



Granular IgA Deposits in the Skin of Patients with Coeliac Disease: Is it Always Dermatitis Herpetiformis?

Veronica BONCIOLINI¹, Emiliano ANTIGA¹, Beatrice BIANCHI¹, Elena DEL BIANCO¹, Alessandra NINCI¹, Vincenza MAIO², Nicola PIMPINELLI¹ and Marzia CAPRONI¹

Department of Surgery and Translational Medicine, ¹Section of Dermatology, and ²Section of Pathological Anatomy, University of Florence, Florence, Italy

Coeliac disease is an immune-mediated enteropathy driven by gluten, which can be associated with dermatitis herpetiformis. The presence of granular IgA deposits, detected by direct immunofluorescence, is the hallmark of dermatitis herpetiformis; nevertheless, IgA deposits have also been demonstrated in healthy skin of patients with coeliac disease. The main objective of this study was to investigate whether IgA deposits could be found in the skin of patients with coeliac disease who have non-dermatitis herpetiformis inflammatory skin diseases. Direct immunofluorescence was performed on perilesional skin biopsies of 6 patients with coeliac disease with non-dermatitis herpetiformis inflammatory skin diseases and, as control, on 12 non-coeliac patients with inflammatory skin diseases. IgA deposits were found in all of the patients with coeliac disease, but were absent in the control group. In conclusion, IgA deposits may be considered an immunopathological marker for coeliac disease; therefore, patients with coeliac disease showing skin manifestations with positive direct immunofluorescence should be investigated carefully in order to make a differential diagnosis between dermatitis herpetiformis and other non-dermatitis herpetiformis inflammatory skin diseases.

Key words: coeliac disease; skin IgA deposits; skin manifestations of coeliac disease.

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Corr: Veronica Bonciolini, Department of Surgery and Translational Medicine, Section of Dermatology, University of Florence, Viale Michelangiolo, 41, IT-50129 Florence, Italy. E-mail: vbonciolini@gmail.com

Coeliac disease (CD) can be defined as an autoimmune disorder where the ingestion of wheat gliadins and other cereal prolamins leads to damage in the small intestine in genetically susceptible individuals (1). The pathogenetic mechanism is related to a T-cell response against an external trigger, the gluten peptides, and to the ubiquitous enzyme tissue transglutaminase, which, as autoantigen (2), enhances the immunogenicity of gluten peptides (3–5).

Several extraintestinal manifestations of CD affect different organs and systems; among them, many mucocutaneous diseases have been described (6). In particular, dermatitis herpetiformis (DH) is considered to be a speci-

SIGNIFICANCE

Coeliac disease is a chronic enteropathy characterized by a permanent intolerance to gluten that is frequently associated with several extraintestinal conditions, including skin diseases. Dermatitis herpetiformis is the specific cutaneous manifestation of coeliac disease; however, many other dermatoses are reported in celiac patients. The immunopathologic hallmark of dermatitis herpetiformis is the presence of IgA deposits at the dermal–epidermal junction of perilesional skin as detected by direct immunofluorescence. Our study showed that such deposits can be found also in celiac patients with inflammatory skin diseases different from dermatitis herpetiformis and, therefore, could be considered as a marker of coeliac disease.

fic cutaneous manifestation of CD, although several other inflammatory skin diseases have been shown to be more frequent in patients with CD, including psoriasis, atopic dermatitis, alopecia areata, chronic urticaria, chronic ulcerative stomatitis, etc. (6).

The presence of granular IgA deposits along the basement membrane, with accentuation at the tips of the dermal papillae, seen on direct immunofluorescence (DIF) of uninvolved skin, is the pathognomonic immunological marker of DH (7–11). Despite minor and not-critical differences in the pattern, in the localization and in the composition of the immune deposits, due to its high specificity, this finding represents the gold standard for diagnosis of DH.

In 2007, Cannistraci et al. (12) also showed the presence of granular IgA deposits in the healthy skin of patients with CD, who were not affected by any skin diseases, suggesting that such deposits could be considered not only a marker of DH, but, more generally, of CD. Thus, the main objective of this study was to investigate whether IgA deposits can be found not only in the healthy skin of patients with CD, but also in non-DH inflammatory skin diseases of such patients.

METHODS

Study design

In order to assess whether IgA deposits could be found in patients with CD who have non-DH inflammatory skin diseases, a comparative prospective study was conducted on patients with

CD presenting to the immunodermatology outpatient clinic of our hospital.

As control, 12 non-coeliac patients with inflammatory skin diseases were enrolled. The study was approved by the local institutional review board and was conducted according to the principles of the Declaration of Helsinki. All patients and controls provided written informed consent to participate in the study.

Patients

Patients included into the study were divided into 2 groups: (i) patients with CD who had non-DH inflammatory skin diseases ($n=6$) (mean age 41 years; median age 41.5 years: male (M): female (F)=0:6; F=100%; mean duration of skin disease: 5 years), including eczema ($n=2$), atopic dermatitis, pityriasis rosea Gibert, granuloma annulare and lichenoid dermatitis; and (ii) non-coeliac patients with non-DH inflammatory skin diseases ($n=12$) as control group (mean age 34.8 years; median age 35.5 years; M:F=2:10; F=83.3%; mean duration of skin disease: 2.7 years), including 5 patients with psoriasis, 4 with eczema, 2 with vasculitis and 1 with nodular prurigo (Table I). All the inflammatory skin diseases were diagnosed based on clinical, histopathological and laboratory findings to exclude atypical variants of DH.

All the patients were screened for CD at the Department of Gastroenterology at the University of Florence by antibody assay (anti-endomysial and IgG and IgA anti-tissue transglutaminase (TG) antibodies) and multiple duodenal biopsies, expressed according to Marsh's classification (5) modified by Oberhuber (13). The most important findings of the enrolled patients in the groups described above are summarized in Table I. None of the

patients with CD were on a gluten-free diet at the time of sample collection.

After an accurate whole-body clinical examination and characterization of the skin manifestations presented by all enrolled patients in order to exclude any sign of DH, they underwent a cutaneous biopsy on perilesional skin to perform DIF, and lesional punch biopsy for histological examination to confirm the diagnosis of the skin disease and to exclude with certainty the diagnosis of DH.

Direct immunofluorescence

Skin samples were collected from all the patients and controls and immediately frozen at -80°C in liquid nitrogen. The frozen specimens were cut into $5\text{-}\mu\text{m}$ thick sections and 2 sections were layered on each slide. The slides were stored at -20°C until they were stained. For staining, sections were brought to room temperature. Optimally diluted fluorescein isothiocyanate (FITC)-labelled monospecific immunoglobulins (IgG, IgA, IgM, C3; DAKO, Copenhagen, Denmark) were layered onto the sections and incubated at 24°C for 30 min. Then, the sections were washed in phosphate-buffered saline (PBS) (pH 7.2, 0.1 M) twice and mounted in buffered glycerin and, finally, viewed under a Nikon C2 confocal microscope. The following features were documented: (i) composition of the immune deposits: IgG, IgA, IgM, C3; (ii) site of the immune deposits: dermal-epidermal junction (DEJ), intercellular spaces (ICS) or perivascular area; (iii) semiquantitative grading of intensity of the fluorescence: from 0 (no intensity) to +++ (highest intensity); (iv) pattern of the immune deposits: granular, linear or mixed (granular/linear).

Table I. Results of the enrolled patients: personal data, gastrointestinal disease and clinical, histological and immunopathological features of the skin involvement

Pat. No.	Sex/age, years	Skin disease	Histological features	DIF features		Duration of skin disease	Coeliac disease	Marsh grading	Serological assay	
				DEJ	PV				AEA	TgA (U/ml)
1	F/58	Eczema	Epidermis: hyp, aca, spo ede, lym	Dermis: IgA, IgM, C3	IgA, IgM	3 years	Yes	IIIb	++	IgA: 30 IgG: 25
2	F/26	Atopic dermatitis	Epidermis: hyp, aca, spo ede, lym	Dermis: IgA, IgM, C3	IgA, IgM, C3	23 years	Yes	IIIa	++	IgA: 28 IgG: 24
3	F/42	Pityriasis rosea Gibert	Epidermis: hyp, aca, spo ede, lym	Dermis: IgA, C3		1 month	Yes	IIIc	+++	IgA: 91 IgG: 75
4	F/41	Granuloma annulare	Epidermis: hyp, aca, spo ede, lym, mucin deposition	Dermis: IgA, IgM, C3	IgA, IgM, C3	1 year	Yes	IIIa	++	IgA: 23 IgG: 31
5	F/37	Eczema	Epidermis: hyp, aca, spo ede, lym	Dermis: IgA, C3		1 year	Yes	IIIa	+	IgA: 33 IgG: 16
6	F/42	Lichenoid dermatitis	DEJ: Infi; Kcyt	Dermis: IgA, IgM, C3	IgA, C3	2 years	Yes	IIIb	++	IgA: 61 IgG: 54
7	F/40	Eczema	Epidermis: hyp, aca, spo ede, lym	Dermis: IgM	C3	2 years	No	0	Absent	Absent
8	M/50	Psoriasis	Epidermis: hypP, aca, hypG Dermis: ede; torV; lym			5 years	No	0	Absent	Absent
9	F/39	Eczema	Epidermis: hyp, aca, spo ede, lym	Dermis: IgM, C3		1 year	No	0	Absent	Absent
10	M/28	Eczema	Epidermis: hyp, aca, spo ede, lym	Dermis: C3		1 year	No	0	Absent	Absent
11	F/37	Psoriasis	Epidermis: hypP, aca, hypG Dermis: ede; torV; lym	Dermis: C3, IgG	IgG, IgM	1 year	No	0	Absent	Absent
12	F/30	Psoriasis	Epidermis: hypP, aca, hypG Dermis: ede; torV; lym	Dermis: IgM, C3	IgM	4 years	No	0	Absent	Absent
13	F/21	Psoriasis	Epidermis: hypP, aca, hypG Dermis: ede; torV; lym	Dermis: IgM, C3		2 years	No	0	Absent	Absent
14	F/23	Psoriasis	Epidermis: hypP, aca, hypG Dermis: ede; torV; lym	Dermis: C3, C3		3 years	No	0	Absent	Absent
15	F/34	Vasculitis	Dermis: swelling EC, FD; Neu	Dermis: IgM, C3		1 year	No	0	Absent	Absent
16	F/25	Eczema	Epidermis: hyp, aca, spo ede, lym	Dermis: IgM, C3		2 years	No	0	Absent	Absent
17	F/41	Vasculitis	Dermis: swelling EC, FD; Neu	Dermis: C3		1 year	No	0	Absent	Absent
18	F/50	Nodular prurigo	Epidermis: hyp, aca			1 year	No	0	Absent	Absent

DIF: direct immunofluorescence; DEJ: dermal-epidermal junction; PV: perivascular; AEA: anti-endomysial antibodies; tTgA: anti-tissue transglutaminase antibodies; hyp: hyperorthokeratosis; aca: acanthosis; spo: spongiosis; ede: oedema; lym: lymphocytes infiltrate; Infi: inflammatory infiltrate; Kcyt: keratinocytes cytolysis; hypP: hyperorthoparakeratosis; hypG: hypogranulosis; torV: tortuous vessel; EC: endothelial cells; FD: fibrin deposits; Neu: neutrophils infiltrate; TgA: transglutaminase.

Confocal microscopy

Approximately 10- μ m serial sections of fresh frozen skin biopsies from 4 out of 6 patients with CD with non-DH-inflammatory dermatoses were investigated for IgA and epidermal TG (eTG), as described previously (14). Frozen sections were fixed with ice-cold acetone then blocked with 0.25% casein in Tris-buffered saline (TBS; 0.88% NaCl, ThermoFisher, 0.24% tris(hydroxymethyl)aminomethane, and distilled water). FITC-labelled antibodies against human IgA1 (Abcam, Cambridge, UK) and unlabelled mouse anti-human epidermal transglutaminase primary antibodies (Zedira, Darmstadt, Germany) were prepared in TBS containing 1% FCS and incubated on sections for 1 h at room temperature. Secondary rabbit antibodies against mouse isotypes IgG2b AlexaFluor 555 (Molecular Probes, Eugene, OR, USA) at 1:200 were prepared and incubated on sections for 1 h. Sections were visualized with a Nikon C2 confocal microscope.

RESULTS

Patients with coeliac disease who have non-dermatitis herpetiformis inflammatory skin diseases

All of the patients in group (i) (patients with CD who had non-DH inflammatory skin diseases), who presented to our department due to the occurrence of an inflammatory skin disease, had newly diagnosed CD confirmed by the gastroenterologist after our consultation. Detailed clinical, histological and immunopathological skin features are shown in Table I and **Figs 1–3**.

None of the patients in this group had IgG deposits. However, granular IgA deposits along the DEJ were found in 6 out of 6 cases (100%), 1 of which had ac-

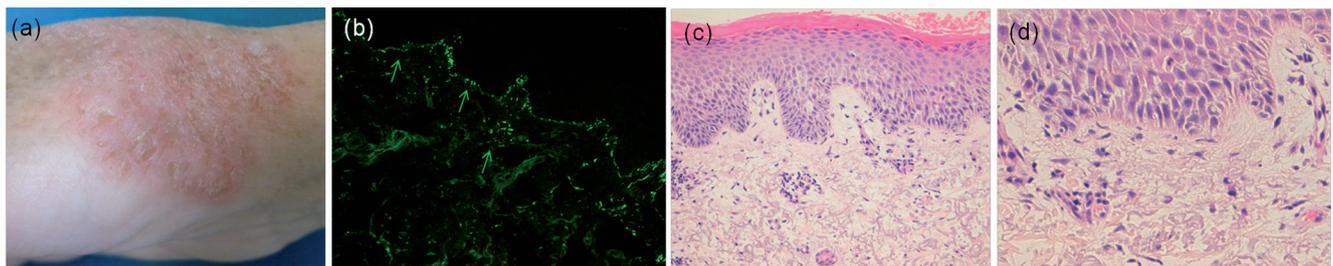


Fig. 1. Patient 1 with eczema. (a) Erythematous lesion with crust on the back of the hand; (b) granular IgA deposits at the dermal-epidermal junction found by direct immunofluorescence of perilesional skin (100 \times); (c-d) Compact orthokeratosis, acanthosis and spongiosis in the epidermis, subepidermal oedema and lymphocytes and histiocytes in the upper dermis (haematoxylin-eosin stain; c 200 \times , d 400 \times).

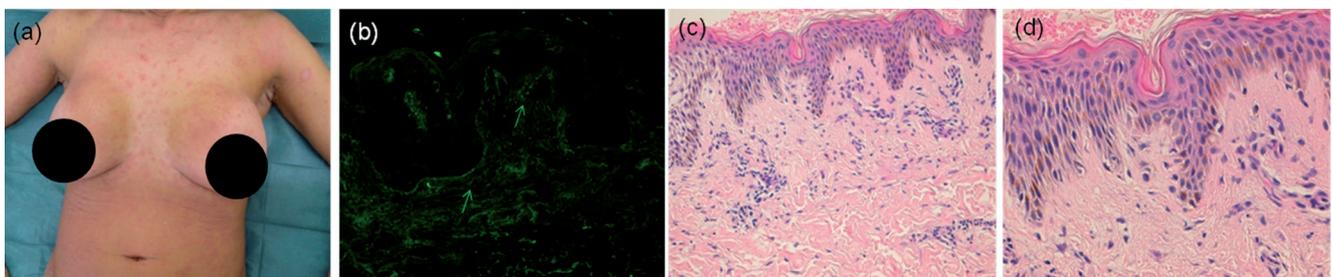


Fig. 2. Patient 3 with pityriasis rosea Gibert. (a) Scaly erythematous papules and plaques with collarette scaling on the trunk, abdomen and upper limbs. The "herald patch" on the left arm. (b) Granular IgA deposits at the dermal-epidermal junction with accentuation at the papillary tips, found by direct immunofluorescence of perilesional skin (400 \times). (c) Hyperorthokeratosis, acanthosis and spongiosis in the epidermis, perivascular lymphocytic and eosinophilic granulocytic infiltrate in the upper dermis. (d) Hyperorthokeratosis, acanthosis and spongiosis in the epidermis. Perivascular lymphocytic infiltrate in the upper dermis (haematoxylin-eosin stain; c 200 \times , d 400 \times).

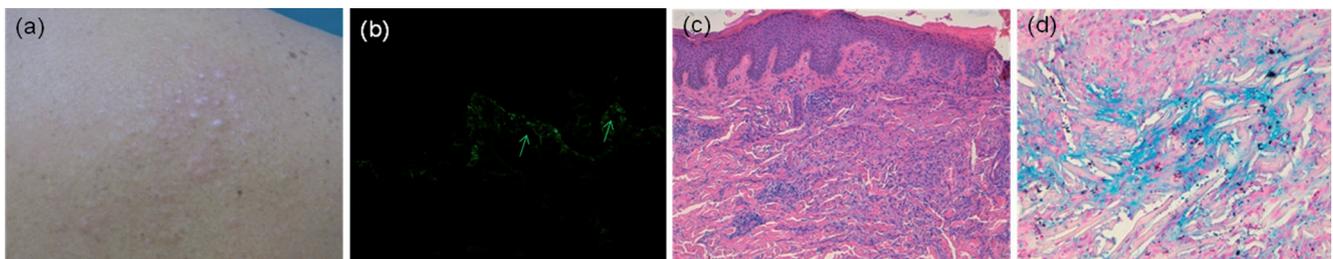


Fig. 3. Patient 4 with granuloma annulare. (a) Grouped pink non-scaly papules with annular disposition on the shoulder. (b) Granular IgA deposits at the dermal-epidermal junction with accentuation at the papillary tips, found by direct immunofluorescence of perilesional skin (400 \times). (c) Compact orthokeratosis and acanthosis in the epidermis, interstitial areas of mucinous degeneration of collagen, lymphocytes and histiocytes in the upper dermis (haematoxylin-eosin stain 100 \times). (d) Mucin deposition is more prominent after staining with Alcian blue (400 \times).

Table II. Direct immunofluorescence features of all enrolled patients

Study group	Immunological deposits							
	Dermal-epidermal junction				Perivascular			
	IgG n (%)	IgA n (%)	IgM n (%)	C3 n (%)	IgG n (%)	IgA n (%)	IgM n (%)	C3 n (%)
Group 1 (n=6)	0 (0)	6 (100)	4 (66.7)	6 (100)	0 (0)	4 (66.7)	3 (50)	3 (50)
Group 2 (n=12)	0 (0)	0 (0)	2 (16.7)	5 (41.7)	1 (8.3)	0 (0)	4 (33.3)	5 (41.7)

centration at the papillary tips; moreover perivascular IgA deposits were found in 4 of the patients (66.7%).

Four out of 6 patients (66.7%) had granular IgM deposits along the DEJ, one of them showing accentuation of the deposits at the papillary tips in a DH-like pattern, while perivascular IgM deposits were found in 3 of the cases (50%).

Moreover, granular C3 deposits along the DEJ were found in all 6 cases (100%), with accentuation at the papillary tips in one of them, while perivascular C3 deposits were documented in only 3 patients (50%) (Table II).

Double-staining for the detection of both IgA and eTG was performed in 4 out of 6 patients with CD with non-DH-inflammatory dermatoses, using confocal microscopy. None of these patients presented eTG deposits at the dermal papillae; thus, co-localization between IgA and eTG could not be detected within the dermis of the skin specimens (Fig. 4).

Non-coeliac patients with inflammatory skin diseases

Detailed clinical, histological and immunopathological skin features of non-coeliac patients with inflammatory skin diseases are summarized in Table I. None of the patients in this group showed IgG deposits along the DEJ, while perivascular IgG deposits were present in only one patient (8.3%).

Moreover, none of the patients showed IgA deposits at the DEJ or in the perivascular areas. In contrast, granular IgM deposits along the DEJ were found in 2 out of 12 cases (16.7%) (Fig. 5), none of them showing accentuation at the papillary tips in a DH-like pattern; moreover, perivascular IgM deposits were present in 4 patients (33.3%) (Fig. 5).

Finally, granular C3 deposits along the DEJ could be detected in 5 out of 12 cases (41.7%) (Fig. 5), with no accentuation at the papillary tips, while perivascular C3 deposits were also found in 5 of the 12 cases (41.7%) (Fig. 5, Table II).

DISCUSSION

The most important finding of this study was the presence of IgA deposits at the DEJ in patients with CD with non-DH inflammatory skin diseases.

Granular IgA deposits at the dermal papillae and/or along the DEJ are considered the immunopathological

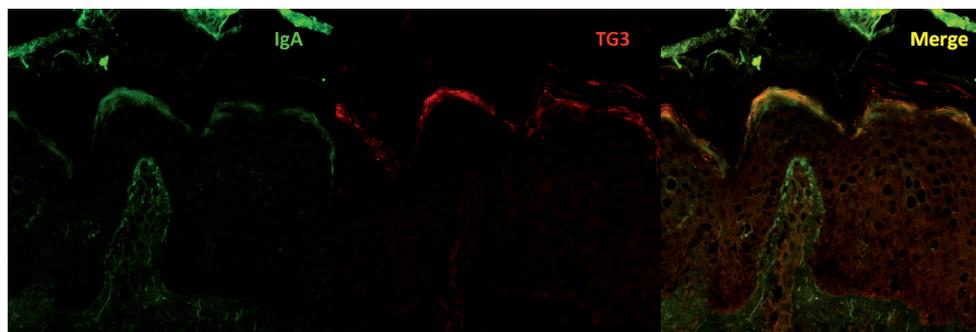


Fig. 4. IgA 1 and anti-transglutaminase 3 staining detected by confocal microscopy in a patient with coeliac disease. Granular IgA deposits were localized at the tips of the dermal papillae; anti-transglutaminase 3 antibodies stained the upper layers of the epidermis, while no transglutaminase 3 deposits could be detected within the dermal papillae. No co-localization was found in the dermis between IgA and transglutaminase 3 (400×).

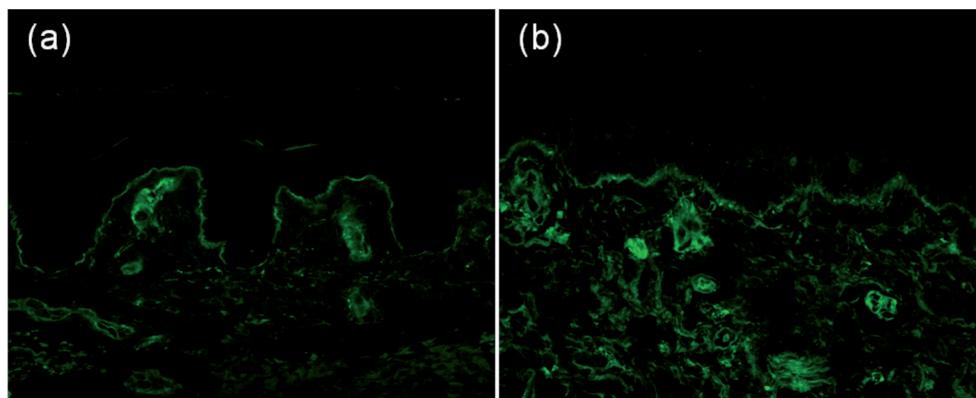


Fig. 5. Direct-immunofluorescence findings in a patient with eczema. (a) Granular C3 deposits at the dermal-epidermal junction found by direct immunofluorescence of perilesional skin (400×). (b) Granular IgM deposits at the dermal-epidermal junction found by direct immunofluorescence of perilesional skin (400×).

hallmark of DH, and are included within the diagnostic criteria of the disease as the gold standard for the diagnosis, due to the high sensitivity and to a specificity close to 100% (15). However, Cannistraci et al. (12) found IgA deposits in 9 patients with CD (6 on a normal diet and 3 on a gluten-free diet) without any cutaneous diseases, including DH.

The current study investigated the perilesional skin of patients with CD with non-DH-inflammatory skin diseases, using DIF, and showed the presence of IgA deposits at the DEJ in all the tested patients. Therefore, IgA deposits might be considered not only as a distinct feature of DH, but, more in general, as an immunopathological marker of CD that could even have a diagnostic role for the disease. Thus, none of the non-coeliac patients in the control group had IgA deposits, confirming the high specificity of such a finding.

The low number of patients included is a major limitation of this study, hindering statistical analysis. However, although further studies should be performed to confirm our hypothesis, our study raised an important point about the differential diagnosis of skin diseases in patients with CD.

As a consequence, several cases of clinically atypical DH reported in the literature that were diagnosed based only on DIF findings should be critically revised. Among them, purpuric and petechial lesions on the palmo-plantar surfaces or the fingertips (16–21), palmoplantar keratosis (22), wheals of chronic urticaria (23) and lesions mimicking prurigo pigmentosa (24) in the absence of clinical and histopathological findings suggestive for DH could be better diagnosed as IgA-positive dermatoses in patients with CD, rather than as true DH.

The current study also raises some questions about the pathogenetic role of IgA deposits in DH. Recently Görög et al. (25), employing a newly developed sandwich enzyme-linked immunoassay (ELISA) on the plasma and serum, demonstrated the presence of circulating IgA-TG3 immunocomplexes in patients with CD who were affected by DH, that disappeared when they adopted a gluten-free diet. Moreover, IgA-containing immunocomplexes were found also in patients with CD without DH (26). In patients with DH, the dermal deposition of these circulating immunocomplexes is thought to trigger chemotaxis and activation of neutrophils, with consequent development of skin lesions.

By contrast, in our case-series as well as in patients with CD without any skin lesions, the amounts of such deposits may be not enough to trigger the inflammatory response. Therefore, other pathogenetic factors may play a role in such a process, such as the deposition of eTG at the dermal papillae, which was not found in our patients.

Regarding the other kind of deposits found at DIF in our investigation, the presence of C3 at the DEJ may be related to the activation of innate immunity. Indeed, recent evidence regarding CD has increasingly shown

the role of innate immunity in triggering the immune response by stimulating the adaptive immune response and by mucosal damage. The interaction between the gut microbiota and the mucosal wall is mediated by the same receptors, which can activate innate immunity. Thus, changes in gut microbiota may lead to activation of this inflammatory pathway (27, 28).

By contrast, IgM or C3 deposits, which were found in some of the patients in the control group, should be considered non-specific, as it is not uncommon to detect these deposits in the skin of patients with inflammatory diseases, such as psoriasis, that may be more evident in sun-exposed areas (29).

In conclusion, this study showed that DH-like IgA deposits in the skin may represent an immunopathological marker of CD, which might play a diagnostic role if confirmed in larger series.

Moreover, this study also raises some questions about the diagnosis of DH, since granular IgA deposits along the DEJ can also be found in perilesional skin of patients with CD with skin diseases different from DH. Thus, the diagnosis of DH should be the result of an overall assessment, including clinical, histological and immunopathological findings. This may be important for the management of the patients; in fact, whilst a gluten-free diet should be used in all patients with CD, a medication such as dapsone would be effective only in patients with DH and, therefore, the need for a correct diagnosis in this setting becomes paramount.

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The authors have no conflicts of interest to declare.

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