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ORIGINAL ARTICLE

Pathogenic relevance of antibodies against desmoglein 3 in patients with oral lichen planus

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Summary

Background and objectives: Oral lichen planus (OLP) is a T cell driven disorder that significantly impairs patients' quality of life. Previous reports suggest that both cellular and humoral activities against desmoglein (dsg) 1 and 3 may be involved in OLP pathogenesis. Here, we aim to analyze the frequency of occurrence and pathological significance of anti-dsg antibodies in a large cohort of OLP patients.

Materials and methods: OLP patients were screened for anti-dsg antibodies by enzyme-linked immunosorbent assay in three tertiary referral centers. OLP sera with anti-dsg antibodies were further analyzed by Western blot and dispase-based keratinocyte dissociation assay (DDA) to identify the targeted dsg ectodomains and to assess their pathogenicity.

Results: Of 151-screened individuals with OLP, only four patients (2.6%) with erosive OLP showed serum IgG against dsg1/3. Western blot analysis with recombinant dsg3 ectodomains revealed preferential recognition of the extracellular domain 5. By DDA with spontaneously immortalized human keratinocytes, none of the sera from these four patients induced acantholysis.

Conclusions: Activation of humoral immunity occurs prevalently in patients with erosive OLP, probably due to epitope spreading. OLP serum antibodies are unable to induce loss of intercellular adhesion in vitro, strongly suggesting that they are not disease causing but rather an epiphenomenon.

KEYWORDS
autoantibodies, desmoglein 3, oral lichen planus

INTRODUCTION

Lichen planus (LP) is a common human inflammatory skin disorder, which mainly affects skin, mucosa and/or scalp.[1] Oral lichen planus (OLP) is a strongly debilitating, often treatment refractory, chronic inflammatory disorder of the oral mucosa. Two main clinical types are described: Type I (plaque type) OLP is characterized by the presence of papules and plaques, which display a white lace-like net, the so-called Wickham stripes. Type II (erosive type) OLP is less frequent yet more aggressive and is clinically characterized by extensive erosions, which may also extend to the esophagus. While plaque type OLP is commonly easier to manage, the erosive type is more painful, tends to be treatment unresponsive, and strongly impairs eating behavior leading to a significant reduction in quality of life.[2] Furthermore, the chronic inflammation that arises from OLP lesions may lead to the formation of strictures and/or scars and is associated

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with an increased risk of malignant transformation.[3] In OLP, cellular immunity is mainly pathogenically relevant for the disease. Mixed $CD4^+/CD8^+$ type I/interferon (IFN)-γ secreting T cells, which migrate to the skin and reside in the upper part of the dermis, play a major role and create the histological LP hallmark of band-like lymphocytic infiltrate. Cytokine secretion of these skin-infiltrating T cells leads to direct damage and apoptosis of basal epidermal keratinocytes.[4–5]

The autoantigen of OLP, which elicits T-cell migration into the skin, is unknown. Diseases such as lichen planus pemphigoides, paraneoplastic pemphigus (PNP), in which clinic-pathological characteristics of LP and autoimmune bullous diseases overlap, suggest that epidermal or dermal-epidermal antigens including desmogleins and bullous pemphigoid (BP) antigen 180 could also serve as an autoantigen in LP. We corroborated this hypothesis by demonstrating the presence of autoreactive type 1/17 T-cells against BP180 and dsg3 in patients with LP and OLP.[5] Literature also reports that humoral activity with production of antibodies against dsg1 and/or dsg3 is present in a minority of OLP patients.[6–10] This suggests that these hemidesmosomal/desmosomal proteins, which are responsible for dermal-epidermal stability, might be involved in the pathogenesis of OLP.[5]

Pemphigus vulgaris (PV) is an autoimmune disorder characterized by blistering and erosions of the oral mucosa and the skin elicited by IgG antibodies against dsg1 and dsg3.[11] While skin lesions of PV and LP are morphologically different, oral lesions of erosive OLP and PV share common features. In patients with chronic mucosal erosions, it is sometimes difficult to clinically differentiate OLP from PV. Occasionally, serum antibodies against dsg antigens can be found in OLP patients suggesting a not yet identified immunological link between the two disorders. Furthermore, the identification of anti-dsg antibodies in OLP patients might confound physicians and lead to wrong diagnosis and treatment. As far as we know, the exact prevalence of anti-dsg antibodies in OLP and their potential biological function remains unknown. In this study, we addressed these questions by analyzing the frequency and further characteristics of anti-dsg-specific circulating antibodies in a large cohort of OLP patients.

METHODS

Study design

A retrospective multicenter study was performed in three tertiary referral centers (Berlin, Marburg, Florence) for OLP. A total of 151 patients with OLP (35 males and 116 females) were included in this cross-sectional study. After ethical approval for medical record review, medical records and/or databases were reviewed at each institution. In Berlin 36 patients, in Marburg 105 patients and in Florence ten patients were recruited. Patients with circulating antibodies against desmosomal components were identified in Marburg (n = 2) and Berlin (n = 2). Diagnosis of OLP was made based on the clinical appearance and histopathological findings. Presence of IgG serum antibodies against dsg1 and dsg3 was assessed using a commercially available enzyme-linked immunosorbent assay (ELISA, Euroimmun, Lübeck, Germany) according to the manufacturer's protocol. Disease severity was assessed using the oral disease severity score (ODSS), which reflects both the extent and severity of disease. The ODSS is a disease severity scoring system validated for use in OLP. The composite score (total ODSS) includes 17 oral sites (site score), an activity score, and a subjective pain score (VAS), with a maximum score of 106.[12,13]

Immunoblot analysis

Human recombinant dsg3 (entire ectodomain, amino acids 1–566) and its extracellular subdomains (EC1, EC2, EC3, EC4, EC5) were produced in a baculovirus expression system as previously described.[14] Detection of serum IgG reactivity against subdomains of human dsg3 was performed by Western blot (WB) analysis according to an established protocol.[14] For specific detection of the dsg3 recombinants, primary murine antibodies (1:100) and a monoclonal rabbit anti-E-Tag antibody (1:7,000; Abcam, Cambridge, UK) were used. Horseradish peroxidase (HRP)-conjugated anti-mouse IgG or anti-rabbit IgG (1:2,000; Dako, Glostrup, Denmark) served as secondary antibodies. Antibody binding was visualized by using a commercial HRP substrate (Immobilon Western Chemiluminescent HRP substrate; Millipore, Billerica, MA). Signals were detected with a digital chemiluminescence reader (PEQLAB, Erlangen, Germany).

Dispase-based keratinocyte dissociation assay

The dispase-based keratinocyte dissociation assay (DDA) is the method of choice to examine the pathogenic effect of serum antibodies on cell-cell adhesion of human epidermal keratinocytes in vitro. The method was performed under previously established conditions.[15]

In short, HaCaT spontaneously immortalized human keratinocytes (kindly provided by P. Boukamp, formerly DFKZ Heidelberg) were seeded onto 24-multiwall plates (Greiner AG, Kremsmünster, Austria; Cat. no. 10177380) and cultured in Dulbecco's Modified Eagle Medium (DMEM) (PAN-Biotech GmbH, Aidenbach, Germany, Cat. No. P04-04515) supplemented with chelated Fetal Bovine Serum (FBS standard (PAN-Biotech GmbH, Aidenbach, Germany, Cat. No. P30-3306)) (1.6 mM final concentration of Ca^{2+}) at 37°C in 5% CO_2 atmosphere. After reaching confluency of HaCaT monolayers, the medium was aspirated; the respective stimulus diluted in DMEM supplemented

TABLE 1 Demographics of a cohort of patients affected by oral lichen planus.

	Number of patients	Sex	Mean age	Ratio male: female	Patients with circulating anti-dsg antibodies (%)
Total	151	F = 116 M = 35	F = 57.3 M = 55.2	1: 3.3	4/151 (2.6%)
Type I Plaque type	95	F = 70 M = 25	F = 54.25 M = 50.72	1: 2.8	0
Type II Erosive type	56	F = 46 M = 10	F = 61.6 M = 68.9	1: 4.6	4/56 (7.1%)

Abbr.: F, female; M, male; OLP, oral lichen planus; dsg, desmoglein

with chelated FCS was added to the monolayer and was incubated overnight at 37°C and 5% CO_2. To detach the monolayer from the cell culture dish, the wells were washed once with Hanks' Balanced Salt Solution (HBSS with Ca^{2+} [Thermo Fisher Scientific Inc., Waltham, MA, USA, Cat. No. 14025-050]) and dispase (2.5 U/mL) (Dispase II powder, Thermo Fisher Scientific Inc., Waltham, MA, USA, Cat. No. 17105041) was added to each well for 30–40 min. thereafter. After replacing the dispase solution by HBSS, the layers were stained with thiazolyl blue tetrazolium bromide (MTT, Invitrogen by Thermo Fisher Scientific Inc., Waltham, MA, USA, Cat. No. M6494) at 37°C and 5% CO_2 for 10 min. The staining solution was replaced by HBSS and the monolayers were subjected to mechanical stress by pipetting with an electrical 1 mL pipette (Eppendorf Xplorer® electrical pipette, Eppendorf AG, Hamburg, Germany, Cat. No. 4861000040) in a standardized manner. Resulting fragments were quantified using ImageJ software and evaluated using Microsoft Excel software.

Statistical analysis

All data were analyzed and plotted using GraphPad Prism 8.4.3 software. Statistical analyses were performed by using the Mann-Whitney and student's T-test. Values of $p < 0.05$ (*) were considered significant.

RESULTS

Epidemiological characteristics of patients with oral lichen planus

We here assessed the prevalence of anti-dsg serum antibodies in a cohort of 151 OLP patients from three tertiary referral centers. Overall, 95 of 151 (63%) patients showed a plaque-type OLP while 56 (37%) showed an erosive type OLP. Of note, 116 (76.8%) OLP patients were female while 35 (23.2%) were male. This result is in line with the observation that OLP most commonly occurs in women (male to female ratio 1 : 2.5). Mean age of onset of OLP was similar between the two genders (male 55.2; female 57.3 years old). Especially erosive type OLP seems to have an even higher female prevalence. Of 116 women, 39.6% had erosive OLP while the prevalence in men was 28.6% (Table 1).

Antibodies against desmosomal autoantigens are restricted to patients with erosive type oral lichen planus

Among the 151 studied OLP patients, four patients with erosive type OLP had serum IgG against dsg3 (2.6% of the entire study population; 7.1% of all erosive-type OLP patients) (Figure 1, Table 2). In contrast, none of the patients with plaque type OLP showed IgG serum reactivity against dsg3. Histopathological exam of lesional mucosa from the four anti-dsg3 IgG positive OLP patients showed the characteristic features of LP such as the band-like T-cellular infiltrate in the upper dermis, apoptosis of basal epidermal keratinocytes and thickening of the stratum granulosum while acantholysis was absent (Figure 1). Given the presence of IgG antibodies against dsg1 and dsg3, we performed direct immunofluorescence (DIF) of buccal mucosa and indirect immunofluorescence (IIF) with the sera of the four OLP patients. Of note, DIF and IIF were found to be negative in these patients (not shown).[16] Further, we analyzed the presence of antibodies against additional desmosomal antigens. Patients 1, 2 and 4 showed IgG antibodies against desmocollin (dsc) 2 and 3, while patient 3 did not (Table 2). Neither did these patients show clinical nor laboratory signs for solid or hematological malignancies nor antibodies against periplakins and envoplakins, allowing us to rule out paraneoplastic pemphigus, which may clinically resemble OLP.[17] Likewise, there was no evidence of solid or hematological malignancies in all the tested patients. All four patients with circulating antibodies were of white Caucasian ethnicity, presented negative history and serology for hepatitis B or C infection and absence of oral human papilloma virus infection.

OLP sera target distinct subdomains of desmoglein 3

We sought to investigate the exact ectodomains of dsg3 recognized by the sera of OLP patients. By WB analysis, all four patients showed IgG directed against the EC5 of dsg3, while IgGs against other ECs were less frequently detected (Figure 2a,b). These results suggest that anti-dsg antibodies in OLP are preferentially directed against the EC5 subdomain but also other subdomains can be targeted.

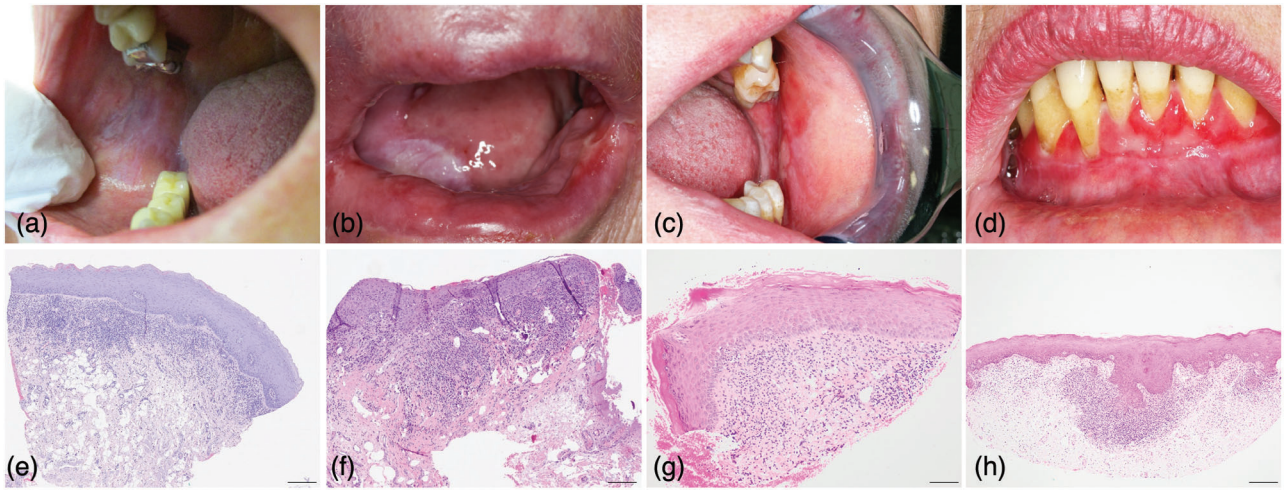


FIGURE 1 (a–d) Clinical and (e–h) histological appearance of four patients with erosive oral lichen planus presenting antibodies against desmoglein 1 and/or 3 (Scale bar: 250 µm).

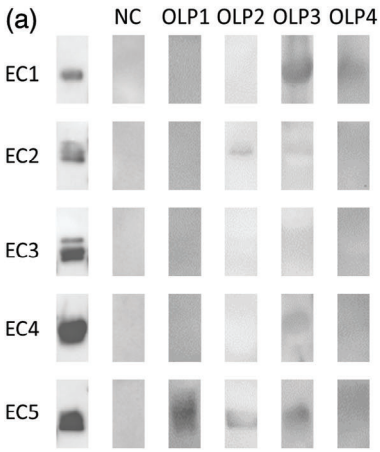
TABLE 2 Characteristics of patients with oral lichen planus and circulating IgG antibodies against desmoglein 1 and 3.

Patient No.	Sex	Age	OLP type	Antibody profile	ODSS	Direct and indirect Immunofluorescence
1	F	73	Erosive	dsg1 92 U/ml, dsg3 135 U/ml dsc 2 and 3 positive (Western Blot)	39	Negative
2	F	81	Erosive	dsg1 129 U/ml, dsg3 121 U/ml dsc2 and 3 positive (Western Blot)	34	Negative
3	F	49	Erosive	dsg1 32 U/ml, dsg3 48 U/ml	35	Negative
Patient 4	F	82	Erosive	dsg1 26 U/ml, dsg3 52 U/ml dsc2 and 3 positive (Western Blot)	37	Negative

Abbr.: ODDS, Oral Disease Severity Score; F, female; OL,P oral lichen planus; dsg, desmoglein; dsc, desmocollin

Level of anti-desmoglein serum antibodies do not correlate with disease activity in oral lichen planus

In three patients with erosive type OLP, the serum levels of anti-dsg IgG antibodies were monitored prospectively over several months (Figure 3a). Here we observed that first detection of anti-dsg antibodies was made months after initial symptoms of OLP. This serological monitoring also revealed that changes in anti-dsg3 IgG values were not related to disease activity. The three patients, over the period illustrated in the serological monitoring, neither achieved remission nor showed clinical improvements which can be correlated to antibody decrease (Figure 3a).



(b)

PT	EC1	EC2	EC3	EC4	EC5
NC	-	-	-	-	-
OLP1	-	-	-	-	+
OLP2	-	+	-	-	+
OLP3	+	+	-	+	+
OLP4	+	-	-	-	+

FIGURE 2 Antibodies against desmogleins are prevalently directed against the ectodomain 5. (a) Western Blot with recombinants desmoglein ectodomain recombinants show prevalence of antibodies against ectodomain 5, while antibodies against ectodomain 1 and 2 might also be present. (b) Table resuming western blot results in four patients with circulating antibodies against desmogleins. *Abbr.*: EC, ectodomain; NC, negative control; PT, patient; OLP, oral lichen planus

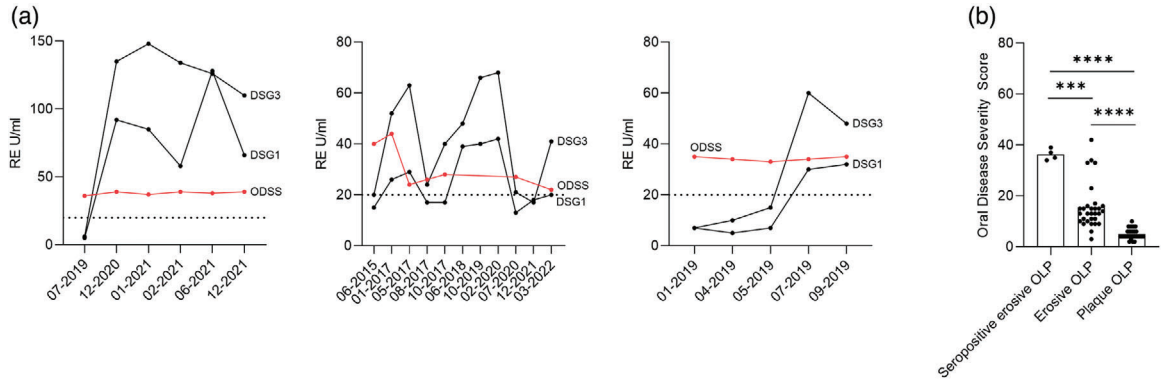


FIGURE 3 Anti-desmoglein antibodies in oral lichen planus are linked to severe disease and treatment resistance. (a) Serological monitoring for anti-dsg antibodies in two oral lichen planus patients shows that activation of humoral immunity sets in months after first clinical diagnosis of oral lichen planus. The red line shows variations in disease activity throughout the serological monitoring. (b) Comparison of the oral disease severity score (ODSS) in 30 patients with plaque OLP, 30 patients with erosive OLP and four patients with erosive OLP displaying antibodies against desmoglein 1 and 3. ***p < 0,0005, ****p < 0,0001, Mann-Whitney Test. *Abbr.*: EC, ectodomain; OLP; oral lichen planus; DSG, desmoglein; ODSS, oral disease severity score

OLP patients with circulating antibodies against desmoglein show higher disease severity

To understand whether occurrence of anti-dsg antibodies is linked to more severe forms of OLP we compared ODSS of four OLP patients with anti-dsg antibodies with 25 seronegative patients with plaque OLP and 25 seronegative patients with erosive OLP. Mean ODSS of patients with plaque OLP showed a significantly lower ODSS compared to the other two groups while patients with anti-dsg antibodies presented the highest ODSS, thus suggesting that humoral activity in OLP is a rare event occurring in patients with severe disease (Figure 3b).

Anti desmoglein antibodies in OLP cannot induce loss of cell-cell adhesion

In a final step, we analyzed the potential of anti-dsg serum antibodies of OLP patients to induce loss of cell-cell adhesion by utilizing the DDA. In contrast to the anti-dsg3 monoclonal antibody (AK23) or PV serum, none of the sera from the four OLP patients induced intercellular loss of adhesion in vitro. DDA with PV serum or AK23 induced monolayers fragmentation, while neither HC sera nor OLP sera with or without dsg antibodies, induced monolayer fragmentation (Figure 4). Overall, these results strongly suggest that the occurrence of antibodies against dsg is a rare phenomenon in severe erosive-type OLP, yet these antibodies seem to lack pathogenicity.

DISCUSSION

In this study, we analyzed the prevalence of anti-dsg3 serum IgG in a large cohort of patients with OLP. Our findings offer further evidence that activation of humoral autoimmunity occurs in a restricted subset of patients.

The study confirmed that erosive-type OLP is generally less common than plaque-type OLP and that OLP more frequently affects female patients in their fourth or fifth decade.

Activation of the humoral immunity and production of antibodies against dsg in OLP is a rare event, observed only in four patients out of 151 of the total OLP cohort. Interestingly, all four affected patients presented an erosive type of OLP.[18,19] This result is in agreement with previous reports.[20] One explanation for this finding could be that severe inflammation associated with the erosive phenotype exacerbate keratinocyte disruption and promote autoimmunity against dsg3. More precisely, steady apoptosis of basal cell keratinocytes may induce uncontrolled exposure of self-epitopes, leading to autoantibody production.[21] This hypothesis is supported by the following: *(1)* production of antibodies appears to be a late event during the course of OLP and is not present in the initial phase of disease (Figure 3a); *(2)* the presence of dsg3 antibodies is associated with a more aggressive OLP forms (Figure 3b). Overall, these results suggest that dsg3 antibodies may be a biomarker of disease severity in erosive OLP and indicate that the molecular mechanisms of erosive OLP may differ from those of plaque OLP.

The presence of anti-dsg3 antibodies poses the question of whether these patients might have been affected by an overlapping form of OLP and PV, or rather developed PV on a previous background of OLP. We were able to exclude these hypotheses since histological analysis of these four patients never showed microscopic findings such as suprabasal acantholysis and consistently revealed typical LP hallmarks, including a band-like lichenoid T cell infiltrate, thickening of the stratum granulosum and apoptosis of the basal cell keratinocytes (Figure 1). Secondly, antibodies from OLP patients were not able to induce acantholysis in vitro (as antibodies from PV patients could; Figure 4).

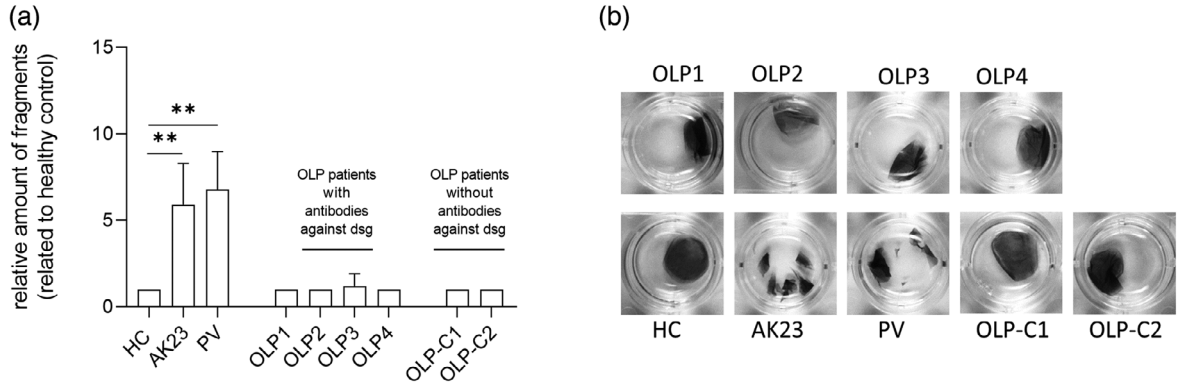


FIGURE 4 OLP sera containing anti-desmoglein antibodies do not lead to acantholysis in dispase-based keratinocyte dissociation assay. (a) Quantification of the monolayer fragments. Sera from patients with oral lichen planus (OLP) with or without circulating anti-dsg-antibodies do not show acantholysis. Serum from a patient with PV and the specific anti-dsg3-ab (AK23) serve as a positive control. Serum from a non-affected person serve as a negative control. Quantification of the monolayer fragmentation in three independent experiments. Error bars represent the SEM. **$p < 0.01$, Student´s T-test. (b) Macroscopic pictures of detached HaCaT monolayers showing fragmentation when treated with pemphigus sera or AK23 while treatment with serum of patients with oral lichen planus with circulating antibodies against desmoglein does not lead to fragmentation. *Abbr.*: HC, healthy control; PV, pemphigus vulgaris; OLP, oral lichen planus

Of note, we observed a discrepancy between ELISA index and IIF/DIF: While all the four patients showed elevated anti-dsg antibody levels, IIF/DIF were negative (not shown). This finding suggests the formation of antibodies with low avidity against their dsg target. Of note, similar discrepancies between these serological assays were described in both mice models for pemphigus and humans affected by pemphigus. In mice, immunization with pemphigus autoantigens resulted in activation of humoral immunity without phenotypical skin changes, suggesting that correct epitope targeting is essential for development of the clinical phenotype of PV.[22] Likewise, PV patients, who maintain elevated anti-dsg antibodies although in clinical remission, showed to produce non-pathogenic antibodies undetectable by IIF/DIF.[23]

Previously, it was demonstrated that pathogenic anti-dsg antibodies are directed against Ca^{2+}-dependent epitopes and only recognize mature dsg proteins, whereas antibodies directed against precursor dsgs are not pathogenic, regardless of whether they are directed specifically or non-specifically against precursor dsg. Our immunoblot analysis suggests that antibodies to DSG in OLP patients mainly target EC5. This finding can be explained by the fact that autoimmunity to dsg3 in OLP is directed against the precursor form of the protein, which is found in the cytoplasm, while B-cell tolerance to the mature protein is largely preserved.[24–26] In line with these findings, in a previous report of two OLP patients with circulating anti-dsg antibodies it was shown that antibodies targeted both mature and precursor dsg3.[27]

Interestingly, similar to OLP, activation of humoral immunity has previously been demonstrated in patients with vulvar lichen sclerosus, another T cell-mediated chronic inflammatory disease.[28]

All four patients were anti-dsg1/3^{+}. Dsg1 plays an important role in epithelial morphogenesis and its production is altered in patients affected by OLP.[29,30] In line with this, one previous study showed that chronic inflammation in OLP leads to an alteration of dsg1 expression.[30] However, it is also possible that antibodies to DSG1 are the result of epitope spreading. In both prospectively monitored patients levels of anti-dsg3 antibodies were constantly higher than those against dsg1 (Figure 2c). Furthermore, our serological analysis showed that these patients also display antibodies against dsc. Dsc are desmosomal components that play a relevant role in cell-to-cell adhesion and epidermal integrity.[31] In pemphigus, the detection of antibodies to dsc is rare, mostly seen in atypical variants of pemphigus, such as paraneoplastic pemphigus, and mainly associated with anti-dsg antibodies.[17,32]

Dsc2 and dsc3 are strongly expressed in the basal epidermal layers, which in OLP continuously undergoes apoptosis as a result of inflammation.[33] Anti-dsc antibodies can be directly pathogenic, and their occurrence has been related to more aggressive pemphigus disease.[32,34] Based on the results of our DDA assay, anti-dsc antibodies in our OLP patients are also non-pathogenic and their presence is probably an effect of chronic antigen exposure from apoptotic basal cells.

This study also has some limitations, the first being the limited number of patients included. Second, we did not analyze whether patient sera recognize Ca2+-independent regions and whether these antibodies are directed against premature dsg proteins since these techniques are not established in our centers. Nevertheless, we were able to show by DDA that anti-dsg antibodies in OLP are a non-pathogenic epiphenomenon. A possible explanation for the rarity of humoral immunity activation in OLP is that this disease is mainly Th1 driven, whereas activation of humoral

activity requires Th2 activation. Consistent with this, Th1 anti-dsg T cells are much more common in OLP patients.[5] Other factors (i.e., genetic predisposition) may be required to induce humoral activation.

In conclusion, in this study we demonstrate that only a limited number of patients with OLP, a recognized T-cell driven disease, show concomitant activation of humoral immune responses. This supports the concept that in certain cases skin autoantigens and especially dsg play a role in the pathogenesis of OLP. Our analysis showed that regardless of the autoantibody titer, the specificity of the antibodies is different from that of PV and the antibodies lack acantholytic pathogenicity. However, the presence and titer of dsg antibodies seems to predict a more aggressive disease course. Further mechanistic studies are needed to elucidate the role of humoral immunity in OLP.

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CONFLICT OF INTEREST STATEMENT

None.

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