Acta Dermatovenerol Croat 2022;30(3):129-139 ORIGINAL SCIENTIFIC ARTICLE

Main Clinical Features of Patients with Irritant and Allergic Contact Dermatitis on the Hands in Correlation with Skin CD44 Expression: A Prospective Study

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Received: February 3, 2021
Accepted: September 1, 2022

ABSTRACT Contact dermatitis (CD), including its irritant (ICD) and allergic (ACD) types, is a complex, often chronic and therapy-resistant disease that significantly affects patient quality of life and healthcare systems. Objective of this study was to examine the main clinical features of patients with ICD and ACD on the hands through follow-up in correlation with baseline skin CD44 expression. Our prospective study involved 100 patients with hand CD (50 with ACD; 50 with ICD) who initially underwent biopsies of skin lesions with pathohistology, patch tests to contact allergens, and immunohistochemistry for lesional CD44 expression. The patients were subsequently followed-up on for a year, after which they filled out a questionnaire designed by the authors examining disease severity and disturbances/issues. Patients with ACD had significantly higher disease severity than those with ICD (P<0.001), with more frequent systemic corticosteroid treatments (P=0.026) and greater areas of affected skin (P=0.006), exposure to allergens (P<0.001), and impairment of everyday activities (P=0.001). No correlation between ICD/ACD clinical features and initial lesional CD44 expression was observed. Due to the commonly severe course of CD, especially ACD, more research and prevention are needed, including the analysis of the role of CD44 in connection with other cell markers.

KEY WORDS: contact dermatitis, irritant contact dermatitis, allergic contact dermatitis, CD44, hand eczema

INTRODUCTION

Contact dermatitis (CD), including its irritant (ICD) and allergic (ACD) forms, poses a significant burden to healthcare systems, especially considering that ACD makes up 5-15% of all inflammatory dermatoses, and ICD is even more frequent (1-5). Contact dermatoses occur in all age groups, even in children, and are more common in some occupations (4-7). The most common type of contact dermatosis is ICD, which is considered the most frequent cause of hand eczema and also represents approximately 80% of occupational

CD (8,9). In the general population, the estimated prevalence of hand eczema is approximately 4%, women being more frequently affected than men (9). Since CD frequently relapses and is persistent, it often impacts work and daily activities; patients commonly have difficulties coping with the disease.

Because of the complexity of the disease and its significant burden on patients and healthcare systems, many different studies have been conducted on CD, including those on concomitant, disease-related problems and their accompanying discomforts, which can be chronic and severe (3,10). In looking at possible skin/lesional inflammation biomarkers of CD, it has recently been suggested that the major cell-surface receptor CD44 could be an important inflammation skin marker (11-15). According to our recent study, CD44 expression was greatest in ICD lesions, followed by ACD lesions, psoriatic lesions, and healthy skin. CD44 expression in patients with contact dermatoses was significantly higher, especially in those with ICD compared with those with psoriasis and healthy skin. This was true for the epidermis and the dermis as well as the lymphocytes (11). This significantly elevated CD44 expression observed in ICD lesions might be related to the role of CD44 in maintaining and preserving the skin barrier (11,16-18). However, the relationship between lesional CD44 expression and clinical characteristics of the patients has not been examined thus far. Additionally, there are only a small number of studies that have tracked patients with CD over a long period of time. Therefore, we wanted to further this research topic by examining patient experiences/conditions over a long period of time and comparing them with lesional CD44 expression at baseline, with the aim of gathering more information on the characteristics of ICD and ACD.

PATIENTS AND METHODS

Patients

This prospective study was conducted at the Department of Dermatovenereology of the Sestre milosrdnice University Hospital Center and involved 100 patients: 50 patients with hand ACD and 50 patients with hand ICD, which were confirmed to be CD (clinically, pathohistologically, and by patch test) and with lesions lasting more than 3 months. Between April 2016 and June 2018, patients were examined and recruited by a dermatologist who had treated the patients over a period of one year at the Department of Dermatovenereology.

We looked for CD by reviewing each patient's history of contact with suspected substances and performed a biopsy for pathohistological analysis to exclude other diagnoses. Thus, patients with any other hand dermatoses, with mycological infections, or with inconclusive pathohistological findings were excluded. ACD diagnoses were established when sensitization to contact allergens was confirmed by a patch test and when lesions improved after the patient avoided the causative allergens. Patients who did not have significant patch test reactions were not included on the study.

Skin biopsies were analyzed by a pathologist at the above-mentioned hospital at the Clinical Department of Pathology "Ljudevit Jurak". Additionally, immunohistochemistry for lesional CD44 expression was analyzed using an optical microscope. The results were visualized semiquantitatively by determining the percentage of immunoreactive cells in the epidermis, dermis, and lymphocytes.

After initial clinical, histopathological, and patch-test findings confirmed either hand ICD or ACD, patients were treated and observed for a year, after which the dermatologist and patient filled out a questionnaire together about disease severity and accompanying problems/issues (conducted between April 2017 and June 2019).

The Ethics Committee of the aforementioned hospital approved the research (No. EP-4433/15-14). Each patient signed a consent form, and the study proceeded in accordance with the Helsinki Declaration guidelines.

Histopathology and immunohistochemistry of skin biopsies and patch testing

First, patients underwent biopsies of skin lesions and patch testing to contact allergens (19,20).

Pathohistological analysis: Processed skin samples (punch biopsies 4 mm in diameter) were stored in paraffin blocks and then analyzed. To process the samples, we used the standard method of tissue fixation in 10% buffered formalin. The samples were then put in paraffin blocks and cut into 4 µm-thick sections/slices, and then the hematoxylin and eosin method was finally used to stain the samples.

Patch testing was conducted for patients with manifestations resembling a clinical picture of hand contact dermatoses. Patch testing was done on normal, hairless skin of the upper back and under the guidelines of the European Society of Contact Dermatitis with the baseline series of allergens (Patch Test Strips Curatest® Lohman & Rauscher International, Rangsdorf, Germany) (19). Baseline allergen kits were supplied by the Institute of Immunology, Zagreb, Croatia (20). These allergen kits contained various

metals, preservatives, adhesives, rubber accelerants and antioxidants, such as nickel sulfate (5.0% pet.), potassium dichromate (0.5% pet.), cobalt chloride (1.0% pet.), fragrance mix (8.0% pet.), p-phenylenediamine (PPD) (0.5% pet.), epoxy resin (1.0% pet.), carba mix (3.0% pet.), mercapto mix (2.0% pet.), paraben mix (15.0% pet.), thiuram mix (1.0% pet), neomycin sulfate (20.0% pet.), balsam of Peru (25.0% pet.), colophony (20.0% pet.), formaldehyde (1.0% water), N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD) (0.1% pet.), thimerosal (0.1% pet.), lanolin (30.0% pet.), mercury (0,5% pet.), quaternium-15 (1.0% pet.), sulfur precipitate (10.0% pet.), phenylmercuric acetate (0.01% water). Patch test results were read after 48, 72, and 96 hours (19).

Immunohistochemical analysis was used to determine lesional CD44 expression. The primary antibody to CD44 (anti-human CD44 from monoclonal mice; clone DF1485, Dako) was used in a 1:50 dilution. The automated DAKO TechMate TM (DAKO, Denmark) and LSAB staining method were utilized to visualize the target antigen. A human tonsil section was used (1:50 dilution) as a positive control for the CD44 antibody, while, the primary CD44 antibody was omitted for the negative control. In these specimens, we estimated the percentage of immunoreactive cells in the epidermis, dermis, and lymphocytes in order to analyze CD44 expression. Separate lymphocyte cells were easily identified, most of which were seen in the dermis and to a significantly lesser extent in the epidermis, and when observing the dermis and epidermis we specifically looked at elastic fibers, the collagen network, and the glycosaminoglycan matrix. Lesional CD44 expression was determined by light microscopy and was semi-quantitatively presented: no reaction (0); low reaction (<33% positive); moderate reaction (33-66% positive); strong reaction (>66% positive).

Questionnaire

After one year of prospective treatment and monitoring, ICD and ACD severity was assessed by a questionnaire filled out together by the patient and dermatovenerologist to compare data on disease characteristics with initial lesional CD44 expression. Our team designed the questionnaire ourselves to obtain data on CD severity that would be collected after a longer period of time (one year) (Table 1). The questionnaire covered the most important CD indicators and disease features, i.e., the clinical picture, treatment, relapse, and follow-up of patients after a year. Patient data included in the questionnaire was: age, gender, allergies proven by patch test, number of relapses/exacerbations within one year, extent of skin affected over the last year, lesion severity, application of topical corticosteroids, application of topical immunomodulators, administration of systemic corticosteroids for exacerbation, hospitalization due to disease deterioration within one year, exposure to allergens (to which hypersensitivity was confirmed), exposure to strong irritants, wearing protective gloves, and restrictions to daily activities due to skin lesions (Table 1).

Based on the questionnaire, patients with ICD and ACD were classified into three groups by disease severity (mild, moderate, severe). Each response was scored with points, and the total sum gave a result for each patient. A total of up to 10 points was considered mild disease severity, 10 to 20 points was moderate, and 21 or more points was classified as severe.

Statistical analysis

We used descriptive statistics for all the research variables. Parametric and nonparametric regression analyses were used to look for correlations between individual variables. We used the Chi-Quadrat-Test or the Fischer's exact test to compare qualitative variables between subgroups. The Fisher's exact test (2×2 tables) was used to analyze CD44 expression between the study groups. The Fisher-Freeman-Halton's exact test was used for larger number combinations. We used one-way variance analysis to analyze differences in age between the ACD and ICD groups. We considered an absolute correlation coefficient value >0.600 as a strong correlation. Medium-strong values ranged from 0.300 to 0.599, while values <0.300 were considered weak, whether negative or positive.

We performed statistical analyses with the STATISTICA 6.0 software (StatSoft Inc., Tulsa, OK, USA) and IBM SPSS 25.0 (IBM Corp., Armonk, USA). For the power test analysis, we used G*Power for Windows, version 3.1.9.2. Statistical significance, seen in the tables in bold font, was set at $P<0.05$.

RESULTS

According to analysis results of CD44 expression in lesions from the three different parts of the skin (Table 2) (Figure 1, Figure 2, Figure 3), positive CD44 expression was found in the majority of the patients. Positive lesional CD44 expressions were observed as follows: ICD 98% vs. ACD 100% for the epidermis; ICD 58% vs. ACD 80% for the dermis; ICD 80% vs. ACD 78% for lymphocytes. For dermal lesions, positive CD44 reactions were significantly more frequent in subjects with ACD than with ICD ($P=0.030$).

Based on our questionnaire (taken after one year together with age and gender data) and data

Table 1. Patient questionnaire and follow-up over a period of one year

Examinee_____	AGE_____	SEX F/M
QUESTION:	ANSWERS	POINTS
1. Allergies proven by epicutaneous (patch) test: YES/NO	0, only irritant reaction to patch	0.5
	1 allergen	1
	2 or more allergens	2
2. Number of relapses / exacerbations within a year	×1	0
	×2	1
	3 or more x	2
3. How many weeks in duration within a year has the skin been affected by changes?	Up to 2 weeks	1
	2 to 6 weeks	2
	6 weeks to 3 months	3
	More than 3 months	4
4. The severity of changes on the skin of the hands	Skin dryness only, itching, mild erythema	1
	Severe erythema plus the above manifestations	2
	Erythema, blisters, flaking	3
	Erythema, fissures, skin thickening	4
	All of the above	5
5. Application of topical corticosteroid preparations: how many times within a year	Up to 3 weeks in total	1
	3 to 6 weeks in total	2
	Over 6 weeks in total	3
6. Application of topical immunomodulators: how long within one year	Up to 3 weeks in total	1
	3 to 6 weeks in total	2
	6 to 8 weeks in total	3
	More than 8 weeks	4
7. Systemic corticosteroid therapy for exacerbation	Up to 3 days	1
	4 to 10 days	2
	More than 11 days	3
8. Hospitalization due to worsening of skin changes within a year	NO	0
	YES, ×1	1
	YES 2 or more	2
9. Exposure to allergens to which hypersensitivity has been demonstrated	Never, does not know	0
	Occasionally	1
	Daily	2
10. Exposure to strong irritants (acids, alkali)	Sometimes	1
	Often	2
	Almost daily	3
11. Safety glove use: cotton + rubber	Never	2
	Occasionally	1
	Regularly	0
12. Do skin changes limit your daily routine?	It does not bother me because they rarely occur	0
	It bothers me because changes on the skin of the hands are occasionally visible	1
	It bothers me because there are often changes on the skin, and there is often itching, burning, or pain	2
	It bothers me a lot because there are changes almost constantly, and it is difficult to do tasks	3
*Evaluation of the results: Up to 10 points: a mild form of the disease 10 to 20 points: medium severe disease 21 points or more: severe disease The questionnaire is filled out by a dermatology specialist together with the subject		

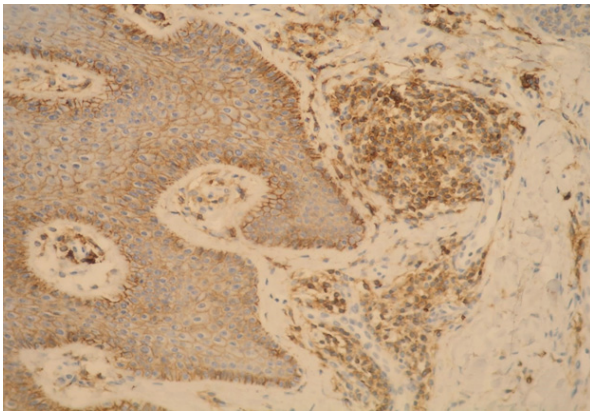

Figure 1. Groups of patients with ICD and ACD according to disease severity (mild, moderate, severe) determined by questionnaire and patient follow-up for a period of one year ($P<0.001$)

on disease severity (Table 3), patients with ACD had more severe disease features when compared with patients with ICD ($P<0.001$). Specifically, they had a significantly longer duration of lesions (higher total period of lesion involvement) ($P=0.006$), they more commonly used systemic corticosteroids ($P=0.026$), and had greater allergen exposures ($P<0.001$) and limitations in daily activities ($P=0.001$) (Table 3).

Moderate disease severity predominated equally for both patients with ICD and with ACD, (ICD 56%; ACD 56%) (Figure 1). Among patients with ICD, we observed no severe disease, only mild and moderate severity. Patients with ACD, on the other hand, predominantly exhibited moderate severity, followed by severe and mild severity (Figure 1). In summary, patients with ACD had more severe clinical pictures.

A comparison between lesional CD44 expression (in the epidermis, dermis, and lymphocytes) and the clinical parameters of patients (determined after one year) is presented in Table 4 and Table 5. According to our results, there was no significant correlation/association between skin CD44 expression and the severity of disease.

In patients with ICD, there were no significant correlations between skin CD44 expression and clinical severity of the disease (epidermis $P=0.457$; dermis $P=0.673$; lymphocytes $P=0.813$) (Table 4). For patients with ACD, the comparison of their disease severity (measured after one year) and initial lesional CD44 expression showed no significant correlations (epidermis $P=0.761$; dermis $P=0.653$, lymphocytes $P=0.403$) (Table 5). Finally, according to the comparison of disease severity for patients with ICD and with ACD together and CD44 expressions, there were no significant correlations between initial lesional CD44 expression (in the epidermis, dermis and lymphocytes) and the severity of the two diseases determined after one year (Table 6).

DISCUSSION

Because courses of ICD and ACD are commonly prolonged and cause associated problems, researchers have attempted to better understand the different aspects of the disease and its negative impact on patients (12,13,21-27). However, there are generally no tools for evaluating multiple disease characteristics specific to CD, and there is little literature data regarding tools/indicators to clinically evaluate disease severity and features over a longer period of time or responses to therapies (21). We have therefore designed our own study questionnaire to examine at severity and many disease-related factors. According to our questionnaire data, patients with ACD had significantly more severe clinical characteristics/presentations (e.g., greater areas of affected skin, higher impairment of everyday activities, more frequent use of systemic corticosteroid treatments) than patients with ICD, while patients with ICD had more pronounced lesional CD44 expressions (measured at baseline). Previous data on the role of CD44 in skin inflammation indicated that CD44 is required for skin epidermal permeability, barrier homeostasis, and keratinocyte differentiation (12). According to previous research, including our own, lesional CD44

Table 2. A comparison of CD44 expression in the epidermis, dermis, and on lymphocytes in skin biopsies of patients with ACD and ICD (Fisher exact test).

N		ICD		ACD		*P*
		%	N	%		
Epidermal CD44	No reaction	1	2.0	0	0.0	1.000
	Positive reaction	49	98.0	50	100.0	
Dermal CD44	No reaction	21	42.0	10	20.0	**0.030**
	Positive reaction	29	58.0	40	80.0	
CD44 on lymphocytes	No reaction	10	20.0	11	22.0	1.000
	Positive reaction	40	80.0	39	78.0	

Table 3. Statistical analysis of patient parameters associated with confirming disease severity in patients with ICD and ACD (Fisher-Freeman-Halton exact test)

		Group				*P*
		ICD		ACD		
		N	%	N	%	
Allergens identified based on patch test	Only irritative reaction on test tape	50	100.0	0	0.0	**<0.001**
1 allergen	0	0	33	66.0		
>=2 or more allergens	0	0	17	34.0		
Number of relapses	×1	18	36.0	9	18.0	0.138
×2	21	42.0	25	50.0		
>=×3	11	22.0	16	32.0		
Duration of skin involvement	<2weeks	25	50.0	14	28.0	**0.006**
2-6 weeks	7	14.0	9	18.0		
6 weeks to 3 months	3	6.0	2	4.0		
>3 weeks	7	14.0	2	4.0		
3-6 months	8	16.0	23	46.0		
Type of skin changes	Only dryness, itching	17	34.0	10	20.0	0.488
Mild erythema	20	40.0	24	48.0		
Severe erythema with the above-mentioned	7	14.0	8	16.0		
Erythema, blisters, flaking, fissures, skin thickening	6	12.0	8	16.0		
	All of the above	0	0.0	0	0.0	
Application of local corticosteroids	<3 weeks in total	19	38.0	17	34.0	0.369
3 to 6 weeks in total	23	46.0	19	38.0		
More than 6 weeks in total	8	16.0	14	28.0		
Immunomodulator use	No therapy at all	26	52.0	25	50.0	0.734
<3 weeks in total	20	40.0	17	34.0		
3 to 6 weeks in total	4	8.0	6	12.0		
6 to 8 weeks in total	0	0.0	1	2.0		
>8 weeks	0	0.0	1	2.0		
Th systemic corticosteroid use	No therapy	37	74.0	24	48.0	**0.026**
<3 days	10	20.0	21	42.0		
4-10 days	3	6.0	3	6.0		
>11 days	0	0.0	2	4.0		
Hospitalization	None	40	80.0	34	68.0	0.224
Only once	10	20.0	14	28.0		
More than once	0	0.0	2	4.0		
Allergen exposure	Never, does not recall	50	100.0	10	20.0	<0.001
Periodically	0	0.0	26	52.0		
On a daily basis	0	0.0	14	28.0		
Irritant exposure	Sometimes	42	84.0	37	74.0	0.344
Often	7	14.0	9	18.0		
On a daily basis	1	2.0	4	8.0		
Glove use	Regularly	7	14.0	9	18.0	0.126
Periodically	33	66.0	38	76.0		
Never	10	20.0	3	6.0		
Limitations to performing everyday tasks	It does not bother me because they rarely occur	14	28.0	2	4.0	**<0.001**
It bothers me because skin lesions of the hand are occasionally visible	23	46.0	22	44.0		
It bothers me because there are often visible changes on the skin, and there is often itching, burning, and pain	9	18.0	22	44.0		
It bothers me a lot because changes are almost always visible, and I can hardly perform daily tasks	4	8.0	4	8.0		
Disease severity	Less severe	22	44.0	9	18.0	**<0.001**
Medium severe	28	56.0	28	56.0		
Severe-	0	0.0	13	26.0		

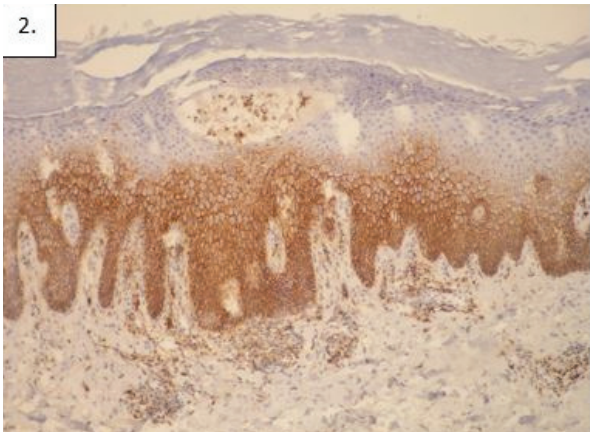

Figure 2. CD44 expression in the epidermal basal and spinous layers and on dermal lymphocytes and stroma in a lesion of irritant contact dermatitis (magnification ×400).

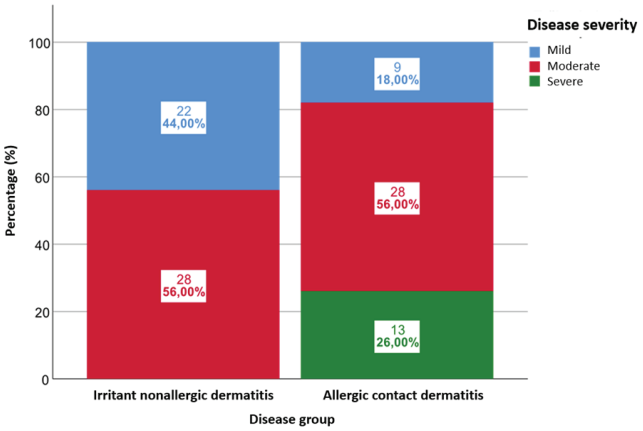

Figure 3. CD44 expression in the epidermal basal layer and a part of the spinous layer, and on dermal lymphocytes in an allergic contact dermatitis lesion of (magnification ×200).

expression could be a useful marker of disease inflammation, which is supported by the high expression demonstrated in ICD and ACD lesions. Nevertheless, new results from this latest study show CD44 expression is not an indicator of disease prognosis/outcome. Thus, we can assume that this marker primarily acts as a marker for acute disease, though some other studies have shown it can also play a prominent role as a marker for the chronic form (12,13,20). Although we did not analyze how expression of CD44 changes over time (no new biopsy/immunohistochemistry was performed after one year), such information could be useful for future research on the course of ACD/ICD. Therefore, we can conclude that lesion persistence and severity depend not only on the initial inflammatory status or local immune milieu (assessed by CD44 levels), but primarily on the duration of allergen/irritant exposure in the period preceding the baseline reading/expression and during patient follow-up, i.e., that it seems more likely that skin exposure is the key factor. Additionally, the analysis of other cell markers, such as hyaluronic acid (hyaluronan, or HA) together with CD44 would be useful in further research.

Various studies have been conducted on different groups with hand CD and eczema with varying results (24-29). According to a recent German study on patients with chronic hand eczema that looked at disease outcomes (physician-assessed and patient-reported) with up to 5 years of follow-up, 5.4% of patients had changed or quit their job due to their disease (24). Chronic hand eczema lesions lasted 6.1 years on average, but severe disease forms were not common (22.4% of patients) and systemic treatment (alitretinoin, acitretin, and methotrexate) was

Table 4. A comparison of CD44 expression in the epidermis, dermis, and on lymphocytes in patients with ICD by disease severity (Fisher-Freeman-Halton exact test)

		Disease severity: groups						*P*
		MILD		MODERATE		SEVERE		
		N	%	N	%	N	%	
Epidermal CD44	No reaction	0	0.0	1	3.6	0	0.0	0.457
	1-33% of cells positive	7	31.8	6	21.4	0	0.0	
	33-66% of cells positive	8	36.4	15	53.6	0	0.0	
	> 66% of cells positive	7	31.8	6	21.4	0	0.0	
Dermal CD44	No reaction	8	36.4	13	46.4	0	0.0	0.673
	1-33% of cells positive	9	40.9	11	39.3	0	0.0	
	33-66% of cells positive	5	22.7	4	14.3	0	0.0	
	> 66% of cells positive	0	0.0	0	0.0	0	0.0	
CD44 on lymphocytes	No reaction	5	22.7	5	17.9	0	0.0	0.813
	1-33% of cells positive	13	59.1	16	57.1	0	0.0	
	33-66% of cells positive	4	18.2	7	25.0	0	0.0	
	> 66% of cells positive	0	0.0	0	0.0	0	0.0	

Table 5. A comparison of CD44 expression in the epidermis, dermis, and on lymphocytes in patients with ACD by disease severity (Fisher-Freeman-Halton exact test)

		Disease severity						*P*
		MILD		MODERATE		SEVERE		
		N	%	N	%	N	%	
Epidermal CD44	No reaction	0	0.0	0	0.0	0	0.0	0.761
	1-33% of cells positive	3	33.3	9	32.1	5	38.5	
	33-66% of cells positive	5	55.6	18	64.3	8	61.5	
	> 66% of cells positive	1	11.1	1	3.6	0	0.0	
Dermal CD44	No reaction	3	33.3	4	14.3	3	23.1	0.653
	1-33% of cells positive	6	66.7	23	82.1	9	69.2	
	33-66% of cells positive	0	0.0	1	3.6	1	7.7	
	> 66% of cells positive	0	0.0	0	0.0	0	0.0	
CD44 on lymphocytes	No reaction	2	22.2	5	17.9	4	30.8	0.403
	1-33% of cells positive	7	77.8	23	82.1	8	61.5	
	33-66% of cells positive	0	0.0	0	0.0	1	7.7	
	> 66% of cells positive	0	0.0	0	0.0	0	0.0	

prescribed at least once for 39.0% of patients during follow-up (24). According to another study, patients who received systemic treatment had significantly higher "global satisfaction" and treatment adherence compared with those who used only topical therapy (27). A recent Italian study on patients with chronic hand CD saw disease severity decrease and quality of life (QL) increase over two years, though 20% of patients still had moderate to severe disease at their 2-year follow-up (25). This study noted that a more difficult clinical course and decreased QL were observed in men and were related to contact allergens (ACD), frequent exposure to environmental factors, occupational skin diseases, a chronic disease course, widespread lesions, and lesions on the palms (13). One multicenter study on hand CD severity showed more severe disease severity in men even though patient QL did not differ significantly by gender, meaning that QL in women was more easily affected (28). Additionally, disease severity significantly positively correlated with patient age (28). Furthermore, QL had a pronounced adverse effect on these patients and negatively correlated with the severity of the disease. According to previous research data, place of residence is also related to CD occurrence: the worse forms of occupational hand CD were more common in non-metropolitan areas, while the more negative impacts on health-related quality of life (HR-QoL) were observed in metropolitan areas (26). According to a recent study on patients with hand eczema, the highest impact on patient HRQoL (greater decreases in HRQoL) was found in women, in those with more severe hand eczema, and those with lower treatment satisfaction (27).

Table 6. Correlation between lesional CD44 expression in the epidermis, dermis, and on lymphocytes in patients with ICD and ACD and ICD and ACD severity (Spearman's correlation coefficients).

		ICD	ACD
		Disease Severity	Disease Severity
Epidermal CD44	Correlation coefficient	0.021	-0.192
	P value	0.885	0.182
	N	50	50
Dermal CD44	Correlation coefficient	-0.067	0.032
	P value	0.642	0.825
	N	50	50
CD44 on lymphocytes	Correlation coefficient	0.048	0.030
	P value	0.742	0.835
	N	50	50

The more severe ACD seen in our patients was caused by the long duration of lesions and greater exposure to allergens and resulted in greater total area of affected skin, more frequent systemic corticosteroid usage, and more severe limitations in performing daily tasks. These factors could have also affected one another, leading to the greater disease severity and limitations. The patients with ACD may have also had difficulties avoiding the ubiquitous

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allergens in everyday life or might have taken less care in avoiding the confirmed allergens, thus advancing the spread of lesions, extending lesion duration, and increasing the need for systemic corticosteroids. Still, it is very important for patients to try to consistently avoid allergens which are known to cause reactions, especially in cases of occupational CD (30,31). Furthermore, the relevance of positive patch tests results needs to be based on long-term patient monitoring during avoidance of an offending allergen.

According to certain previous studies, some subjects with hand CD did not take any allergy tests despite the observed chronic lesions (26,28,29). Unfortunately, in another study on subjects with occupational ACD (Danish study), some patients could not even remember to which allergens they had tested positive when asked at a two-year follow-up after patch testing (32). Thus, testing and other appropriate measures, including skin protection (hand washing, glove use), should be promoted to prevent disease, decrease the severity of skin lesions, and improve patient disease outcomes (7).

Concerning frequent hand CD occurrence, patients should be aware that the skin of the hand requires special care and protection (meaning protective clothing must be introduced along with work-related and treatment measures according to the patient's clinical picture/condition) (29,30). According to our previous study results on the habits of healthcare workers with CD and eczema, good habits are related to gender, since women used protective hand cream more often than men (97% vs. 73%) (29). According to our study on healthcare workers with CD, many (45%) had not even visited a dermatovenerologist but had employed self-treatment (29). The patients were sometimes unaware of the need to protect their skin with creams and soaps for sensitive skin. Thus, the importance of protecting the epidermal barrier with creams should continually be emphasized to patients, especially for ICD lesions, as this may even prevent the onset of the disease. Regular daily skin care for patients is important and can include various therapeutic options based on a diagnosis, clinical severity, and the individuals themselves (7,29,31).

Another important dimension of severe chronic hand CD is its negative impact on the socioeconomic status of patients (10). With regard to data on the economic burden, the average cost to the patient of severe chronic hand CD was 418.3 EUR per month (10). This figure includes costs incurred by productivity loss (43.7% of total cost), hospitalization (16.1%), and increased travel (10.3%). The most frequent consequences of CD observed in these patients were the loss of QL and productivity (10). Since CD can be a major problem for people in the workforce (absence from work or the need for job change), appropriate preventive measures are crucial to increase productivity and opportunities (33,34). Furthermore, patient education and adequate and timely testing for allergies are very important factors for the course of the disease. Public preventive and educative skin care programs and measures are especially useful, including individual counseling, particularly for patients with contact allergies (ACD), with the aim of preventing hand CD.

To our knowledge, this the first study that has examined the relationship between lesional CD44 expression and ICD/ACD severity with a longer patient follow-up. One limitation of this study, however, is that the patch testing set included only limited number of allergens, meaning that a negative patch test was not an absolute exclusion of a contact sensitization/allergy (i.e., there could have been a missed allergen in the set). All of this could have influenced our final results. In addition, we did not use the Hand Eczema Severity Index (HECSI), which could have been a useful additional parameter. We also did not take into account other additional factors, as other baseline clinical data was not presented and compared with patient follow-up results. Additionally, detailed data on exposure and therapy was not included when looking for a correlation between CD44 expression and ICD/ACD severity and characteristics. Although an association was not demonstrated by our study, useful clinical patient data on CD features were obtained.

CONCLUSION

ACD and ICD pose a continuous scientific challenge for researchers because of how common they are and due to the consequent high socioeconomic and healthcare burden on both the patients and the system. Although lesional CD44 did not correlate with clinical characteristics of patients with ICD and ACD in our study, useful clinical data was obtained concerning disease severity, treatments, affected skin, exposure to allergens, and impairment of everyday activities. Thus, the role of CD44 should be further studied to advance therapeutic options in order to achieve better disease management and improved quality of life.

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