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Correlation between anti-desmoglein and mucocutaneous lesions in patients with pemphigus vulgaris or foliaceus

Correlação entre anti-desmogleína e lesões mucocutâneas em pacientes com pênfigo vulgar ou foliáceo

Correlación entre anti-desmogleína y lesiones mucocutáneas en pacientes con pénfigo vulgar o foliáceo

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This research was a non-probability cross-sectional. The aim of the present study was to correlate the immunodetection of anti-desmoglein 1 and 3 in the serum of pemphigus vulgaris (PV) or pemphigus foliaceus (PF) patients with the presence of mucocutaneous lesions. Patients were selected through convenience sampling based on spontaneous demand at the Dermatology and Oral Medicine units of the Universidade Federal de Pernambuco, Recife, Brazil at February until November of 2012. Twenty-six individuals (18 women, 69.2% and 8 men, 30.8%) were evaluated, 20 diagnosed with PV (73.1%) and 6 with PF (26.9%). ELISA test was used to determine the presence of anti-desmoglein 1 and 3 in the serum. Anti-desmoglein 1 positivity was associated to skin lesions (p=0.038) and anti-desmoglein 3 to mucosal lesions (p = 0.041). On this study, ELISA was shown to be highly sensitive for DSG1 and DSG3 in accordance with the phenotype of the disease.
Descriptors: Pemphigus; Enzyme-linked immunosorbent assay; Skin disease vesiculobullous; Autoimmune diseases.

Essa é uma pesquisa não-probabilística e transversal. O objetivo deste estudo foi correlacionar a imunodetecção de anti-desmogleína 1 e 3 no soro de pacientes com pênfigo vulgar (PV) ou pênfigo foliáceo (PF) com a presença de lesões mucocutâneas. Pacientes foram selecionados por uma amostra de conveniência baseada na demanda espontânea nas unidades de Dermatologia e Medicina Oral da Universidade Federal do Pernambuco, Recife, Brasil, de fevereiro a novembro de 2012. Vinte e seis indivíduos (18 mulheres, 69,2% e 8 homens, 30,8%) foram avaliados, 20 diagnosticados com PV (73,1%) e 6 com PF (26,9%). O teste ELISA foi usado para determinar a presença de anti-desmogleína 1 e 3 no soro. A presença de anti-desmogleína 1 foi associada a lesões na pele (p=0,038) e a de anti-desmogleína 3 a lesões mucosais (p = 0,041). Nesse estudo, o ELISA se mostrou altamente sensível ao DSG1 e ao DSG3, de acordo com o fenótipo da doença.
Descritores: Pênfigo; Ensaio de imunoadsorção enzimática; Dermatopatias vesicolobolhosas; Doenças autoimunes.

Esta es una investigación no-probabilística y transversal. El objetivo de este estudio fue correlacionar la inmunodetección de anti-desmogleína 1 y 3 en el suero de pacientes con pénfigo vulgar (PV) o pénfigo foliáceo (PF) con la presencia de lesiones mucocutáneas. Pacientes fueron seleccionados por una muestra de conveniencia basada en la demanda espontanea en las unidades de Dermatología y Medicina Oral de la Universidad Federal de Pernambuco, Recife, Brasil, de febrero a noviembre de 2012. Veintiséis individuos (18 mujeres, 69,2% y 8 hombres, 30,8%) fueron evaluados, 20 diagnosticados con PV (73,1%) y 6 con PF (26,9%). El *test* ELISA fue usado para determinar la presencia de anti-desmogleína 1 y 3 en el suero. La presencia de anti-desmogleína 1 fue asociada a lesiones en la piel (p=0,038) y de anti-desmogleína 3 a lesiones mucosas (p = 0,041). En este estudio, el *test* ELISA se mostró altamente sensible al DSG1 y al DSG3, de acuerdo con el fenotipo de la enfermedad.
Descriptores: Pénfigo; Ensayo de inmunoadsorción enzimática; Enfermedades cutáneas Vesiculoampollosas; Enfermedades autoinmunes

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INTRODUCTION

Pemphigus is a group of chronic vesiculobullous autoimmune diseases including pemphigus vulgaris (PV), pemphigus foliaceus (PF), vegetating pemphigus, paraneoplastic pemphigus, immunoglobulin A pemphigus, pemphigus erythematosus and drug-induced pemphigus. This group of conditions is characterized by the loss of intraepithelial cell adhesion (acantholysis), formation of blisters and ulcers affecting the mucous membranes and/or skin and the presence of autoantibodies directed against desmogleins (DSGs)[1-3].

The autoantibodies produced in pemphigus are directed to DSGs found on the surface of keratinocytes, causing the separation of epithelial cells and leading to intraepithelial blisters[2]. DSGs belong to a family of desmosomal cadherins that act as intercellular adhesion molecules, binding epidermal keratinocytes[2,4,5].

DSG1 is mostly found in the superficial layer and DSG3 is more abundant in basal and suprabasal layers. In addition, DSG3 is significantly expressed in the oral epithelium[6]. This distribution explains why PV affects the skin and the mucous membranes while PF is often seen as cutaneous lesions[1-3,7]. Clinically, the mouth can be the initial and only site of PV involvement, leading to delayed diagnoses and inappropriate management[6].

PV and PF are the most common subtypes of pemphigus, with an estimated incidence of 0.1 to 0.5 cases in 100,000 individuals for PV and around 0.5 cases of PF for each 100,000 individuals[8,9]. In endemic regions, the prevalence of PF can reach 3.4%[10]. In addition, they present distinctive clinical and immunopathological characteristics[1]. Nevertheless, the co-existence of combined PF and PV features in the same patient or even the transformation of one type into the other are well described[11-14]. This possibly occurs because patients with PV produce anti-DSG3 immunoglobulin G (IgG) and/or anti-DSG1 IgG, while patients with PF produce only anti-DSG1 IgG[1,3,4,7].

In this clinical setting, detection of circulating autoantibodies seems to become more relevant to an adequate diagnosis of pemphigus[1,11,15]. For many years, indirect immunofluorescence was the most used technique for this purpose. However, it does not differentiate between the subtypes of the disease, which can be performed by immunoblotting and immunoprecipitation. Unfortunately, these methods are time-consuming, exclusively qualitative, and impractical for use on a large number of cases [2,9,16].

The production of the recombinant DSG1 and DSG3 antigens in the 1990s has led to the development of an enzyme-linked immunosorbent assay (ELISA) capable of identifying pemphigus autoantibodies[17-20]. This test showed elevated sensitivity and specificity in diagnosis of PV when compared to other serological tests, being capable of detecting and quantifying the autoantibodies, which seems to be related to disease severity[9,15].

Detecting the presence of surrounding autoantibodies is a reality in the diagnosis of pemphigus, hence the importance of studies on the subject. Thus, the aim of the present study was to correlate the immunodetection of anti-desmoglein 1 and 3 in the serum of PV or PF patients with the presence of mucocutaneous lesions.

METHOD

This research was a non-probability cross-sectional. Patients were selected through convenience sampling based on spontaneous demand at the Dermatology and Oral Medicine units of the Universidade Federal de Pernambuco (Recife, Brazil), from February until November of 2012.

The study was carried out in compliance with the ethical principles stipulated by the Brazilian National Health Council and was approved on the local IRB under the number 291/08. All participants signed a statement of informed consent.

All patients were previously diagnosed and treated on the Dermatology Unit. Diagnoses were based on clinical presentation and microscopic aspects.

Patients were interviewed and physical exams were performed at the Oral Medicine Unit, UFPE. Blood samples were obtained and placed in 9mL dry tubes and rested for 30 min. After this period, the tubes were centrifuged for ten minutes at 3250 rpm and the serum was then transferred to labelled, sterile microtubes and stored at -20ºC until testing.

The detection of DSG1 and DSG3 was performed using the MBL Mesacup DSG-1 & DSG-3 ELISA Test System© (Medical and Biological Laboratories - MBL®, Nagoya, Japan) in accordance with manufacturer's instructions. Briefly, 100 µl of a diluted serum sample (1:101) from each patient was deposited in duplicate on the microplate. Positive and negative controls for each desmoglein were used and microplates were incubated for 60 minutes at 23 ± 0.3ºC, washed four times, then the IgG peroxidase conjugate was added. After 60 min, the plate was washed and the peroxidase substrate was added (TMB substrate solution) for 30 minutes, then 100 µl of the stop solution was added. Prompt reading was performed using a spectrophotometer (TP-Reader Plus, Thermoplate) at 450 nm. Results are given as absorbance (Abs), and the concentration (U/mL) was determined according to the manufacturer's formula.

This result was interpreted using the cut-off point table recommended by the manufacturer, which quantifies results as positive, negative or undetermined, as follows the Table 1.

Table 1. Cut-off point table recommended by the manufacturer.

DSG1 < 14U/mL DSG3 < 9U/mL	Negative
14 < DSG1 < 20U/mL 9 < DSG3 < 20U/mL	Undetermined
DSG1 and DSG3 > 20U/mL	Positive

Abbreviations: DSG1, Desmogelin type 1; DSG3, Desmoglein type 3.

For data analysis, absolute distributions, univariate and bivariate percentages were obtained and Pearson's chi-square test was applied. Statistical calculations were carried out using the Statistical Package for the Social Sciences (version 17.0). The margin for error used in the decisions on the statistical tests was 5.0%.

RESULTS

The sample comprised 26 individuals, with mean age of 43.2 years, ranging from 14 to 74 years. Eighteen participants were female (69.24%) and eight male (30.76%), twenty had PV (73.1%) and six had PF (26.9%), and all were born in the state of Pernambuco, Brazil. The diagnoses were performed through clinical testing and histopathological exams. At the time of clinical examination, 18 (69.23%) of the 26 patients had active lesions and 18 (69.23%) were on treatment with systemic steroids.

It could be noted that among the 26 patients diagnosed with pemphigus, twenty (73.1%) had PV and six (26.9%) had PF. Fifteen patients (57.7%) had a history of mucocutaneous lesions, 7 (26.9%) had only skin lesions and 4 cases (15.4%) had mucosal lesions alone. Table 2 reports the relationship between the presence of anti-DSG1 and the subtypes of the disease. Briefly, two patients (10%) with PV presented with anti-DSG1, seven (35%) with anti-DSG3, and seven (35%) with both DSGs. Among the six patients with PF, five (83,3%) were positive to anti-DSG1 and one (16,7%) had a negative result (Table 2).

Table 2. Correlation between Anti-DSG1 and Anti-DSG3 positivity and disease. Recife, Brazil, 2012.

Disease	DSGs			
	DSG-1 Positive	DSG-3 Positive	DSG-1 Negative	DSG-3 Negative
Pemphigus Vulgaris	7	11	6	4
Pemphigus Foliaceus	7	3	2	5
Total	14	14	8	9

Abbreviations: DSG1, Desmogelin type 1; DSG3, Desmoglein type 3.

The presence of Anti-DSG1 antibodies was associated with skin and mucosal lesions (p = 0.038 and p = 0.009, respectively). Among the 19 patients with a history of skin lesions, eight (30.8%) were positive to anti-DSG1 (Table 3). Fourteen out of 22 patients with mucosal lesions had positive results for anti-DSG-1 (Table 4). No statistically significant correlation was found between anti-DSG3 activity and skin lesions (p = 0.850), whereas a statistically significant correlation was found between anti-DSG3 positivity and mucosal lesions (p = 0.041) (Tables 3 and 4). Among the 22 patients with a history of mucosal lesions, 13 tested positive for the presence of serum anti-DSG3 (Table 4).

Table 3. Correlation between Anti-DSG1/DSG3 positivity and the presence of skin lesions. Recife, Brazil, 2012.

Skin lesions	DSGs					
	Anti-DSG1	Anti-DSG3	Both positive	Both negative	Total	*p*
Present	2	6	6	5	19	0.038
Absent	5	1	1	0	7	
Total	7	7	7	5	26	

Abbreviations: DSG1, Desmogelin type 1; DSG3, Desmoglein type 3.

Table 4. Correlation between Anti-DSG1/DSG3 positivity and mucosal lesions. Recife, Brazil, 2012.

Mucosal lesions	DSGs					
	Anti-DSG1	Anti-DSG3	Both	Negative	Total	*p*
Present	4	7	6	6	23	0.009
Absent	0	1	0	2	3	
Total	4	8	6	8	26	

Abbreviations: DSG1, Desmogelin type 1; DSG3, Desmoglein type 3.

DISCUSSION

PV and PF are bullous diseases of the skin and/or mucous membrane, characterized by circulating IgG autoantibodies against DSG1 and/or DSG3[17]. PF is endemic to the states in some areas in Brazil and other sub-tropical countries[16,21,22]. PV is the most common subtype of pemphigus, in which lesions develop in the mucous membrane and/or skin[14].

In the present study, 73.1% of the patients suffered from PV. In the present study, the majority of the sample (69.23%) was composed by female patients, most of them between 24 and 62 years of age. These findings seem to be in concordance with other studies, which usually report pemphigus is more common in females between 15 and 34 years of age[8].

DSG3 and DSG1 are 130 kDa and 160 kDa glycoproteins members of the desmosomal cadherin superfamily. These proteins are organized and concentrated in the desmosomes, being responsible for maintaining the integrity of the stratified epithelium[7,19]. They are also the most common anti-antigens for PV (DSG3) and PF (DSG1)[1,2,5,23]. DSG3 is a determinant for

mucosal lesions and DSG-1 is a determinant for skin lesions.

Patients with PV who have mucocutaneous lesions may exhibit both anti-DSG1 and anti-DSG3 antibodies[4,9,21,23,24], and more than 50% of patients present with both DSG1 and DSG3. Studies have suggested that this is an important factor in determining the phenotype of the disease, since patients suffering predominantly from skin lesions have higher DSG1 autoantibody levels compared to those with predominantly mucosal lesions[4,7,24].

In the present study ELISA for DSG-1 and DSG-3 proved to be a highly sensitive and specific tool for the diagnosis of pemphigus. This finding is in keeping with a number of other studies, which report that ELISA for DSG-1 and DSG-3 is highly sensitive and can also be used to evaluate the severity and activity of the disease[7,18,21]. ELISA has a number of other advantages over indirect immunofluorescence as it does not require a qualified observer and it is a simple manner to differentiate between PV and PF[21].

In the present study, all the patients with PF presented skin lesions and were positive for DSG-1, while the majority of PV patients (75%) presented with mucocutaneous lesions and tested positive for both DSG-1 and DSG-3. This desmoglein profile seems to be consistent with the phenotype of the disease. Despite the fact that the clinical phenotype of a disease generally relates to the type of antibody, there are some cases in which the phenotype and antibody are different. Such discrepancies may be due to genetic variations or the presence of other antigens involved in the pathogenesis of pemphigus[24]. Interestingly, 3 patients with PF were positive for both DSG1 and DSG3. This may be associated to a phenotype switch from PF to PV, as previously described[11-14].

The treatment of pemphigus involves a high dose of systemic corticosteroids, especially prednisone, which may be combined with immunosuppressors, such as azathioprine, cyclophosphamide, methotrexate, cyclosporine and, more recently, mycophenolate mofetil. Anti-inflammatory drugs, such as dapsone, chloroquine and combinations of nicotinamide and tetracycline are also used[2,23].

Some case reports exist of the use of rituximab in patients with pemphigus, mainly pemphigus vulgaris resistant to steroids and immunosuppressants, with favorable results[12]. These are adjuvant therapies, the goal of which is to reduce the often-devastating side effects of corticosteroid treatment[2,10]. Treatment with prednisone often produces excellent results, but resistant forms exist, requiring alternative therapies.

Alternative treatments have been used in cases of corticosteroid-refractory pemphigus, showing favorable results like intravenous immunoglobulin[11,12]. At the time of the present study, 73.1% of the patients were undergoing systemic steroid treatment with adequate control of disease presentation. Those without systemic treatment were clinically stable without treatment or were under topical steroids.

The study presents limitations due to convenience sampling and the methodology used (cross-sectional). It is also worth noting that the findings are local, which adds new study questions that allow the extrapolation of the results to the general population.

CONCLUSION

In summary, ELISA was shown to be highly sensitive for DSG1 and DSG3 in accordance to the phenotype of the disease. Moreover, correlations were found between the presence of anti-DSG1 and skin lesions as well as anti-DSG3 and mucosal lesions. Likewise, both anti-DSG1 and anti-DSG3 were found in patients with mucocutaneous lesions.

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