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HOT TOPIC

Chronic ulcerative stomatitis

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Chronic ulcerative stomatitis (CUS) is a recently described condition with specific immunopathologic findings. Demographics indicate that white women in their late middle age are more susceptible to this condition. The clinical history of CUS patients is of painful, exacerbating and remitting oral erosions, and ulcerations. The histologic features are non-specific, with a chronic inflammatory infiltrate, often appearing similar to oral lichen planus (OLP). Diagnosis of CUS requires surgical biopsy with immunofluorescence microscopic examination. Accurate diagnosis is important because the usual treatment option for immunologically mediated diseases, glucocorticoids, is often not effective in treating CUS. However, hydroxychloroquine pharmacotherapy is beneficial in many cases. The lack of awareness of the condition among clinicians and the technical challenges in specimen processing make diagnosis of CUS a challenge, and hence the true prevalence is unknown. Immunofluorescence studies show circulating and tissue-bound autoantibodies to a protein, ΔNp63α, which is a normal component of stratified epithelia. It is unknown if the antibodies are pathogenic, thus the etiology of CUS is also unknown. Studies are needed to elucidate the pathogenesis of CUS, optimize clinical management, and clarify its relationship to OLP and neoplasia.
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Introduction

Chronic ulcerative stomatitis (CUS) is a mucocutaneous condition that primarily involves mucosal surfaces, and occasionally the skin. CUS is characterized by the presence of chronic or recurrent oral erosive and ulcerative lesions. Diagnosis of CUS requires surgical biopsy with both haematoxylin and eosin (H&E) and immunostaining, and light microscopy and direct immunofluorescence (IF) microscopy, respectively. The condition is often recalcitrant to corticosteroid pharmacotherapy; however, hydroxychloroquine has been successfully used to treat many cases. The antigen in CUS is a nuclear transcription factor, ΔNp63α, which is normally present in basal and parabasal cells of stratified squamous epithelia. Some authors classify CUS as a variant of oral lichen planus (OLP), although the pathogenesis of CUS is unknown. Future studies will foster a better understanding of this oral disease, which is responsible for considerable morbidity in affected patients.

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Clinical features

As CUS is a recently described condition, the number of cases reported in the literature is limited. The recent addition of four cases increased the total number of reported cases to 39 (Islam *et al*, 2007). The average age of CUS patients is 59 years, 90% are white women, and patients often report sore gingiva, painful tongue, difficulty in eating and unintentional weight loss, with exacerbation and remission of symptoms (Islam *et al*, 2007). The majority of CUS patients have a long history of suffering from oral pain without diagnosis or effective treatment.

Gingival lesions (Figure 1a) may present as a desquamative gingivitis (Scully and Porter, 1997); however, a positive Nikolsky's sign has not been described in CUS. The tongue is the most common location of CUS, followed by buccal mucosa (Figure 1b) and gingival tissues; less frequently, CUS-associated lesions may present on the labial mucosa or the hard palate (Solomon, 2004).

The clinical differential diagnosis in CUS includes other mucocutaneous, erosive, and ulcerative mucosal conditions in which oral lesions are prominent. Indeed, the oral lesions may be the earliest or only clinical manifestation. These diseases include pemphigus vulgaris, bullous pemphigoid, mucous membrane pemphigoid, linear IgA disease, dermatitis herpetiformis, epidermolysis bullosa acquisita, and systemic lupus erythematosus (SLE). The clinical and histopathologic

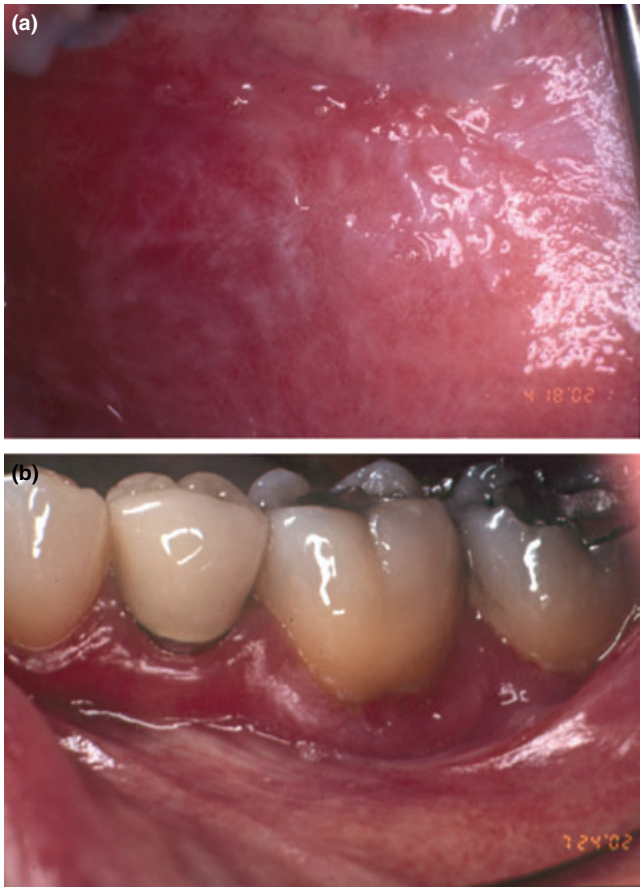

Figure 1 (**a**) Clinical photo shows the left buccal mucosa, which is diffusely erythematous with subtle, irregular diffuse white borders. A shallow, linear erosion is present on the mucosa opposite the maxillary molars. (**b**) Clinical photo of a different CUS patient shows the presentation of CUS as a desquamative gingivitis affecting the buccal gingival of the mandibular left premolar and molar area. A small shallow ulcer is present on the free gingival margin of the first molar

features of these conditions are non-diagnostic. Some cases present desquamative gingivitis, while others present chronic mucosal erosions or ulcerations that undergo periods of exacerbation and remission (Scully and Porter, 1997). In some cases, accompanying skin lesions may give clues as to the nature of the disease, although biopsy with H&E microscopy, and direct and indirect IF are the most reliable methods to arrive at a definitive diagnosis (Jordan *et al*, 2002).

Diagnosis

Histopathology

The histopathologic findings of H&E-stained specimens are non-specific in CUS. In the largest series of CUS cases published (17 cases) the histopathologic features of CUS were described simply as 'inflammatory infiltrates' (Chorzelski *et al*, 1998). Several case reports which provide detailed descriptions of the histologic features of CUS describe features very similar to those of OLP, including atrophic, parakeratinized, stratified squamous epithelium, a 'band-like' interface of inflammatory cell infiltrate, 'saw-tooth' rete ridges, and vacuolar degeneration of the basal cell layer with replacement by an eosinophilic coagulum and cytoid bodies. Other reports simply describe chronic lichenoid mucositis with ulceration.

Direct IF

The current gold standard diagnostic test for CUS is direct IF (Rinaggio *et al*, 2007). Direct IF reveals the presence of IgG antibodies bound to nuclei of keratinocytes of the basal and lower one-third cell layers, with a unique stratified epithelial specific-antinuclear antibody (SES-ANA) pattern (Jaremko *et al*, 1990). This finding (Figure 2) is pathognomonic for CUS. However a caveat is in order; there are other diseases, i.e. SLE, scleroderma, calcinosis, Raynaud's phenomenon, esophageal involvement, sclerodactyly and telangectasia (CREST) syndrome, and mixed connective tissue disease (MCTD), which demonstrate an ANA pattern of autoantibodies in epithelia, although generally these reactions occur in the stratum spinosum, and not the basal layers (Barland and Lipstein, 1996; Jablonska *et al*, 1998; Vassileva, 1998).

Positive deposits of fibrinogen have been reported in direct IF of CUS biopsy samples (Jordan *et al*, 2002). The fibrinogen deposits were described as having a pattern similar to that of LP, i.e. a fluorescence outlining the basement membrane zone with irregular extensions into the superficial lamina propria, giving a shaggy appearance (Figure 3). Interestingly, a review of the 32 CUS cases published at that time shows only two papers in which the fibrin deposition is described; one case supplied a photomicrograph of the fibrin deposition (Lewis *et al*, 1996) and the other single case report described that 'shaggy, irregular fibrinogen was also noted in the BMZ' (Church and Schosser, 1992). There was no description of the pattern of fibrin deposition in five CUS cases that were 'positive' for fibrin deposition at the dermal–epidermal junction (Jaremko *et al*, 1990; Parodi and Cardo, 1990). It is unclear in these cases if

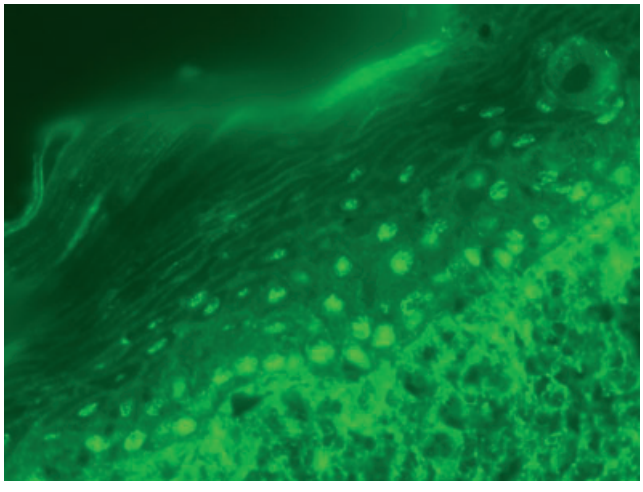

Figure 2 Direct immunofluorescence of an oral mucosal specimen shows lgG autoantibodies bound to the nuclei of basal epithelial cells, demonstrating the SES-ANA pattern. (The specimen is oriented with the epithelial surface at the top of the photomicrograph. Original magnification = 40 ×)

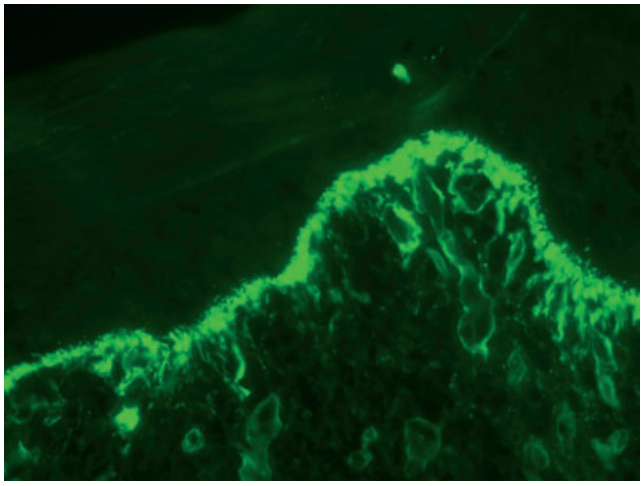

Figure 3 Direct immunofluorescence of an oral mucosal specimen for fibrinogen shows a linear fluorescence outlining the basement membrane zone. Irregular extensions into the superficial lamina propria give a "shaggy" appearance. (The Specimen is oriented with the epithelial surface at the top of the photomicrograph. Original magnification $=40\times$)

the deposits were the shaggy, irregular fibrinogen similar to the LP pattern, or a non-specific fibrin exudation secondary to inflammation.

The majority (27) of CUS case reports do not mention fibrin deposition on direct IF (Beutner *et al*, 1991; Worle *et al*, 1997; Chorzelski *et al*, 1998; Lorenzana *et al*, 2000; Solomon *et al*, 2003). It may be that fibrinogen was not reported because it was not present, or it was not present in the 'LP-like' pattern, or because it is not thought to be part of the diagnostic criteria. The most recent report of four CUS cases described a linear fibrinogen band in two of the four cases, with photomicrographs provided (Islam *et al*, 2007). More reports with a thorough documentation are needed to determine whether or not fibrin deposition is part of the diagnostic criteria for CUS.

Some cases of CUS examined with direct IF show a positive finding of tissue-bound IgA in an SES-ANA pattern (Figure 4), although it is not part of the diagnostic criteria (Jaremko *et al*, 1990; Solomon *et al*, 2003). Immunoblotting with CUS sera of the *in vitro*-produced CUS antigen ΔNp63α, showed that 52% of the sera had IgA antibodies, in addition to IgG (Solomon *et al*, 2007). Although there have been no studies to investigate the clinical significance of IgA antibodies in CUS patients, studies of a related condition, mucous membrane pemphigoid, showed that patients with dual circulating IgG and IgA responses have more severe disease (Setterfield *et al*, 1998).

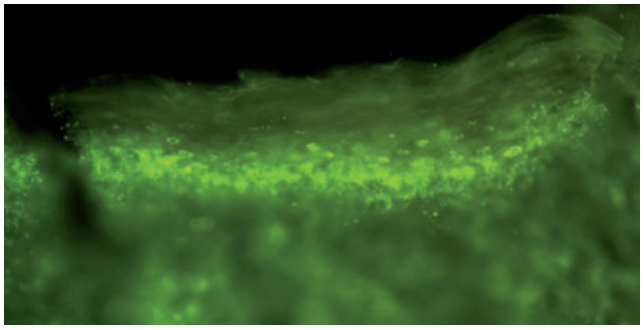

Figure 4 Direct immunofluorescence of an oral mucosal specimen with IgA autoantibodies bound to the nuclei of basal epithelial cells and demonstrating the SES-ANA pattern. (The specimen is oriented with the epithelial surface at the top of the photomicrograph Original magnification $=20\times$)

There are challenges to obtaining a diagnosis of CUS. Biopsy samples from ulcerated areas lack epithelium for diagnosis, thus perilesional mucosa is preferred. Some clinicians are not aware that direct IF requires specimen transport in Michel's media (Michel *et al*, 1972), and not in 10% neutral-buffered formalin. Only certain laboratories are equipped to perform direct IF, which requires a cryostat to section the specimen, which is subsequently stored frozen in the laboratory. Finally, cryostat sectioning of oral mucosa requires skilled technical processing, as *en face* specimen orientation may result in an inconclusive diagnosis. If the epithelium is atrophic or cut tangentially, it may not be possible to evaluate the location of the ANAs. In these cases, indirect IF may be necessary to distinguish CUS from SLE, scleroderma, and MCTD.

Indirect IF

In addition to tissue-bound autoantibodies, CUS patients have circulating antibodies which exhibit the SES-ANA pattern on indirect IF using an esophagus substrate (Jaremko *et al*, 1990). A 10-ml venous blood sample is drawn into a red top tube, allowed to clot, spun for 10 min at 503 g, and the straw-colored serum removed. The serum is applied to a tissue substrate to test for antibody binding. The type of tissue substrate used is extremely important. The substrates used to detect circulating IgG in SLE, CREST, and MCTD patients (Jablonska *et al*, 1998; Parodi and Cozzani, 1998; Vassileva, 1998) are human neoplastic HEp-2 cells or rodent kidney cells, and are not suitable for indirect IF of suspected CUS cases. CUS patient sera are negative or have very low titer in HEp-2 cells and rodent kidney substrates because these are not stratified epithelia.

Esophagus substrates are necessary to demonstrate the circulating IgG in CUS. Guinea pig esophagus is more sensitive and demonstrates higher titers than monkey esophagus substrate (Solomon *et al*, 2003), and some laboratories use human esophagus substrates (Chorzelski *et al*, 1998). Indirect IF with CUS patient sera on esophagus substrates are positive for IgG bound in the basal epithelial layers in the SES-ANA pattern (Figure 5). Indirect IF of sera of patients with SLE, scleroderma and MCTD may also be positive for ANA on esophagus substrates; however, the pattern is different because the antibodies are distributed through the superficial epithelial layers.

Management

Spontaneous remission of CUS without treatment has been reported in three cases, and one reported improve-

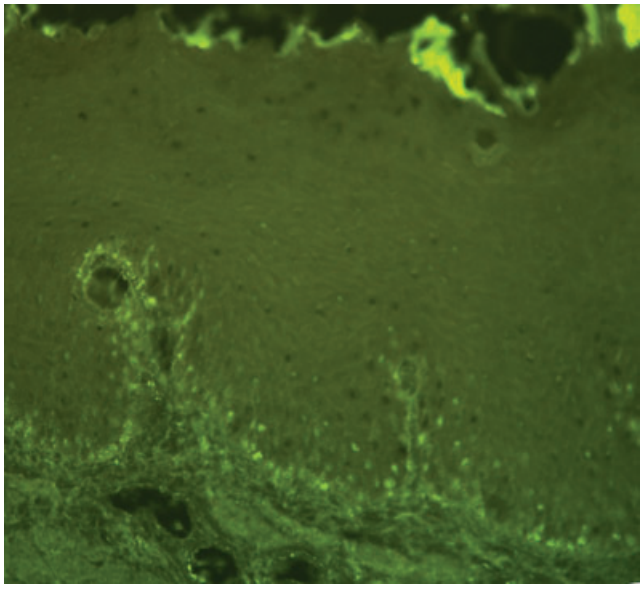

Figure 5 Indirect immunofluorescence of CUS sera on monkey esophagus substrate shows lgG antibodies bound to the substrate in the SES-ANA pattern. (The specimen is oriented with the epithelial surface at the top of the photomicrograph. Original magnification $=20\times$)

ment of symptoms on maintaining a gluten-free diet (Chorzelski *et al*, 1998). Glucocorticoids are the mainstay of treatments for immunologically mediated oral diseases; however, they seem to be less effective in managing CUS.

Glucocorticoids have anti-inflammatory and developmental effects on the cells of the immune system (Watson and Gametchu, 2001). The mechanism of action is interference of the glucocorticoid nuclear receptors with transcription factors and downregulation of genes involved in inflammatory responses. Inflammatory response genes are downregulated via induction of a mitogen-activated protein kinase (MAPK) phosphatase which suppresses MAPK signaling (Saklatvala *et al*, 2003). A variety of topical and systemic corticosteroids, such as fluocinonide, betamethasone, clobetasol, dexamethasone, and prednisone, have been used to treat CUS. All seem to improve symptoms in some patients, although many experience relapse during treatment or after discontinuation of therapy.

Dapsone is a sulphone antibiotic medication long used for treating various skin conditions, aphthous ulcerations, and as prophylaxis and treatment for toxoplasmosis and *Pneumocystis carinii* pneumonia. Side effects that may occur with dapsone treatment are gastrointestinal including nausea or vomiting, headache, and blue coloration of lips and fingertips. More serious side effects include anemia, allergy, and rarely a potentially fatal severe drug hypersensitivity syndrome (Zhu and Stiller, 2001). One case of CUS treated with dapsone and prednisone reported improvement (Chorzelski *et al*, 1998), while another CUS patient had to discontinue dapsone treatment because of side effects (Worle *et al*, 1997).

In general, corticosteroids or dapsone pharmacotherapy is less effective than hydroxychloroquine (Plaquenil) in managing the symptoms of CUS. Clinical remission of CUS, and even reduction in autoantibody titers (Chorzelski *et al*, 1998), have been reported in the majority of patients treated with hydroxychloroquine pharmacotherapy (Islam *et al*, 2007). Doses as low as 200 mg day^{-1} may induce improvement and in some cases complete clearing of oral lesions (Solomon *et al*, 2003). Other regimens reported are 200 mg, two times per day and 800 mg day^{-1}, in four divided doses (Islam *et al*, 2007). Hydroxychloroquine treatment is an off-label use of a potent drug that was initially developed as an anti-malarial agent.

The mechanism of action of hydroxychloroquine is interference with the antigen-processing mechanisms of macrophages and other antigen-presenting cells, resulting in downregulation of the immune response against antigenic peptides (Fox, 1993). Initial data from human clinical trials, showed hydroxychloroquine inhibition of the development of graft-*vs*-host disease in bone marrow transplant patients (Schultz and Gilman, 1997). Caution must be exercised when using hydroxychloroquine because significant side effects (such as retinopathy, toxic psychosis, neuromyopathy, agranulocytosis, and aplastic anemia) may arise, necessitating the discontinuation of therapy. The neuromuscular and hematologic complications are usually reversible whereas retinopathy is not. Therefore, close follow up of patients being treated with hydroxychloroquine is warranted (Church and Schosser, 1992).

Relationship of CUS and OLP

Lichen planus is a relatively common disorder of the stratified squamous epithelia that presents as a mucocutaneous inflammatory disease (Scully *et al*, 1998), and is present in approximately 1% of the general population (Taaffe, 1979). Clinically, the majority of cutaneous lesions are pruritic and self-limiting. Oral involvement in LP is very common and may be the only manifestation in 15–35% of LP patients. OLP lesions tend to present as one of three general types: (1) reticular including white lines, plaques, and papules; (2) atrophic or erythematous and (3) erosive, including ulcerations and bullae (Eisen, 2002).

Oral lichen planus lesions are chronic, rarely undergo spontaneous remission and, in the erosive form, are a potential source of significant morbidity. Direct IF studies of mucosal biopsies in OLP show a characteristic fibrillar pattern of fibrin deposition at the basement membrane zone; however, these findings are not specific to OLP and are interpreted as 'suggestive of' or 'consistent with' OLP. Clinically and histologically, CUS may be indistinguishable from erosive OLP (Parodi and Cardo, 1990). Histopathology of LP shows basal layer degeneration and apoptotic bodies. Studies of the inflammatory infiltrate in LP have shown that $CD4^+$ T cells are common in early lesions and that $CD8^+$ T cells predominate in chronic lesions (Scully *et al*, 1998). The pathogenesis of LP is a lymphocytic

immunologic reaction to the epithelial basal cells; however, no antigen has yet been identified (Scully *et al*, 1998). During the inflammatory process it is likely that normally sequestered proteins, such as the nuclear transcription factor ΔNp63α, are exposed to the immune system and stimulate an autoimmune reaction in susceptible individuals (Chan *et al*, 1998).

Autoimmune diseases are associated with particular HLA types, e.g. HLA-D8, DR3 or DR4. An increase in frequency of these haplotypes has not been shown in LP cases (Scully *et al*, 1998). HLA typing on CUS patients has not been reported. If CUS is a subset of OLP, perhaps the MHC molecules of the CUS patients are particularly adept at presenting the ΔNp63α autoantigen and stimulating a humoral immune response. Other LP patients may present this self-antigen in a form that is not immunogenic. Alternatively, LP patients without autoantibodies may have a primarily T-cell-mediated response, whereas CUS patients may have a primarily B-cell-mediated humoral response. Another theory is that perhaps there is a subset of LP patients who produce IgG in a titer high enough to be discerned as SES-ANAs on direct IF, where a diagnosis of CUS is made.

The specificity of autoantibodies in CUS has been examined in controls used in several studies. In one study, serum from 91 cases of skin LP and 25 cases of OLP was examined immunologically; in none of the cases were there findings characteristic of CUS (Chorzelski *et al*, 1998). A study that examined autoantibodies in serum samples of 63 OLP cases found that 2% showed nuclear staining on a rat esophagus substrate, although the pattern was not described and it is not clear if this was the same SES-ANA pattern that is seen in CUS; none of the 67 oral mucosal disease controls had nuclear antibodies (Lin *et al*, 1992). When using a monkey esophagus substrate, serum autoantibodies were found to be absent in 12 OLP cases studied (Nisengard and Neiders, 1981). In another study, immunoblotting and immunoprecipitation of keratinocyte extracts revealed no antibodies to ΔNp63α in 74 control sera (10 healthy subjects, 24 recurrent aphthous stomatitis, six OLP, two dermatomyositis, 15 subacute cutaneous LE, 15 discoid LE, and two SLE) (Lee *et al*, 1999).

The sensitivity and specificity of the method of antibody detection must be considered when comparing studies of immunologically mediated diseases. Qualitative studies using serum of LP cases for indirect IF and immunoblots of epidermal proteins from human keratinocyte cultures showed that some LP sera were positive for ANAs and led to the recognition of a 70-kDa keratinocyte protein in some cases (Carrizosa *et al*, 1997; Cacciapuoti *et al*, 2004; Parodi *et al*, 2007). These qualitative techniques are imprecise; now that the ΔNp63α antigen in CUS has been discovered and the gene cloned, techniques using quantitative biochemical methods are more likely to give answers regarding the CUS and OLP relationship.

Immunoblotting led to the detection of antibodies against various p63 and p73 isoforms in serum of OLP patients (Ebrahimi *et al*, 2007). The finding of these antibodies in patients who have clinical OLP, some asymptomatic, begs the question of whether they indeed have CUS, and not OLP. Perhaps with future studies CUS will become defined by the presence of serum antibodies to p63 proteins, with or without erosive lesions. To date, only symptomatic cases with oral ulcerations are submitted for direct IF which leads to a diagnosis of CUS. Asymptomatic cases are usually not biopsied, and thus antibodies to ΔNp63α have not been discovered by direct IF of non-erosive lichenoid disease.

The CUS antigen, Δnp63α

ΔNp63α is a nuclear protein which is normally present in basal and parabasal cells of stratified squamous epithelia and was cloned and sequenced in 1999 (Lee *et al*, 1999). p63 protein is one of the p53 family of nuclear transcription factors (Yang *et al*, 2002) which has several isoforms, that are expressed at specific developmental times in various tissues (Kaghad *et al*, 1997; Osada *et al*, 1998; Yang *et al*, 1998; Dellavalle *et al*, 2001). p63 knockout experiments in mice have revealed developmental defects (Yang *et al*, 1998; Ince *et al*, 2002) and several human syndromes are associated with p63 mutations, e.g. ectrodactyly, ectodermal dysplasia, and cleft lip (EEC) with or without cleft palate (Celli *et al*, 1999), acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome (Propping and Zerres, 1993), ankyloblepharon-ectodermal dysplasia-cleft lip/palate (AEC) syndrome, also known as Hay-Wells syndrome (McGrath *et al*, 2001), limb-mammary syndrome (LMS), and non-syndromic split-hand/split-foot malformation (SHFM) (van Bokhoven *et al*, 2001).

ΔNp63α is the p63 isoform preferentially expressed in mature stratified epithelia (Yang *et al*, 1998; Liefer *et al*, 2000), where it is essential for maintenance of proliferative potential (Koster *et al*, 2004) and epithelial integrity. The proliferative potential in stratified squamous epithelia is hypothesized to operate by inverse coordination of cellular levels of p53 and ΔNp63α (Marchbank *et al*, 1999; Ratovitski *et al*, 2001; Barbieri and Pietenpol, 2006). Stratified squamous epithelial integrity is maintained via p63 expression regulation of a membrane protein, Perp, that promotes the stable assembly of desmosomal adhesive complexes (Ihrie *et al*, 2005).

ELISA test for CUS

Currently available testing for CUS is limited to *in situ* IF techniques. Direct IF is the gold standard test for CUS diagnosis, and the cost of a direct IF panel in a commercial laboratory ranges from $480.00 to $1141.00. Aside from the expense, there are technical challenges inherent in CUS diagnosis that were previously described. The actual frequency of occurrence of CUS is unknown because many clinicians treat oral erosive or ulcerative lesions empirically or limit the diagnostic procedures to clinical findings and biopsy with light microscopic examination of H&E-stained slides.

A novel enzyme-linked immunosorbent assay (ELISA) for IgG antibodies in CUS sera has been developed. Immunoblotting and immunoprecipitation of ΔNp63 protein with CUS patient sera showed that the most immunogenic portions are in the N-terminal and DNA-binding domains, amino acids 1–275 (Solomon *et al*, 2007). This portion of ΔNp63 was produced as a recombinant peptide and used as the capture protein in an ELISA that detected IgG antibodies in CUS sera. ELISA is a more sensitive method than immunoblotting, as three CUS serum samples that were positive on direct immunofluorescence, but negative on immunoblot, were positive on ELISA. The results showed good sensitivity (0.80) and specificity (0.75) (exact 95% confidence intervals, *P*-value of <0.001) in detecting antibodies from CUS patient serum samples (Solomon *et al*, 2008). This ELISA test for CUS is not yet commercially available.

Unanswered questions

Many lines of inquiry need to be pursued in order to increase our understanding of CUS. Studies facilitated by a less expensive and technically demanding test such as ELISA are needed to determine the true incidence and prevalence of CUS. The optimal management of CUS needs to be evaluated with double-blinded, randomized, placebo-controlled clinical trials. The etiopathogenesis of CUS is unknown; the autoantibodies may be pathogenic or merely an epiphenomenon, and experiments to examine their role in pathogenesis have not been performed. It is conceivable that the antibodies may interfere with the normal function of ΔNp63α with abrogation of proliferative potential or interference with adhesion complex formation causing epithelial breakdown, which presents clinically as erosions and ulcerations.

It is unknown if CUS patients have HLA haplotypes similar to those of OLP patients. Perhaps LP patients without autoantibodies have a primarily T-cell-mediated response, whereas CUS patients have a primarily humoral response. Another theory is that perhaps there is a subset of LP patients who produce SES-ANAs in a titer high enough to be discerned on direct IF, where a diagnosis of CUS is made, while others have a low titer or no titer at all. Another possibility is that patients with p63 autoantibodies may represent the subset of OLP cases who eventually become malignant; alternatively, these patients may have an occult malignancy that stimulates an immune response similar to paraneoplastic disorders (Abu-Shakra *et al*, 2001). Autoantibodies to ΔNp63 have been shown in cases of lung and head and neck squamous cell carcinoma (Yamaguchi *et al*, 2000; Tominaga *et al*, 2001). This raises the question of occult or future malignancy in CUS patients. The relationship of CUS, OLP and neoplasia is a potential area for future investigations.

Author contribution

Lynn Solomon is the sole author; she drafted, analyzed and interpreted data and critically revised this manuscript.

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