

# Immunoexpression of IgA receptors (CD89, CD71) in dermatitis herpetiformis

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## Abstract

**Introduction.** The role of IgA receptors in dermatitis herpetiformis (DH) pathogenesis is still unknown. CD89 and CD71 may be associated with immune response during DH development. The purpose of this study was to perform semiquantitative analysis of simultaneous immunoexpression of CD89 and CD71 in DH and IgA/neutrophil-mediated non-DH dermatoses (IgAN) in relation to specific IgA autoantibodies/antibodies (tissue and epidermal transglutaminases, nonapeptides of gliadin — eTG/tTG/npG) as well neutrophil activation *via* the release of neutrophil elastase (NE).

**Material and methods.** In total, 48 patients were studied. The study was conducted on skin lesions and sera obtained from DH and IgAN patients. DH and IgAN served as mutually positive control groups. We used immunohistochemical technique with semiquantitative digital morphometry and ELISA to measure serum levels of anti-eTG/tTG/npG IgA.

**Results.** CD89 showed a significantly higher expression in DH than in IgAN. CD71 was overexpressed in DH and IgAN. CD89 immunoexpression correlated negatively with CD71 in IgAN. A positive correlation was revealed between CD89 immunoexpression and anti-npG IgA in DH. No statistically significant correlations were found in DH between the CD89/CD71 and NE immunoexpression, between CD71 immunoexpression and anti-tTG/eTG/npG IgA, or between CD89 immunoexpression and anti-eTG/tTG IgA serum levels.

**Conclusions.** CD89 is probably a key IgA Fc receptor in DH development, where it is associated with immune response to gluten. CD71 may be linked with inflammation in DH and IgAN. We suggest that interaction between CD89 and CD71 can modulate the inflammation in IgAN. (*Folia Histochemica et Cytobiologica* 2017, Vol. 55, No. 4, 212–220)

**Key words:** dermatitis herpetiformis; IgAN; Fc-alpha receptor; CD71; CD89; IHC

## Introduction

Dermatitis herpetiformis (DH) belongs to IgA-mediated autoimmune blistering dermatoses. Its etiology

is multifactorial and still equivocal with involvement of both genetic (HLA DQ2/DQ8 haplotypes) and environmental factors (gluten intake). Autoimmunity as well as inflammation/autoinflammation seem to be involved in DH progression [1] since a typical DH patient presents circulating IgA autoantibodies/antibodies against transglutaminases (mainly epidermal — eTG; tissue — tTG) and nonapeptides of gliadin (npG) coupled with rich neutrophilic infiltration within the dermal papillae. Activated neutrophils may release specific proteolytic enzyme (neutrophil elastase, NE) implicated in the destruction of

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dermal-epidermal junction (DEJ) with the cleavage within lamina lucida [2].

Direct immunofluorescence of perilesional skin revealed pronounced IgA deposits [3, 4], which may take various patterns (fine-granular, fibrillar, in dermal papillae, along the DEJ, a combination of all the above). These deposits are polyclonal, mainly composed of IgA1 [5].

Hendrix *et al.* [6] were the first to show the link between IgA deposition and recruitment of neutrophils in DH and IgA/neutrophil-mediated non-DH dermatoses (IgAN). This study also indicated immune adherence with Fc receptors engagement as the main mechanism of the proposed interaction [6].

Patients with DH have an associated gluten-sensitive enteropathy that is most often asymptomatic [7]. However, the development of skin eruption as well as cutaneous IgA deposits may be reduced by adhering to gluten-free diet.

IgAN are pathogenically closely related to DH sharing specific features of skin pathophysiology as they exhibit prominent infiltration of neutrophils and/or deposition of IgA. IgAN represent a heterogeneous group of autoimmune/inflammatory entities including linear IgA bullous dermatosis, IgA pemphigus, epidermolysis bullosa acquisita and subcorneal pustular dermatosis.

The formation of IgA (IgA1) deposits containing immunocomplexes forms a part of not yet fully elucidated DH pathogenesis. Although the factors that lead to the accumulation of neutrophils in the skin are not known, some key molecular factors contributing to the formation of immunocomplexes and neutrophilic microabscesses have been proposed. The involvement of human IgA Fc receptors, which may be associated with neutrophil activation, production of autoantibodies as well as gluten transport and/or transformation has been suggested in DH. There are several known receptors for IgA in humans (e.g. polymeric Ig receptor, Fc-alpha/microR, CD89, CD71, mannose receptor) [8] differing in ligand preference and response to IgA binding.

CD89 (Fc-alphaRI) is a transmembrane glycoprotein expressed mainly on the surface of cells of the myeloid origin binding both IgA1 and IgA2 [9]. CD89 shows abundant expression on human neutrophils [10, 11] and mediates inflammatory responses to IgA-immunocomplexes [8]. CD71, the transferrin receptor (TfR), is ubiquitously expressed at low levels on normal cells and is expressed at greater levels on cells with a high proliferation rate such as cells of the basal epidermis and intestinal epithelium [12], binding preferentially to polymeric IgA1 [8, 13]. The data about the expression of transferrin receptor on

neutrophils is contradictory; however, specific binding sites for Tf on the neutrophilic membranes was reported [14].

Some researchers showed that CD89 and CD71 were implicated in the pathogenesis of diseases with aberrant IgA synthesis and/or neutrophil tissue damage (IgA nephropathy, celiac disease — CD, rheumatoid arthritis, systemic lupus erythematosus), where functional abnormalities of CD89 and CD71 underlie their onset [8, 14–16]. There are data indicating that the formation of IgA-CD89 may lead to stimulation of CD71 expression [13, 17]. However, no attempts have been made to determine simultaneous expression of CD71 and CD89 in DH patients. Therefore, in the present study we have investigated the cutaneous immunoreexpression of CD89 in concert with CD71 and their relationship with the expression of neutrophil elastase as well as levels of IgA autoantibodies/antibodies against eTG, tTG, npG in the peripheral blood of DH and IgAN patients.

## Material and methods

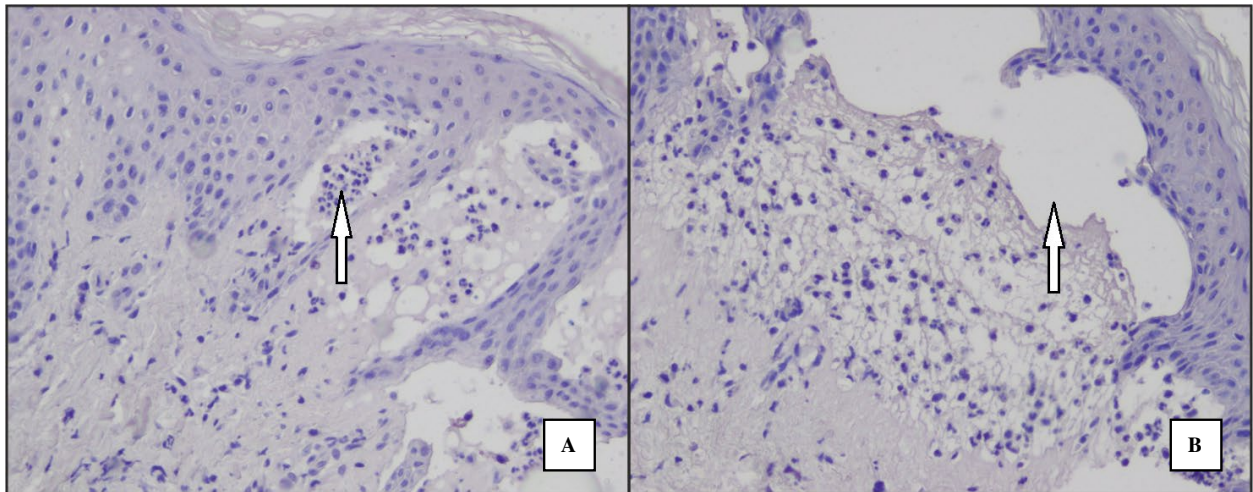
This study was conducted after obtaining the local ethical committee approval (Poznan University of Medical Sciences, 953/14, Poznań, Poland, 2014).

**Patients and sample collection.** Altogether, clinical material from 48 patients with autoimmune blistering dermatoses before initiation of treatments was obtained. The examined material consisted of lesional skin tissues and sera from the examined groups. Samples were obtained from 33 patients with DH with active skin rash and 15 IgAN patients as a positive control group pathogenetically closely related to DH due to ‘neutrophilic endotype’ and/or IgA autoantibodies production (involved 9 cases of linear IgA bullous dermatosis, 2 cases of IgA pemphigus, 3 cases of epidermolysis bullosa acquisita and 1 case of subcorneal pustular dermatosis). The DH and IgAN group served as mutual control groups.

To distinguish from DH and establish the diagnoses of IgAN, direct immunofluorescence and hematoxylin and eosin (H&E) stainings were also done.

Patients were diagnosed and treated as well as samples were collected at the Department of Dermatology, Poznan University of Medical Sciences, Poland. The diagnosis of DH in all DH subjects was established according to: (i) positive DIF of perilesional skin (cutaneous IgA deposition in any of seven possible diagnostic patterns), (ii) histological features of DH (H&E staining), (iii) detection of appropriate autoantibodies.

Paraffin-embedded skin tissue 4  $\mu$ m-thick sections were mounted on poly-L-lysine coated glass slides. The serum used in the serological tests was taken at the time



**Figure 1.** Negative immunocontrols by omission of the primary antibody (antibodies against either human CD89, CD71 or NE were replaced with PBS) for DH patient showing *microabscesses* of neutrophils at the tips of dermal papillae (arrow) with subepidermal cleaves above (A) and for IgAN (a patient with linear IgA bullous dermatosis) showing subepidermal blister (arrow) filled with neutrophils within and below the blister cavity (B). Abbreviations: DH — dermatitis herpetiformis; IgAN — IgA/neutrophil-mediated non-DH dermatoses. Original magnification 200 $\times$ .

of hospital admission/ambulatory care. Only patients, in whom both tissue sections of an adequate quality for processing and serum samples were available for investigation with IHC and ELISA, were subjected to correlation studies.

The NE expression was analyzed in the same patients as CD89 and CD71 expression. However, the group of patients with NE analysis was slightly greater because it was a subject of our previous analyses [18–20] which we broadened here with the detection of IgA Fc receptors.

**Validation of IgA Fc receptors by immunohistochemistry.** Immunohistochemical (IHC) staining with polyclonal rabbit antibodies against human CD89 (anti-CD89, Acris Antibodies GmbH, Herford, Germany), monoclonal murine antibodies against human CD71 (TFRC, Transferrin R antibody, Novus Biologicals, Littleton, CO, USA), monoclonal murine antibodies against human NE (clone NP57Dako, Glostrup, Denmark) and Real EnVision detection kit (Dako) were applied according to previously described procedures [19, 21]. All antibodies were diluted 1:100 in Antibody Diluent (Dako). The tests were conducted according to the classical Peroxidase-DAB staining as described in detail in our recent study [21].

IgA receptor staining was done after heat-induced epitope retrieval in an antigen retrieval solution, high pH (Dako). NE staining followed enzymatic digestion of sections with proteinase K (Dako).

Internal negative IHC procedure control reactions were based on substituting primary antibodies with phosphate-buffered saline (Fig. 1).

**Evaluation of the results and microscopy image analysis.** The slides were examined by light microscopy (BX40,

Olympus, Tokyo, Japan) connected to a digital camera and the images were recorded and archived. The images with positive IHC reaction were subjected to semiquantitative morphometric analysis using “HSV Filter” software originally developed in the Department of Bioinformatics and Computational Biology, Poznan University of Medical Sciences, Poland [21–23].

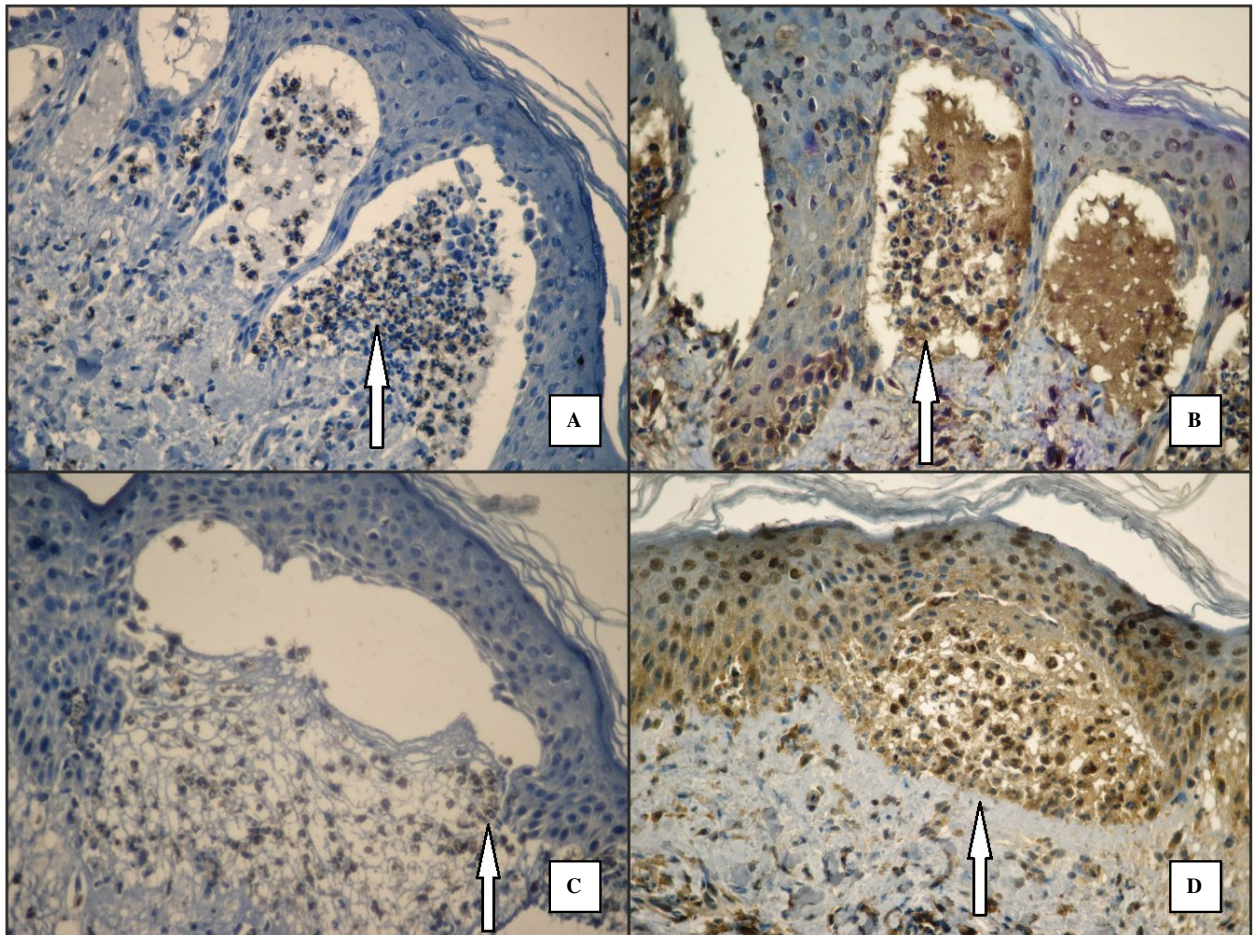
We measured the area of IHC reaction and calculated the staining intensity according to the following formula: (area of positive IHC reaction/area studied)  $\times$  100% [21–23]. Then, the mean value was calculated for every patient and each studied groups (DH, IgAN).

**Immunoenzymatic assay.** The concentrations of specific circulating serum autoantibodies were detected with commercially available ELISA tests. ELISAs were performed using the Euroimmun (Luebeck, Germany) kits to detect IgA autoantibodies/antibodies against (i) the fusion protein containing nonapeptides of gliadin (Antigliadin GAF-3X IgA ELISA), (ii) tTG (Anti-tTG IgA ELISA). The manufacturer-defined cut-off level was 25 RU/ml and 20 RU/ml, respectively. The level of circulating serum IgA autoantibodies against eTG was detected with Anti-eTG ELISA (Immundiagnostik AG, Bensheim, Germany) with the manufacturer’s cut-off value was 18 AU/ml.

All measurements were made in ELISA plate reader (Expert 96, Asys Hitech GmbH, Eugendorf, Austria) equipped with Microwin 2000 software by a single operator following the manufacturer’s instructions.

**Statistical analysis.** Significant differences in expression intensities of CD89/CD71/NE tissue expression were done using Wilcoxon signed rank test (comparison within examined group) and Mann-Whitney test (comparison





**Figure 2.** The cellular localization of CD89 (A, C) and CD71 (B, D) immunoreactivity in a representative DH patient (A and B) as well as IgAN patient (C and D). Areas showing the most intense immunoreactivity are marked with arrows. Abbreviations as in the description of Figure 1. Original magnification 400 $\times$ .

between examined groups) with a significance level of  $p < 0.05$ . Correlations were calculated using Spearman's rank correlation coefficient. Statistical analyses were performed using statistical analysis software Statistica PL 10.0 (StatSoft, Cracow, Poland).

## Results

### *Immunoreactivity of CD89 and CD71 in cutaneous lesions of DH and IgAN patients*

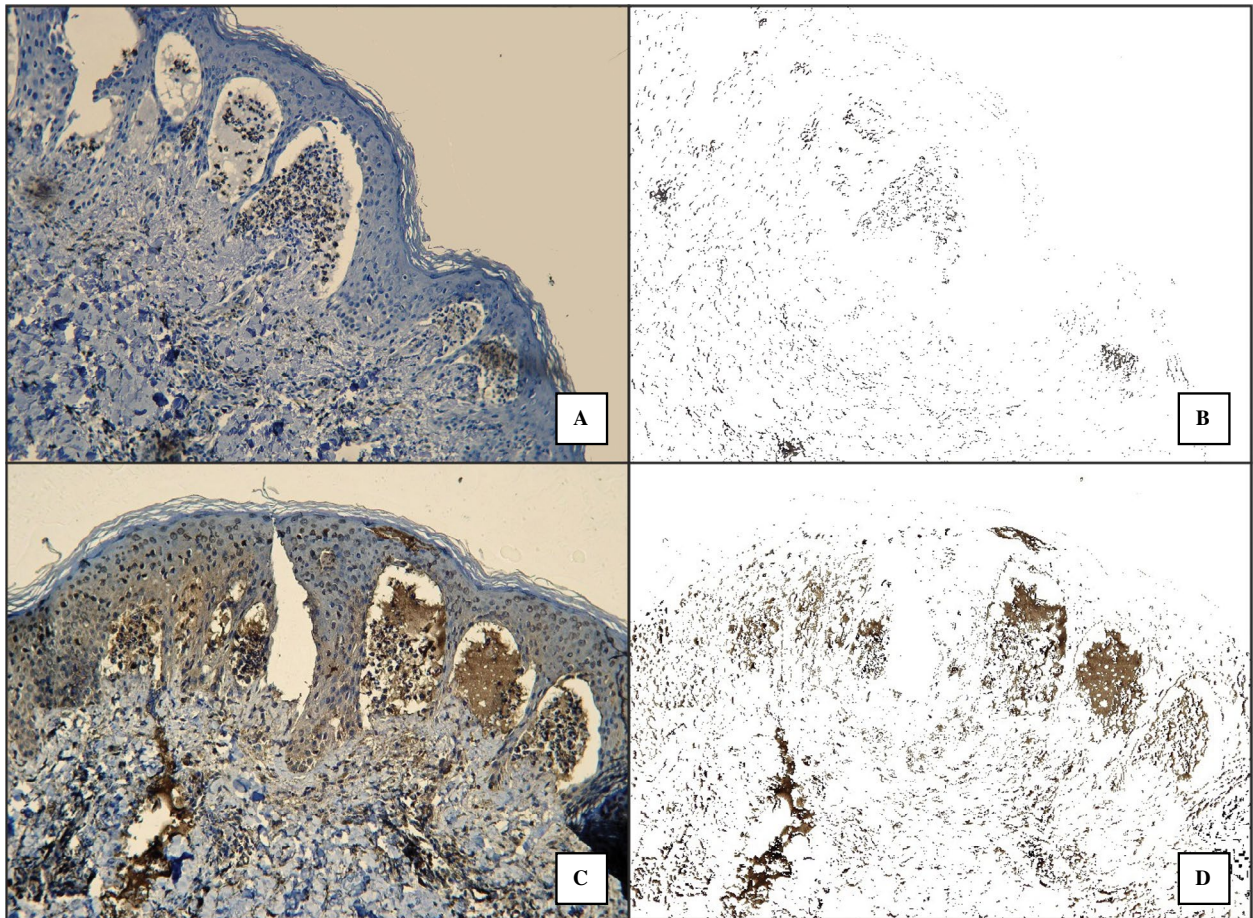
The results of CD89 and CD71 expression analysis in representative DH and IgAN patients are shown on Figures 2, 3 and 4.

The tissue localization of CD89 in the DH involved mostly cell nucleus and membranes of neutrophils within microabscesses at papillary tips (Fig. 2A and 3A, B). CD89 expression in IgAN was poorly accentuated (Fig. 2C and 4A, B). CD71 immunoreactivity in DH and IgAN was observed frequently in the cytoplasm of neutrophils forming inflammatory infiltrates,

however, the intensity of the reaction was irregular (Fig. 2B, D; 3C, D; 4C, D).

Semiquantitative results of CD89, CD71 and NE immunoreactivity in the examined groups were presented in Table 1. The intensity of cutaneous CD89 expression, detected in neutrophil-rich inflammatory infiltrates at the tips of dermal papillae in DH as well as within and below the blister cavity in linear IgA bullous dermatitis, was significantly increased in DH compared to IgAN ( $p = 0.0432$ , Mann-Whitney test). No difference in the cutaneous immunoreactivity of CD71 between examined groups was found. The intensity of CD71 immunoreactivity was significantly higher as compared with CD89 both in DH ( $p = 0.007$ , Wilcoxon test) and IgAN ( $p = 0.0008$ , Wilcoxon test). Significantly lower NE than CD71 immunoreactivity ( $p = 0.0251$ , Wilcoxon test) and slightly higher NE than CD89 immunoreactivity ( $p = 0.0469$ , Wilcoxon test) were observed in DH.





**Figure 3.** CD89 (A) and CD71 (C) immunoreactivity in lesional skin in a representative patient with DH who had serum level of anti-tTG IgA > 200 RU/ml as determined by ELISA. The intensity of CD89 (B) and CD71 (D) immunoreactivity was processed with digital microscopic image analysis as described in Methods. Abbreviations as in the description of Figure 1, tTG — tissue transglutaminase. Original magnification 200 $\times$ .

No correlation between cutaneous CD89/CD71 and NE expression was found in DH. The moderate negative correlation between cutaneous CD89 immunoreactivity and cutaneous CD71 immunoreactivity in IgAN group ( $r = -0.539$ , Spearman's rank coefficient) was observed.

No immunoreactivity was found when control staining procedure was applied (Fig. 1).

#### ***Evaluation of IgA FcRs in relation to the presence of autoantibodies/antibodies in serum***

Detailed analysis of anti-npG, anti-tTG, anti-eTG IgA levels obtained with ELISA tests in DH and IgAN is presented in Table 2. A positive relationship between CD89 expression intensities and the serum level of anti-npG IgA ( $r = 0.664$ , Spearman's rank coefficient) was revealed in DH. No correlations were observed between CD89 expression and anti-eTG, as well as anti-tTG IgA serum levels in DH. There was no correlation between the intensity of cutaneous CD71

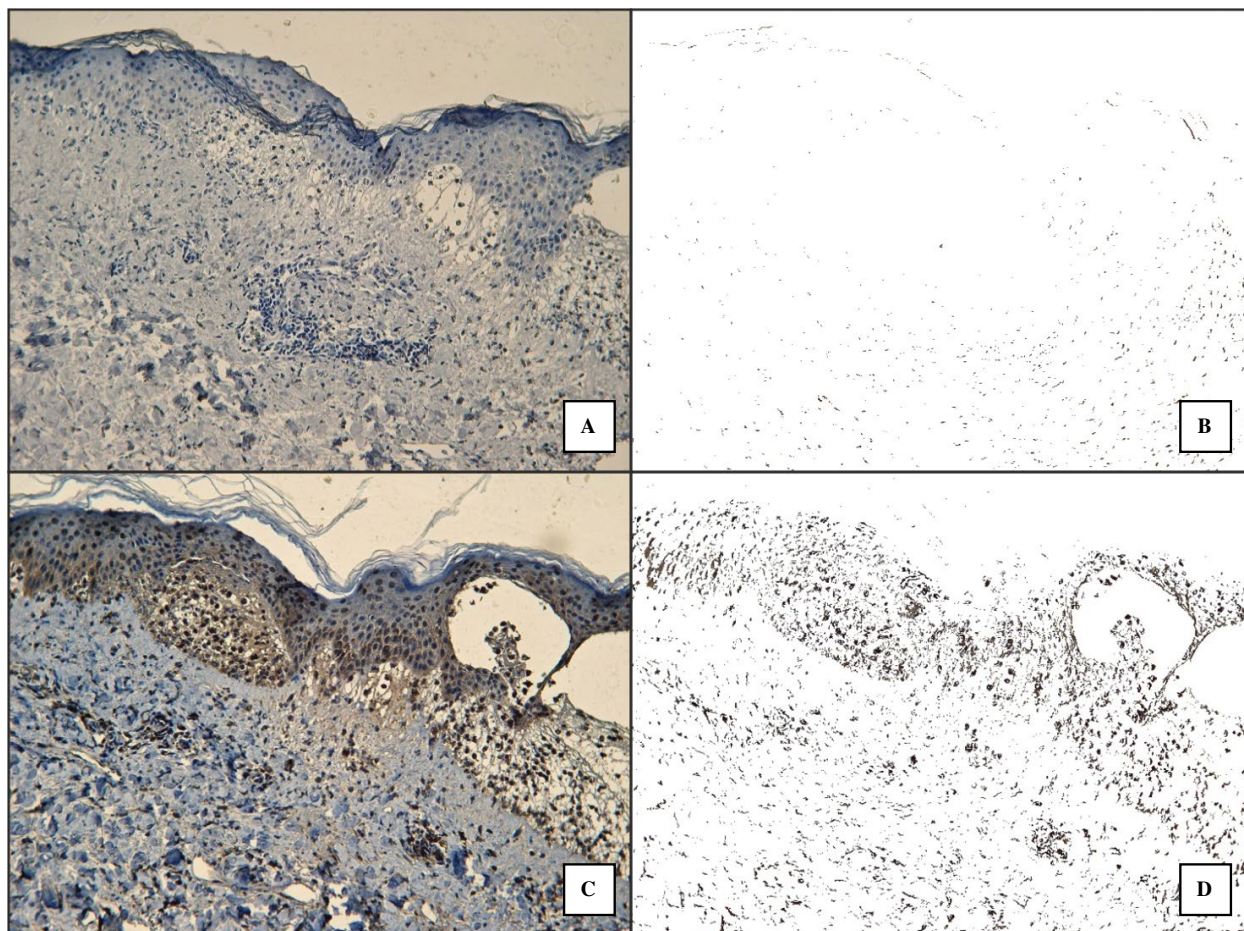
expression and anti-npG, anti-tTG, anti-eTG IgA level in DH. All values of Spearman's rank coefficient between CD89/CD71 expression and IgA autoantibodies/antibodies levels in DH are presented in Table 3.

No correlations were observed between the intensity of cutaneous CD89/CD71 expression and anti-npG ( $r = 0.173$  and  $r = 0.018$ , respectively), anti-tTG ( $r = 0.018$  in both cases) IgA level in IgAN.

#### **Discussion**

The major finding of the present study is that cutaneous immunoreactivity of CD89 was significantly increased in patients with active DH compared with subjects with IgAN. Thus, it seems that CD89 may be associated with the remodeling of dermal-epidermal junction in DH. Nonetheless, additional multicenter study should be required to confirm the statistical data indicating the role of Fc receptors in DH with the use of larger number of untreated DH patients. It should





**Figure 4.** CD89 (A) and CD71 (C) deposits detected by immunohistochemistry in lesional skin in representative patients with IgAN. The intensity of CD89 (B) and CD71 (D) immunoreactivity was processed with digital microscopic image analysis as described in Methods. Abbreviations as in the description of Figure 1. Original magnification 200×.

**Table 1.** Semiquantitative assessment of immunoexpression of CD89, CD71 and NE in dermatitis herpetiformis (DH), and CD89 and CD71 IgA/neutrophil-mediated non-DH dermatoses (IgAN)

Variable	Group	Patients' number	Mean ± SD (%)	Median (%)	Min. (%)	Max. (%)
CD89	DH	19	1.73 ± 1.87	1.19	0.00	8.81
	IgAN	15	0.87 ± 0.51	0.76	0.17	1.76
CD71	DH	17	8.10 ± 4.44	6.17	3.03	19.72
	IgAN	15	12.78 ± 9.45	12.57	1.25	29.60
NE	DH	24	3.46 ± 2.31	3.10	0.00	7.97

Skin samples were stained by immunohistochemistry and the percentage of the area of immunoreaction in the analyzed skin lesions was determined as described in Methods. NS — statistically non-significant.

be noted that DH is a relatively rare skin disorder [24]. Smith *et al.* [7] found no difference in CD89 expression between active, ongoing DH, inactive DH and normal subjects, whereas active DH patients showed enhanced function of CD89 compared with inactive DH and healthy population. It may be postulated that ligand binding to CD89 is regulated via inside-out

signaling — thus cytokine stimulation of cells may modulate binding capacity in response to intracellular signals without affecting receptor expression levels [7]. It has been speculated that CD89 may become primed — as a result of cytokines' production — but surface receptor expression is not highly augmented [7]. Our results demonstrating no relationship between cutane-

**Table 2.** Analysis of the results obtained with ELISA tests in dermatitis herpetiformis (DH) and IgA/neutrophil-mediated non-DH dermatoses (IgAN)

Variable	Group	Patients' number	Mean $\pm$ SD [U/ml]	Median [U/ml]	Min. [U/ml]	Max. [U/ml]
Anti-npG IgA	DH	25	175.05 $\pm$ 185.38	107.55	6.67	644.11
	IgAN	11	3.25 $\pm$ 6.24	0.47	0	16.13
Anti-tTG IgA	DH	33	373.00 $\pm$ 436.15	200.00	4.08	1270.92
	IgAN	11	4.97 $\pm$ 3.40	3.99	1.39	11.48
Anti-eTG IgA	DH	25	14.46 $\pm$ 8.55	13.85	2.37	34.02

Abbreviations: eTG — epidermal transglutaminase; tTG — tissue transglutaminase; npG — nonapeptides of gliadin.

**Table 3.** Values of Spearman's rank coefficient between expression of CD89, CD71 (% immunoreactive area per area of examined skin lesion) and levels of IgA autoantibodies/antibodies to eTG, tTG, npG in DH

Parameter	CD89	CD71
Anti-eTG IgA	0.464	0.300
Anti-tTG IgA	0.359	0.196
Anti-npG IgA	0.664	0.217

Abbreviations: eTG — epidermal transglutaminase; tTG — tissue transglutaminase; npG — nonapeptides of gliadin.

ous CD89 and NE expression are consistent with this thesis. Thus, possibly, CD89 is not directly involved in the activation of neutrophils through their locally enhanced expression in DH.

Our immunophenotypic characteristics of inflammatory cells within cutaneous eruption in DH and IgAN showed enhanced expression of CD71 in both groups of patients. However, the findings demonstrated different cellular localization of the IgA receptors as CD71 immunoreactivity was observed in the cytoplasm and CD89 immunoreactivity was associated with neutrophils. Previous data [25–28] indicated that CD71 is likely to be the most highly expressed as an early precursor with decreasing expression in maturing forms of the examined cells since strong and diffuse cytoplasmic staining for CD71, similarly as in neoplastic cells [28] and erythroid precursors [27], was reported. This may suggest that the overexpression of this protein concurs with the increased expression of its cognate receptor.

It has been suggested that IgA/IgA1 binding to CD71 can circumvent the barrier effect of IgA and promote the entrance of immunogenic peptides into the subepithelial tissue. This effect depends on the upregulation of CD71 [29]. It has been also suggested that IgA/IgA1 bound to CD71 may trigger the activation of local memory CD4+ T cells and thus perpetuate inflammation [30]. Therefore, it cannot be

excluded that the overexpression of CD71, induced in various pathologies, such as anemia or intestinal infections [30], in conjunction with other unknown factors, might trigger the initial events inducing DH lesions in susceptible subjects. Heyman *et al.* [30] showed that protected transport of gliadin peptides occurs in active celiac disease patients *via* a CD71-mediated transcytosis of IgA/gliadin peptide immune complexes. Thus, perhaps, CD71 may be associated with gliadin transport in a similar way in DH.

Interestingly, a significant positive correlation between cutaneous CD89 expression and anti-npG IgA was confirmed here, supporting our previous thesis that CD89 may be associated with gluten intolerance in DH rather than with enzyme-driven DEJ remodeling [20]. On the other hand, some researchers demonstrated the association between CD71 and tTG in CD and IgA nephropathy [31, 32], but our results do not confirm this interaction in DH. Our results about gliadin-CD89 relationship may be in line with certain data on IgA nephropathy. It is known that the chronic inflammation in patients with gluten intolerance may perpetuate the risk of kidney diseases [31]. Wijarnprecha *et al.* [31] found that the risk of kidney diseases was significantly higher among patients with CD. It is postulated that gluten may exacerbate IgA nephropathy *via* gliadin-CD89 interaction. Data regarding CD71 and gluten hypersensitivity indicated that transferrin receptor is overexpressed in patients with CD [31], which was consistent with our findings in DH patients. CD89 seems not to be related with CD71 in DH development. Nonetheless, a negative relationship between CD89 and CD71 was found in IgAN. Thus, the inhibitory interaction of these receptors may be associated with the inflammation process in these dermatoses.

Our findings may help to understand the pathophysiological mechanism involving IgA Fc receptors related to the formation of neutrophilic microabscesses and IgA/IgA1 deposition in DH suggesting CD89 as an important marker for DH, where it is associated with immune response to gluten.

Our work was limited by the relatively small number of DH patients. It was difficult to collect samples from patients with active and untreated DH for epidemiologic reasons and due to the monocenter nature of this study.

This study corroborates the findings of our previous work [19] indicating that there is no close relationship between the activation of neutrophils migrating to the skin and production of IgA autoantibodies to tTG/eTG sharing immunogenic epitopes in DH.

In conclusion, we suggest that CD89 seems to be a key receptor required for DH development acting as neutrophil function modulator. CD71 might be associated with inflammation both in DH and IgAN, probably due to the loss of protective function of IgA. CD71 and CD89 receptors can interact with each other to regulate the inflammation process in IgAN. CD89 seems to be related with gluten induced immune response in DH. Cutaneous CD71 expression is not linked with IgA anti-tTG/eTG/npG autoantibodies/antibodies production in DH as well as IgAN.

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