosis of erosive (atrophic) lichen planus was made. A biopsy was obtained from the buccal mucosa and bisected with one portion sent for routine histopathology and the other for direct immunofluorescence. An additional biopsy was obtained of a minor salivary gland from the lower lip for histologic evaluation.

The biopsy of the buccal mucosa revealed that the specimen was covered with stratified squamous epithelium which was atrophic and parakeratotic (Fig 2). The rete ridges, when present, were somewhat bulbous. There were focal areas of basal cell degeneration with some thickening of the basal lamina. There was a mononuclear inflammatory cell infiltrate within the lamina propria and, in focal areas, a lichenoid pattern of inflammation. The infiltrate also contained occasional plasma cells that are not normally encountered in lichen planus. Although not all diagnostic features of lichen planus were present, some histologic features were compatible with intraoral lichen planus. The histopathologic diagnosis was parakeratosis, epithelial atrophy, and chronic mucositis with lichenoid features. The minor salivary gland biopsy revealed chronic sialadenitis with a Sjögren’s
syndrome grading scale IV. The patient was subsequently referred to the Salivary Dysfunction Clinic for evaluation and treatment of Sjögren’s syndrome.

Direct IF of the buccal mucosal tissue revealed a speckled intranuclear deposition of IgG confined to the lower third to lower quarter of the stratified squamous epithelium (Fig. 3). This conforms to the direct IF characteristics described for chronic ulcerative stomatitis.

The patient returned one week later to discuss the results, to be evaluated by a dermatologist for skin lesions, and for initiation of therapy. No skin lesions were detected. A culture for Candida albicans was obtained but proved negative. Additional tests were ordered in order to confirm or rule out CUS and the patient was given a prescription for fluocinonide, a 0.05% topical corticosteroid gel, for use 4 times daily on the affected sites. A sedimentation rate, urinalysis, and serum profile for ANA, rheumatoid factor, SS-A and SS-B (Sjögren’s antibody), anti-Sm, anti-Sm/RNP, and stratified epithelium-specific antinuclear antibody (SES-ANA) were ordered to evaluate the patient for lupus erythematosus, rheumatoid arthritis, Sjögren’s syndrome, scleroderma, and CUS. All serum tests were negative. After additional conversations with a physician on staff at the referral laboratory, it was determined that the tests used were not calibrated to detect the SES-ANA characteristic of CUS. Conventional serum ANA testing uses Hep-2 cells as a substrate. However, testing for SES-ANA requires the use of monkey or guinea pig esophagus cells as a substrate. After rerunning the serum sample, the expected speckled pattern of intraepithelial ANA was found with a titer of 1:320 using monkey esophagus as the substrate (Fig. 4).

Following 3 weeks of treatment with fluocinonide, the patient reported that the lesions were less painful. Clinically, however, all the initial lesions were still present, albeit with a less diffuse erythema. Her medication was changed to betamethasone dipropionate, a 0.05% topical corticosteroid gel, 4 times daily, in an attempt to achieve remission. Two months after beginning the use of betamethasone dipropionate, the patient reported significant relief of the pain and...
approximately 3 weeks later, she decided to stop using the topical corticosteroid. The pain and soreness of the lesions returned soon after so she began using it again 2 weeks later, just prior to her scheduled recall. At the recall appointment, her gingiva showed little improvement, with erythema present in localized areas. Subsequently, however, complete remission of lesions was achieved and the patient was then able to discontinue betamethasone dipropionate therapy with instructions to reinitiate therapy in the event lesions began to recur (Fig. 5).

At the present time, the patient’s Sjögren’s syndrome condition has worsened, with progressive dryness and redness of her eyes. She is under the care of an ophthalmologist and the Baylor Salivary Dysfunction Clinic.

**DISCUSSION**

Jaremko et al. published the first report on CUS in 1990. They described the condition as featuring chronic oral ulcerations associated with what they called stratified epithelium-specific antinuclear antibodies (SES-ANA), a “peculiar” type of antinuclear antibody (ANA). They performed DIF and serum studies including ANA, anti-dsDNA, anti-RNP, anti-Sm, anti-Ro (SS-A), and anti-La (SS-B) titers. IIF was conducted using monkey esophagus, guinea pig esophagus, Hep-2, and mouse kidney as substrates. DIF was strongly positive for ANA IgG in a speckled pattern within the basal cells of the epithelium. Serum studies yielded negative or insignificant results for routine ANA tests, but SES-ANA titers of 1:10,240 or greater were observed in the basal layer of guinea pig esophagus sections, and usually on monkey esophagus.

Parodi and Cardo attempted to further characterize the nature of the antigen in CUS. They used indirect immunofluorescence, double immunodiffusion, counter-immunoelectrophoresis, enzyme-linked immunosorbent assay (ELISA), enzyme treatments, and immunoblotting. The substrates used in IIF included rat liver, monkey esophagus, rat lip, normal human skin, calf esophagus, Hep-2, and a number of others. Antinuclear IgG binding in the lower layer of the epithelium was found at the final titer of 1:10,240 with IgM binding at 1:320 using monkey esophagus. Other studies have found similarly high...
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et al. in 1996,\textsuperscript{13} indicated that immunoblot tests demonstrated a comigrating line of reaction to a tissue protein in the 70 to 75 kDa range which correlates with Parodi and Cardo’s findings in 1990.\textsuperscript{12}

This case represents only the thirteenth report of CUS described in the world literature. Table 1 outlines the salient features and treatment outcomes of previously reported cases. Eleven of the previous 12

<table>
<thead>
<tr>
<th>Reference</th>
<th>Case</th>
<th>Race</th>
<th>Age</th>
<th>Sex</th>
<th>History of Signs &amp; Symptoms</th>
<th>DIF (Nuclear Rxn/DEJ*)</th>
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<tr>
<td>Parodi and Cardo\textsuperscript{12} 1990</td>
<td>1</td>
<td>†</td>
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<td>F</td>
<td>12 yrs</td>
<td>IgG (speckled)/IgM</td>
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<td>2</td>
<td>†</td>
<td>53</td>
<td>F</td>
<td>2 yrs</td>
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<td>1</td>
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<td>59</td>
<td>F</td>
<td>6-9 mos</td>
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<td></td>
<td>2</td>
<td>C</td>
<td>77</td>
<td>F</td>
<td>†</td>
<td>IgG, IgA (speckled)/fibrin</td>
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<td></td>
<td>3</td>
<td>C</td>
<td>81</td>
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<td>4</td>
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<td>77</td>
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<td>20 yrs</td>
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<td>Beutner et al.\textsuperscript{8} 1991</td>
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<td>C</td>
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<td>F</td>
<td>24 yrs</td>
<td>IgG (speckled)</td>
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<td>M</td>
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<td>C</td>
<td>71</td>
<td>F</td>
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<td>Speckled/fibrinogen</td>
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<td>C</td>
<td>73</td>
<td>F</td>
<td>31 yrs</td>
<td>IgG (speckled)/fibrin</td>
</tr>
</tbody>
</table>

* Dermoeidermal junction.
† Not reported.
‡ Lichen planus.
§ Desquamative gingivitis.
¶ Monkey esophagus.
∥ Guinea pig esophagus.
# First reported by Chorzelski and Olszewska, 1999.

** Attempts to change treatment over 6 months failed: 1) reduction in dose of hydroxychloroquine to 200 mg/day led to relapse; 2) proguanil HCl tried at 100 mg/day also led to relapse (see Beutner et al.\textsuperscript{8} 1991); and 3) combination treatment of hydroxychloroquine 200 mg bid and proguanil HCl 100 mg/day gave no better response.
patients were women, and all were at least 35 years of age at the time of onset, as was the 54-year-old individual in this report. Initial diagnosis in most cases was oral erosive lichen planus, although some authors reported clinical features suggestive of lupus erythematosus (LE). In most instances, systemic therapy using corticosteroids or antimalarial agents were required to achieve remission. This patient is the first carefully documented case in which remission was achieved using only topical corticosteroid therapy. The case was complicated by the presence of xerostomia related to Sjögren’s syndrome.

In the past, the presence of an epithelial ANA on indirect immunofluorescence was generally associated with systemic LE. In IIF, labeled circulating serum antibodies are exposed to normal stratified squamous...
epithelium tissue such as guinea pig, goat, or monkey esophagus. A positive result is obtained if the labeled antibody binds with a tissue antigen. Four patterns are clinically relevant: homogenous, peripheral, speckled, and nucleolar. Some common diseases associated with a speckled pattern of ANA are systemic lupus erythematosus, Sjögren’s syndrome, scleroderma, or rheumatoid arthritis. LE is often mentioned in conjunction with lichen planus and, in this case, CUS, because clinically, the oral presentation of these diseases is similar. In advanced cases, pemphigus vulgaris, cicatricial pemphigoid, erythema multiforme, and lichenoid drug reactions may also be added to the differential diagnosis. Serologic tests for autoantibodies, such as ANA, would rule out systemic involvement in all of these conditions except LE. Systemic LE is characterized by the presence of circulating serum antibodies against the Sm antigen and occasionally by low-titer anti-RNP. Previous reports have found that patients with CUS do not yield positive results in IIF using conventional serum ANA tests against the Smith antigen (Sm), ribonucleoprotein (RNP), SS-A (Ro), or SS-B (La) antigens.

Reports on the use of IIF have continued to shed light on the pathogenesis of a number of vesiculobullous diseases. Olsen et al. in 1983 first reported the discovery of a lichen planus specific antigen (LPSA) in 7 of 8 patients with skin lesions (no oral lesions were reported) following IIF analysis. LPSA was found only in the stratum granulosum and stratum spinosum of the epithelium from the lichen planus skin lesions with no involvement of normal skin from the same patients. A follow-up study by the same group analyzed biopsies and sera from 25 lichen planus patients (5 of whom had concomitant oral lesions), 11 normal patients, and 36 patients with other previously diagnosed dermatoses. LPSA was present in 80% (20/25) of the lichen planus patients, but could not be detected in either the normal subjects nor the subjects with other dermatoses.

Camisa et al. limited their indirect immunofluorescence study to sections of lesional tissue from 6 patients exhibiting only oral lichen planus lesions. The serum of 2 patients was tested in an allogeneic reaction using a LPSA-positive cutaneous substrate and the sera of the remaining 2 patients was tested using a LPSA-negative normal substrate. Two of the 4 patients tested with LPSA-positive substrate demonstrated positive immunoreactivity denoting the presence of LPSA. It was concluded that immunologic reactivity is similar between patients who exhibit only oral lesions and those with cutaneous lesions.

McQueen and Behan described the “string of pearls” phenomenon found upon IIF analysis in 61 patients who were taking a variety of medications, including practolol, penicillin, penicillamine, steroids, phenytoin, and dapsone, among others. The “string of pearls” effect featured a bright intracytoplasmic fluorescence of the basal cells of the substrate. Only the basal cell layer was involved and it was usually detectable at serum titers of 1/10 to 1/40 only using antiserum to IgG. Although the “string of pearls” effect was not consistently associated with overt adverse effects to the medications, the authors felt that its detection may be helpful in monitoring the ill effects of drugs.

Betamethasone dipropionate gel is an ultra-high-potency class of topical corticosteroid, which is often used in our Stomatology Center in treatment of mucosal diseases that are resistant to less potent topical medications. Reports from the dermatology literature suggest that the use of ultra-high-potency topical corticosteroids in treatment of skin diseases results in a detectable systemic uptake of the corticosteroid, and potentially induces suppression of the pituitary/adrenal axis. Delescluse and van der Endt, however, reported only minimal suppression of the hypothalamic-pituitary-adrenal axis following twice-daily applications of 0.05% betamethasone ointment for the treatment of moderate-to-severe eczema. Ezzo et al. reported a minute but detectable serum level of a related ultra-high-potency steroid, clobetasol, following intraoral application to oral lesions. To date, however, there are no reports of adrenal suppression, hypertension, or other untoward systemic effects following the topical use of these medications in the oral cavity.

In this report, the patient’s medication was changed from fluocinonide 0.05% gel to betamethasone dipropionate 0.05% gel after only 3 weeks of treatment. Others have reported success with fluocinonide using longer treatment regimens to control desquamative conditions. While it is possible that further improvement could have eventually been achieved with continued use of the fluocinonide gel, in this case, the patient’s persistent discomfort and the limited response of the lesions to treatment accelerated the decision to change to betamethasone dipropionate gel. It is important to note that there is no universally accepted treatment for desquamative conditions and the literature concerning CUS is too sparse to reach any definitive conclusions. Until large-scale clinical trials can be undertaken, the clinician’s own judgment together with patient feedback are the most important aspects of successful patient management.
Based on the review of the literature regarding CUS and this and other case reports, it appears that clinicians should be suspicious of CUS when encountering oral mucosal lesions consistent with OLP or LE. When indicated, appropriate DIF and IIF may prove essential in obtaining the correct diagnosis. Topical corticosteroid therapy should be considered prior to administering a more potent systemic medication.

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