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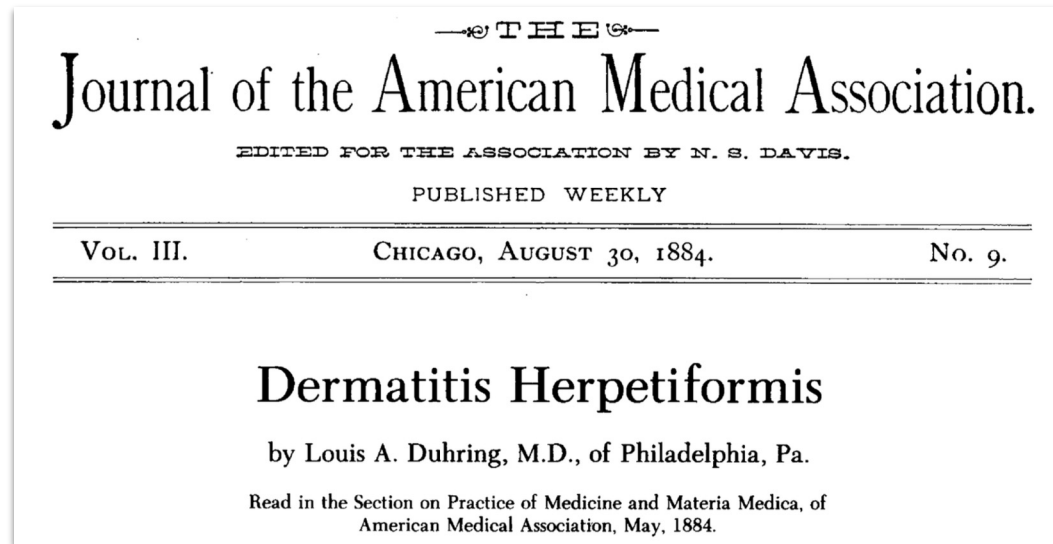


Regione Toscana

DERMATITE ERPETIFORME

Prof.ssa Marzia Caproni

SOS Malattie Rare Dermatologiche, Azienda USL Toscana Centro,
Dipartimento di Scienze della Salute - Università degli Studi di Firenze



- **1884:** Louis A. Duhring sottolinea la somiglianza clinica con infezione erpetica
- **1950:** Pierard descrive istologia tipica
- **1969:** Van Der Meer individua la tipica presentazione all'IFD
- **'60:** correlazione con malattia celiaca
- **2002:** Sardy et al individuano il principale autoantigene nella DH
- Ruolo patogenetico anche dei linfociti T

Epidemiologia: DE Malattia Rara

- Incidenza (EU, USA) 0.4 – 2.6/100.000 persone/anno
- Prevalenza (EU, USA) 11.2 – 75.3/100.000 persone/anno

Malattia molto più rara nella popolazione asiatica (probabilmente per la minore prevalenza di geni HLA predisponenti)

- M:F 3:2
- 30 - 40 anni; possibile sottostima di prevalenza in età pediatrica
- Incidenza di DH in diminuzione

Patogenesi

- Predisposizione genetica: **HLA-DQ2 e DQ8** (85% e 15% dei pazienti)
- Popolazione asiatica: assenza di HLA-DQ2/DQ8, scarsa associazione con CD, coinvolgimento di sede atipiche, deposito fibrillare e non granulare di IgA all'apice delle papille dermiche, scarsa associazione con altre malattie autoimmuni



Dermatitis Herpetiformis: Novel Perspectives

Emiliano Antiga¹, Roberto Maglie^{*1}, Lavinia Quintarelli, Alice Verdelli, Diletta Bonciani, Veronica Bonciolini and Marzia Caproni*

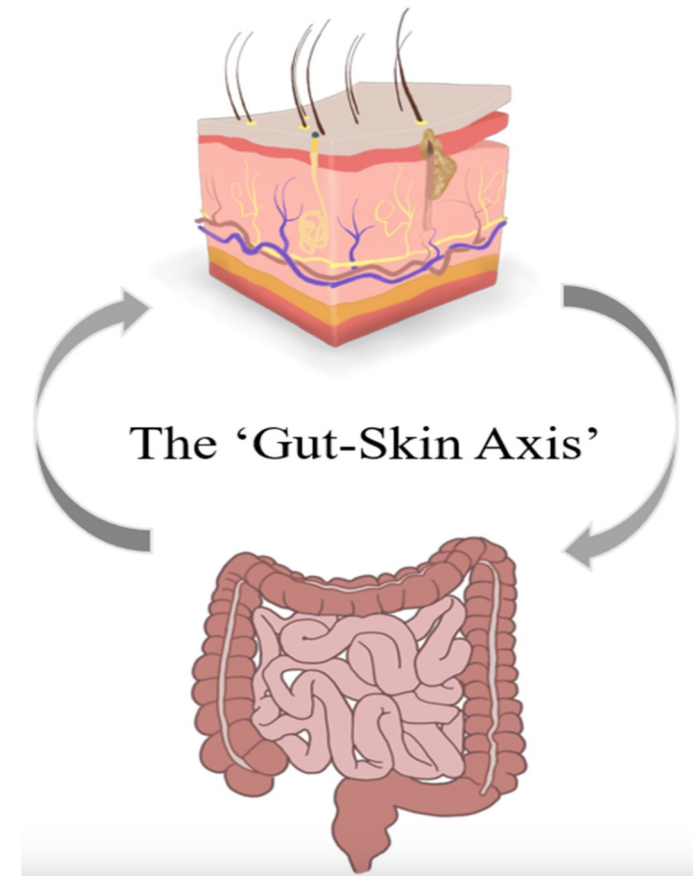
Section of Dermatology, Department of Health Sciences, University of Florence, Florence, Italy

Characteristics	Caucasian DH	Japanese DH
HLA	HLA-DQ2 (DQB1*02:01)—85% HLA-DQ8 (DQB1*03:02)—15%	HLA-DQ2 (DQB1*02:01)—0% HLA-DQ8 (DQB1*03:02)—37%*
Sites of involvement	Elbow, buttock, knee, face, ear, neck, scalp, groin	Elbow, buttock, knee, face, ear, neck, scalp, groin Non-predilection sites, including the extremities and trunk. Whole body
Villous atrophy	Most of the patients	Not known**
Circulating anti-tTG IgA	50–95%	38%
Circulating anti-eTG IgA	50–95%	43%
DIF	Granular IgA deposits	Granular and fibrillar IgA deposits
Response to the GFD	Most of the patients	Lack of consistent data
Association with autoimmune diseases	Frequent	Rare

Patogenesi

- **Fattori scatenanti: GLUTINE**
- **Altri modulatori:**
 - ioduro di potassio (per os o contatto)
 - fattori ormonali (tp progestiniche o l'ormone di rilascio delle gonadotropine GnRH)
 - alcuni farmaci (infliximab, ipilimumab)
 - chirurgia gastrointestinale
 - Infezioni gastrointestinali

- Marakli SS, Uzun S, Ozbek S, Tuncer I. Dermatitis herpetiformis in a patient receiving infliximab for ankylosing spondylitis. Eur J Dermatol. 2008
- Lee HH et al. Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor-alpha antagonists. Br J Dermatol. 2007
- Mochel MC et al. Cutaneous autoimmune effects in the setting of therapeutic immune checkpoint inhibition for metastatic melanoma. J Cutan Pathol. 2016

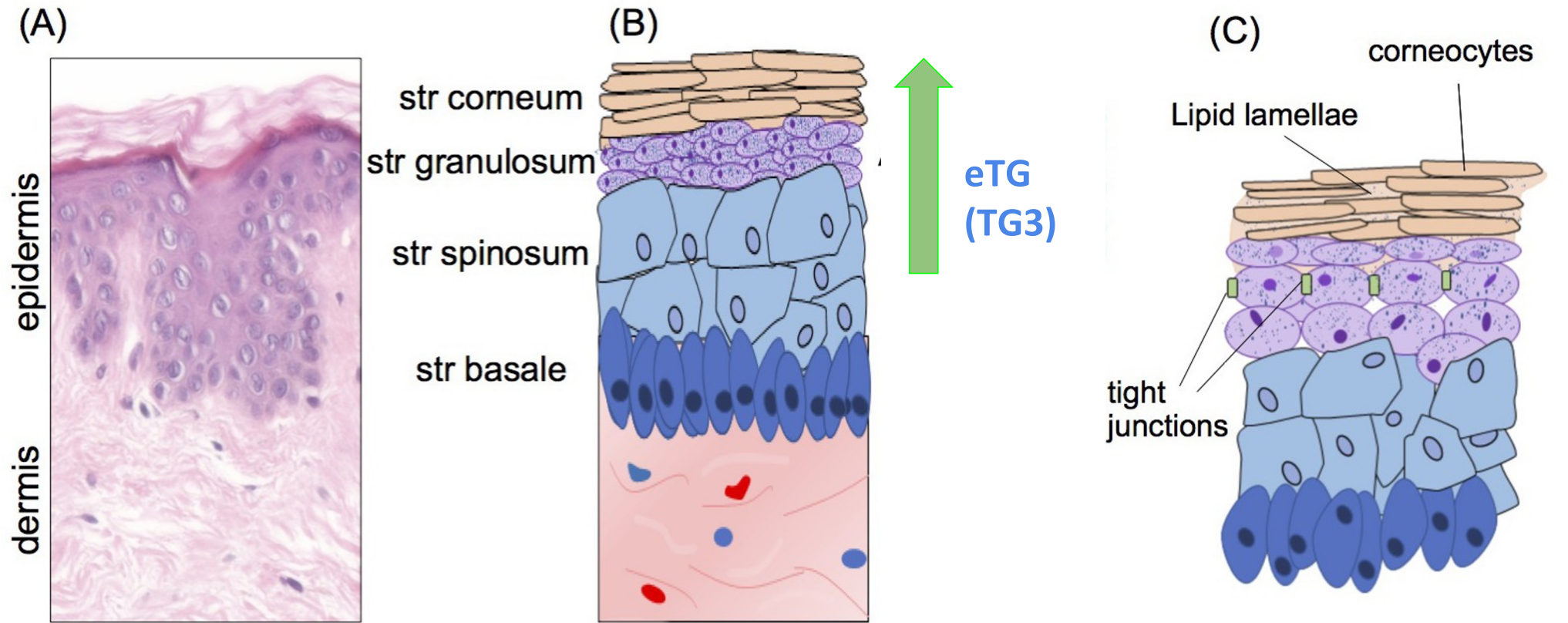


Epidermal Transglutaminase (TGase 3) Is the Autoantigen of Dermatitis Herpetiformis

Miklós Sárdy,¹ Sarolta Kárpáti,¹ Barbara Merkl,² Mats Paulsson,²
and Neil Smyth²

¹*Department of Dermato-Venereology, Semmelweis University, H-1085 Budapest, Hungary*

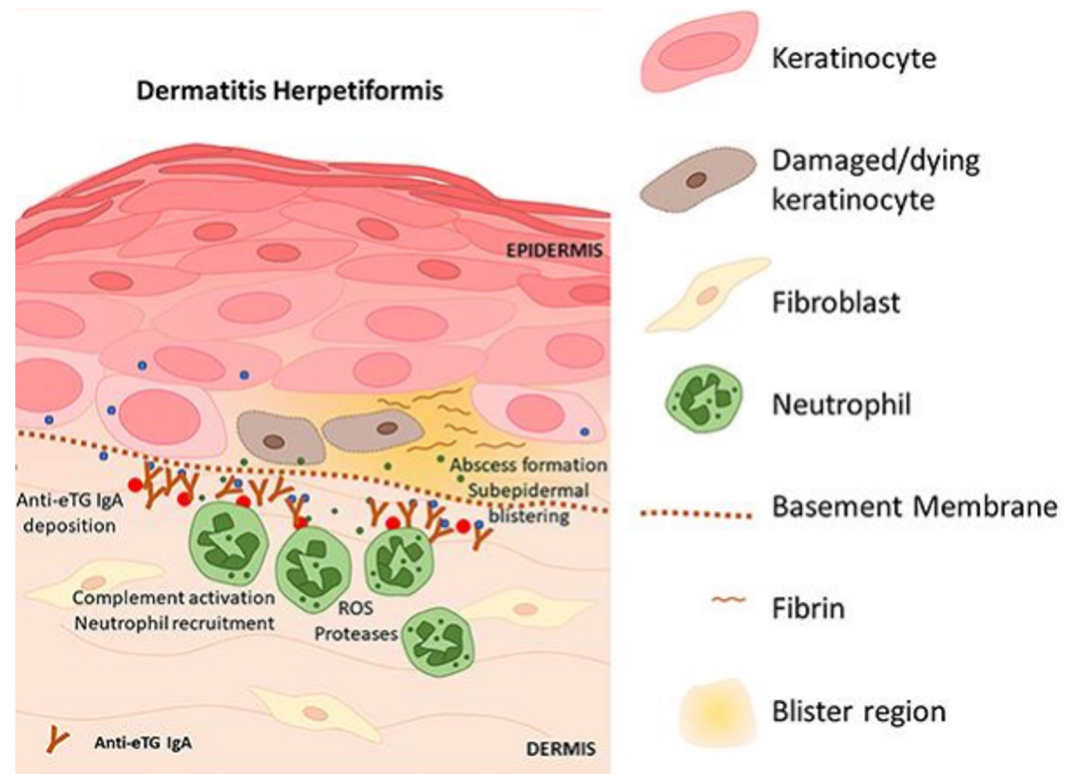
²*Institute for Biochemistry II, Medical Faculty, University of Cologne, D-50931 Cologne, Germany*



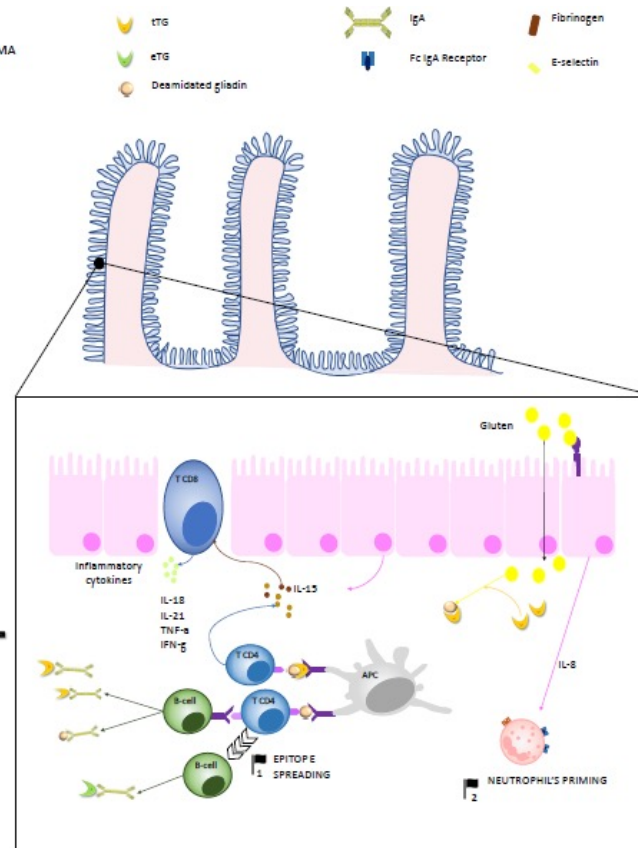
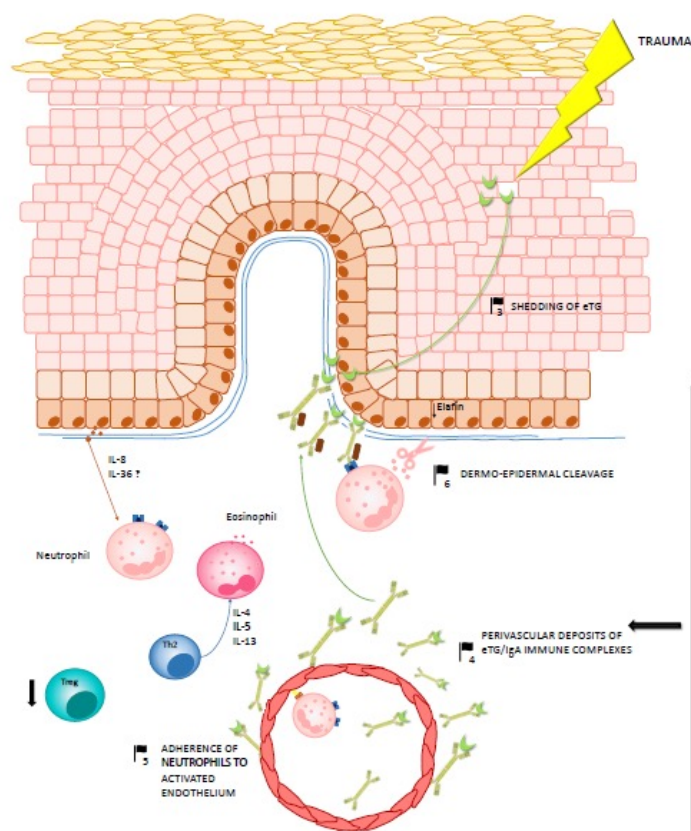
Immunità umorale

Anticorpi IgA anti transglutaminasi epidermica (TG3)

- TG3 si trova principalmente nello strato spinoso e granuloso
- Gli autoAb si formerebbero nell'intestino assieme agli autoanticorpi anti-TG2
- Epitope spreading?



DH: PATHOGENESIS



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HLA + gluten



Gut: eTG-specific B & T cells



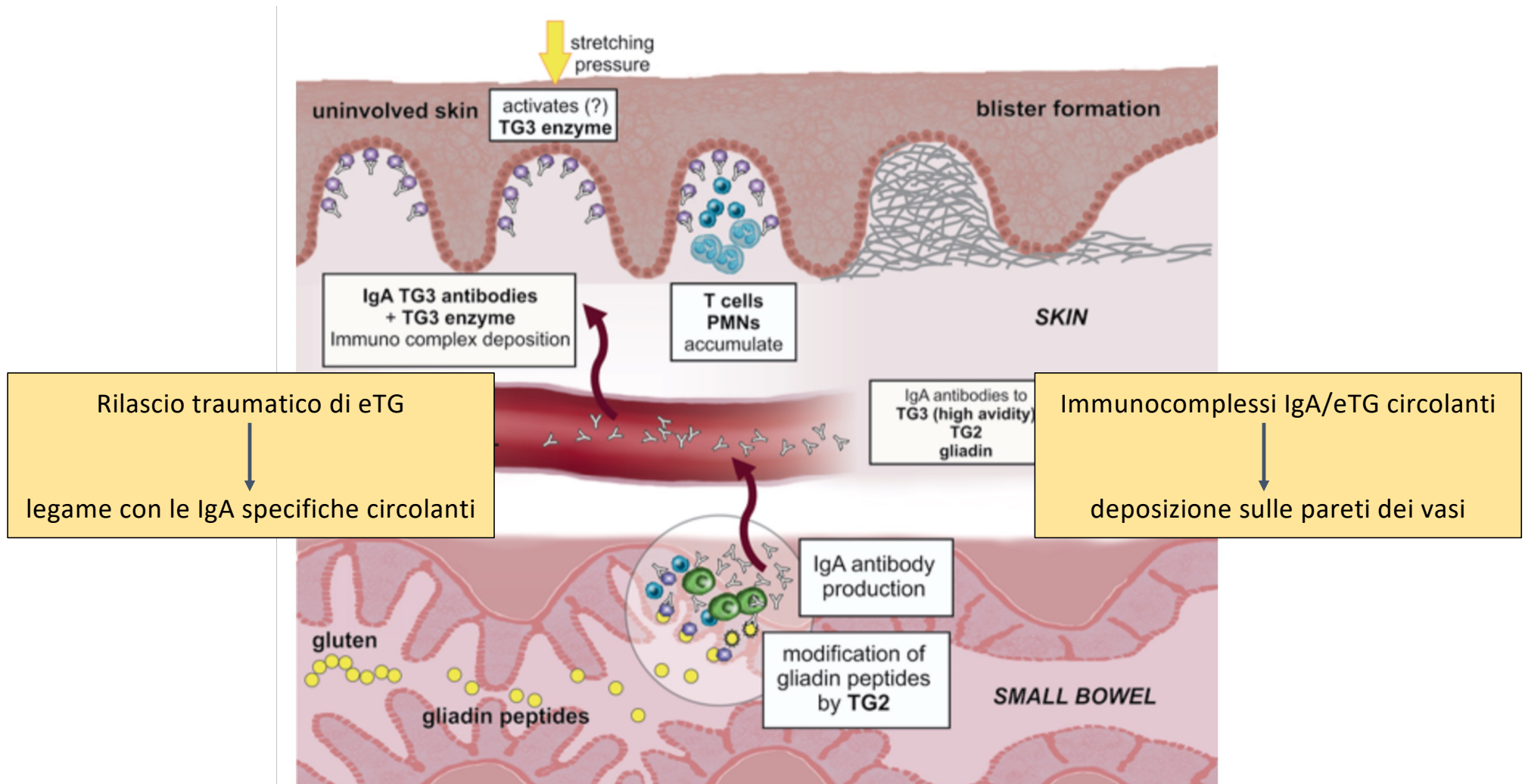
Deposition of circulating IgA/eTG IC and/or their formation in the skin



Activation of neutrophils and other effector cells



Skin damage

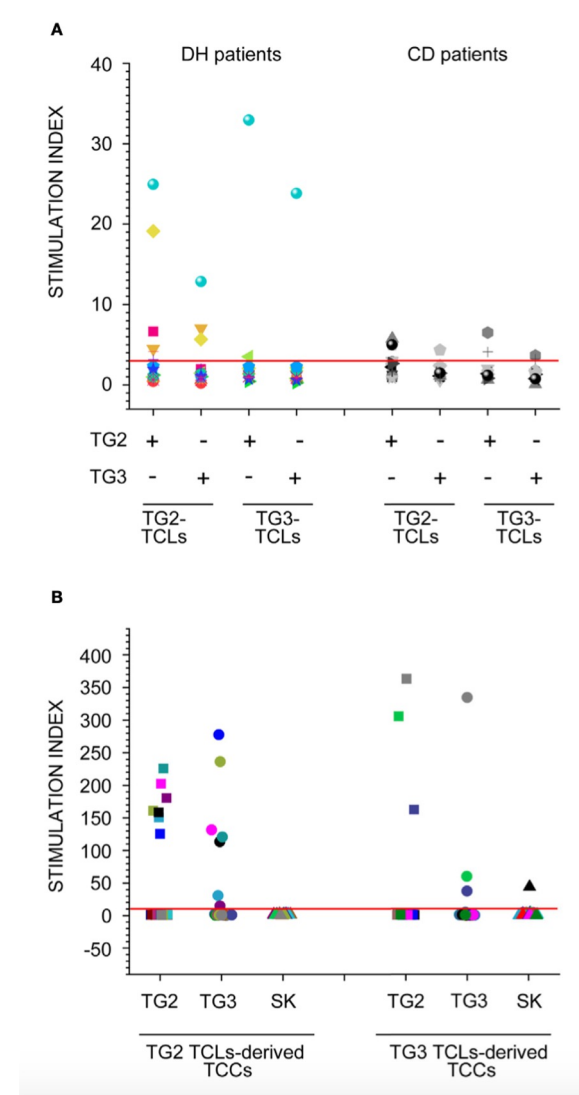


Reunala T, Salmi TT, Hervonen K. Dermatitis herpetiformis: pathognomonic transglutaminase IgA deposits in the skin and excellent prognosis on a gluten-free diet. Acta Derm Venereol. 2015 Nov;95(8):917-22. doi: 10.2340/00015555-2162. PMID: 26059085.

Immunità cellulare

- Garioch et al individuano la presenza di cell T CD4+ nelle lesioni di DH (*Br J Dermatol* (1994))
- Cytokine activity in DH (*Caproni et Br J Dermatol* 1998)
- Ridotta funzionalità immunosoppressiva dei T reg Foxp3+ nella pelle DH rispetto a controlli sani (Antiga E, Caproni et al. 2015)
- Esistenza a livello intestinale di una **risposta T cellulare crociata** verso le due isoforme di transglutaminasi sia nei pazienti CD che nei pazienti DH.

Caproni M, Capone M, Rossi MC et al. T Cell Response Toward Tissue-and Epidermal-Transglutaminases in Coeliac Disease Patients Developing Dermatitis Herpetiformis. *Front Immunol.* 2021 Apr 20;12:645143. doi: 10.3389/fimmu.2021.645143. PMID: 33959126; PMCID: PMC8093623.

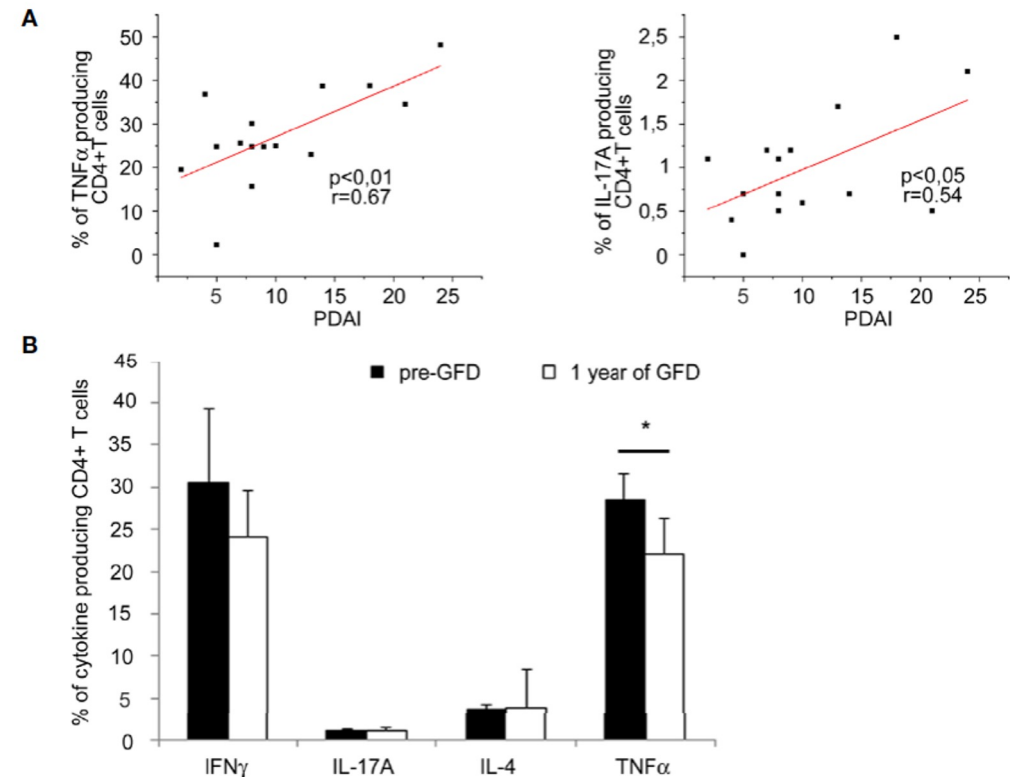


Immunità cellulare

- Nella cute di pazienti DH la frequenza di linfociti T produttori $\text{TNF}\alpha$ è risultata significativamente più elevata rispetto alla cute di pazienti con CD
- Linfociti T circolanti produttori $\text{TNF}\alpha$ e IL-17A correlano positivamente con score di gravità di malattia (misurato mediante score PDAI) e diminuiscono dopo dieta priva di glutine

T Cell Response Toward Tissue-and Epidermal-Transglutaminases in Coeliac Disease Patients Developing Dermatitis Herpetiformis

Marzia Caproni^{1†}, Manuela Capone^{2†}, Maria Caterina Rossi², Veronica Santarlasci², Laura Maggi², Alessio Mazzoni², Beatrice Rossetti², Daniela Renzi³, Lavinia Quintarelli¹, Beatrice Bianchi⁴, Alessandra Ninci⁵, Gabriele Lami³, Antonio Calabrò³, Lorenzo Cosmi², Francesco Annunziato^{2*} and Francesco Liotta²



Caproni M, Capone M, Rossi MC et al. T Cell Response Toward Tissue-and Epidermal-Transglutaminases in Coeliac Disease Patients Developing Dermatitis Herpetiformis. Front Immunol. 2021 Apr 20;12:645143. doi: 10.3389/fimmu.2021.645143. PMID: 33959126; PMCID: PMC8093623.

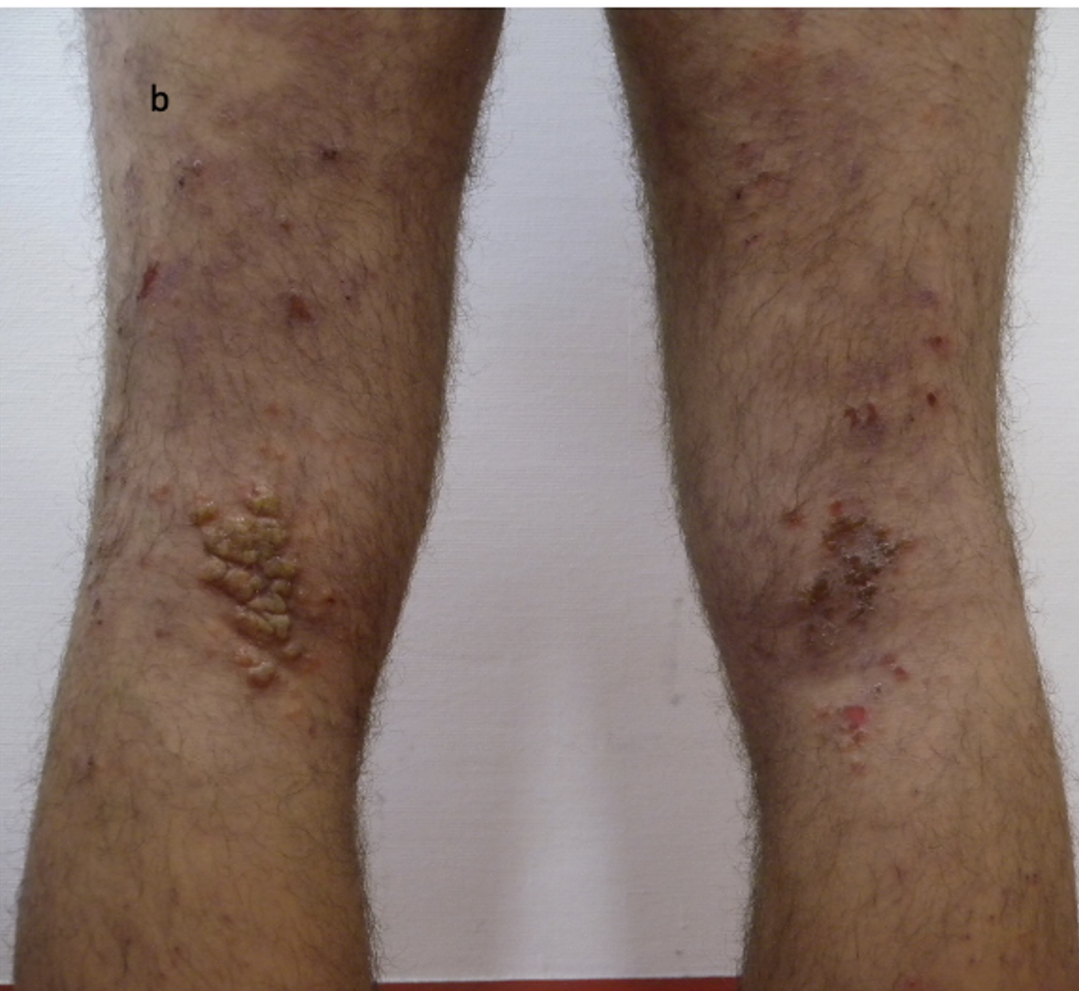
Clinica

- Tipico rash **simmetrico** che coinvolge principalmente gomiti, ginocchia, spalle, regione glutea, nuca
- **Polimorfismo** delle lesioni (eritema, papule, vescicole spesso raggruppate con aspetto erpetiforme)
- Fenomeno di **Koebner**
- **Prurito** incoercibile
- Segno di Nikolsky negativo
- Dubbio coinvolgimento mucosale (possibile manifestazione di malattia celiaca)
- Sintomi gastrointestinali: coinvolgimento intestinale quasi sempre presente alla biopsia anche se spesso pauci- o asintomatico
- Associazione con altre malattie autoimmuni: diabete tipo 1 (1-5% dei pazienti con DH), autoimmunità tiroidea (4.3-5% dei pazienti con DH)







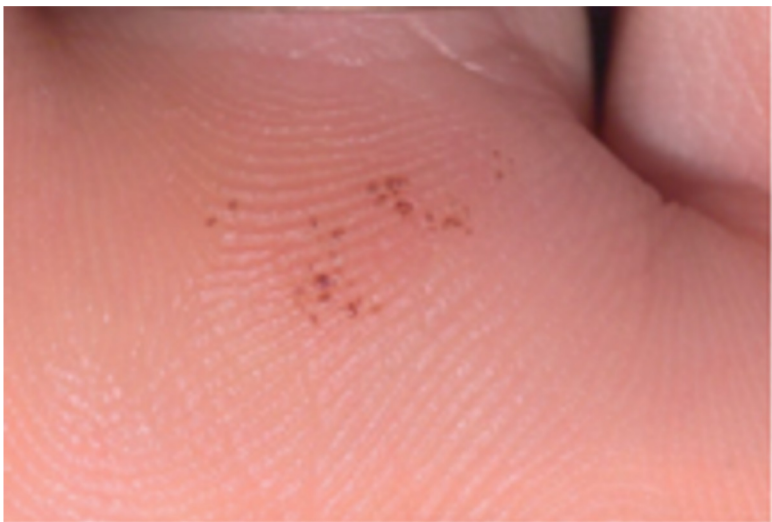




Presentazioni cliniche più rare:

- porpora e petecchie;
- cheratosi palmoplantare;
- orticaria cronica

García-Vázquez A, Guillen-Climent S, Pinazo-Canales MI. Acral Purpura in Dermatitis Herpetiformis. JAMA Dermatol. 2020 Jun 1;156(6):695. doi: 10.1001/jamadermatol.2020.0378. PMID: 32267467.



Flann S, Degiovanni C, Derrick EK, Munn SE. Two cases of palmar petechiae as a presentation of dermatitis herpetiformis. Clin Exp Dermatol. 2010 Mar;35(2):206-8. doi: 10.1111/j.1365-2230.2009.03757.x. Epub 2009 Dec 8. PMID: 20015286.



Sally R, Kim R, Lo Sicco K, Caplan AS.
Urticarial dermatitis herpetiformis: A rare presentation of an uncommon disorder.
JAAD Case Rep. 2022

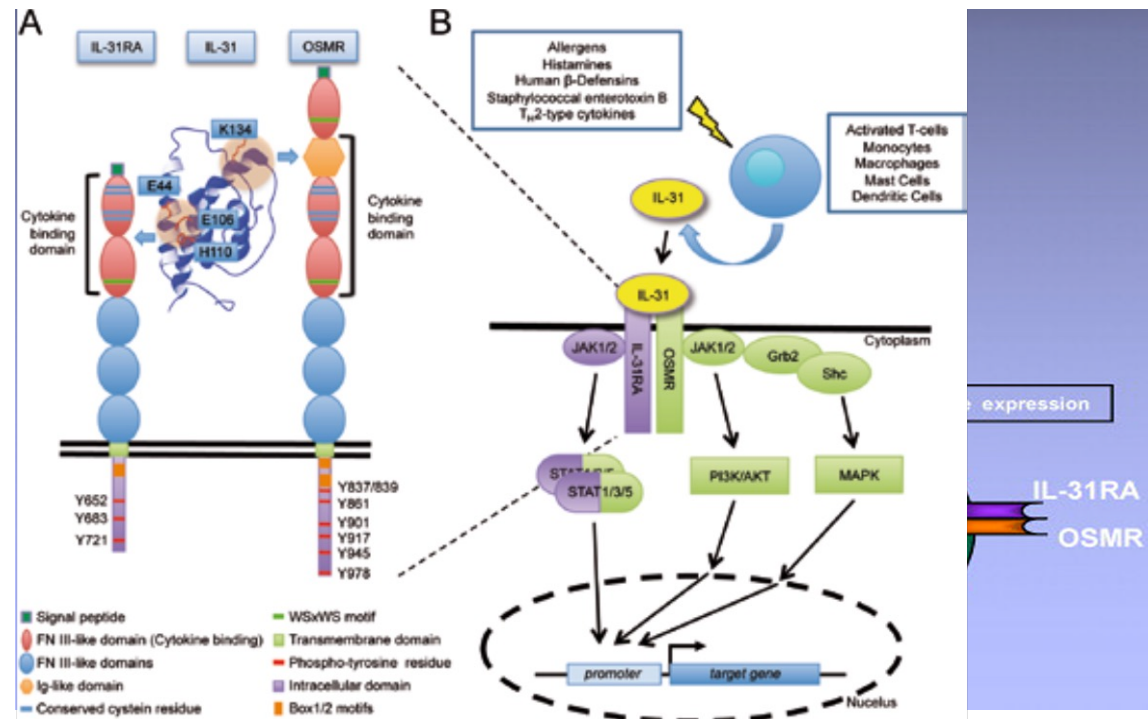
Clinica: prurito

-
- Pruritus is the leading symptom of DH and its absence is a strong argument against the diagnosis of DH
 - Usually very severe → scratching lesions
 - 12-24 h before the development of skin lesions: burning, stinging or drilling sensation



The pathogenesis of pruritus in DH

- Different pathways are involved in the pruritus of DH, including neurogenic inflammation, mechanical itch dyesthesias and release of inflammatory cytokines.
- Among inflammatory cytokines involved in pruritogenesis, IL-31 has gained a major interest
- IL-31 belongs to the cytokine family of IL-6. IL-31 interacts with a heterodimeric receptor, which comprises the IL-31 receptor A (IL-31RA) and the oncostatin M receptor and is expressed on various immune cells including T cells, keratinocytes, dendritic cells, eosinophils, basophils, macrophages and dorsal root ganglia
- IL-31 seems to be particularly implicated in pruritic dermatoses related to a prevalent Th2 type inflammation



Serum levels and tissue expression of interleukin-31 in dermatitis herpetiformis and bullous pemphigoid

Diletta Bonciani ¹, Lavinia Quintarelli ², Elena Del Bianco ², Beatrice Bianchi ², Marzia Caproni ²

Affiliations + expand

PMID: 28465041 DOI: [10.1016/j.jdermsci.2017.04.008](https://doi.org/10.1016/j.jdermsci.2017.04.008)

A recent study by our group demonstrated that IL-31 was found elevated in DH serum and significantly over-expressed in the skin, where it co-localized with IL-31RA

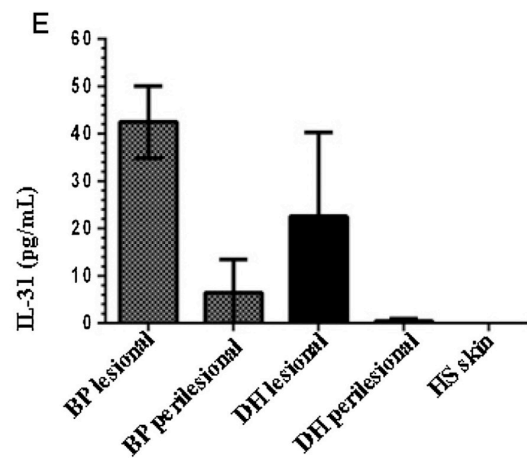
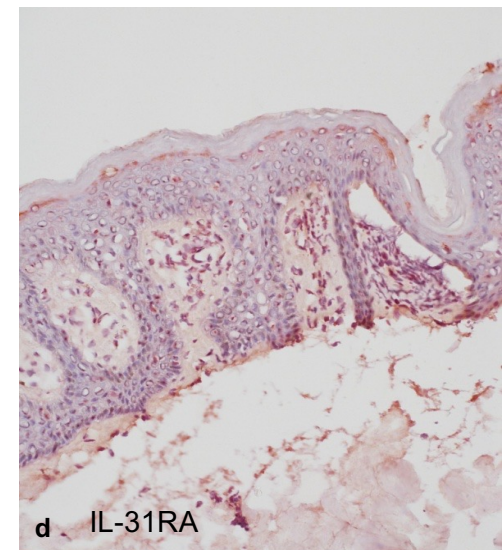
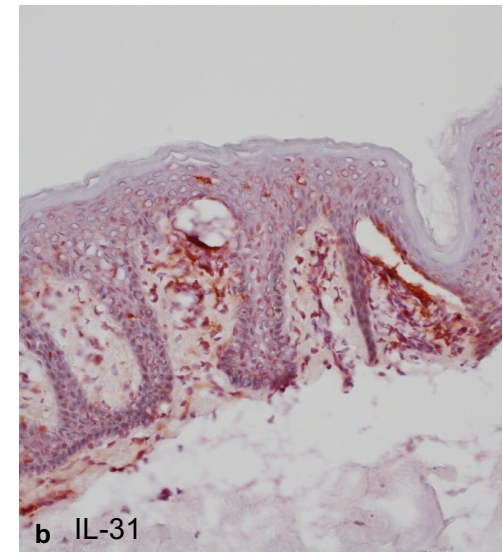
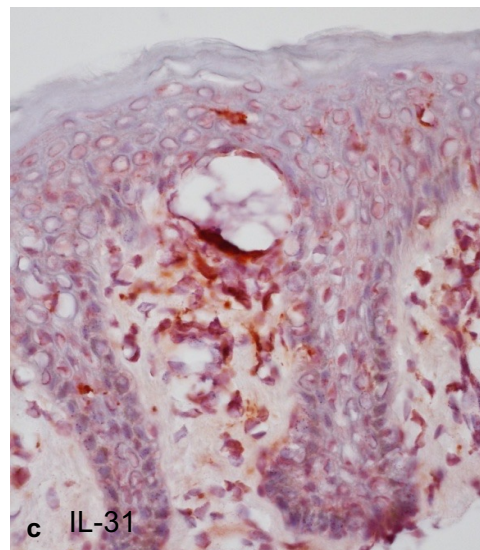
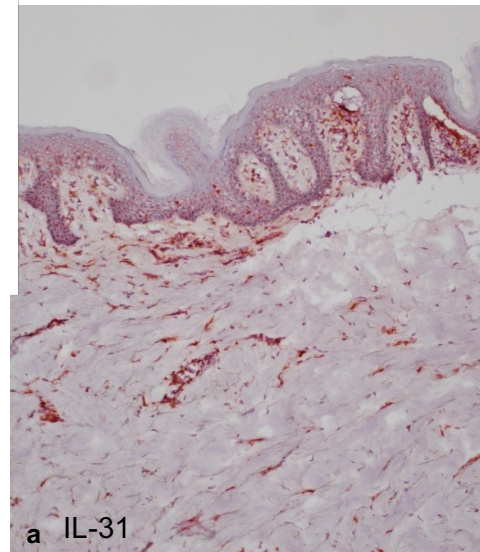


Fig. 1. Representative immunoreactivity for IL-31. A: DH lesional skin; B: DH perilesional skin; C: BP lesional skin; and D: BP perilesional skin. E: Mean $\pm$ SD immunofluorescence intensity of anti-IL-31 staining of the lesional and perilesional skin of BP, and DH, and HS skin.

LESIONAL DH



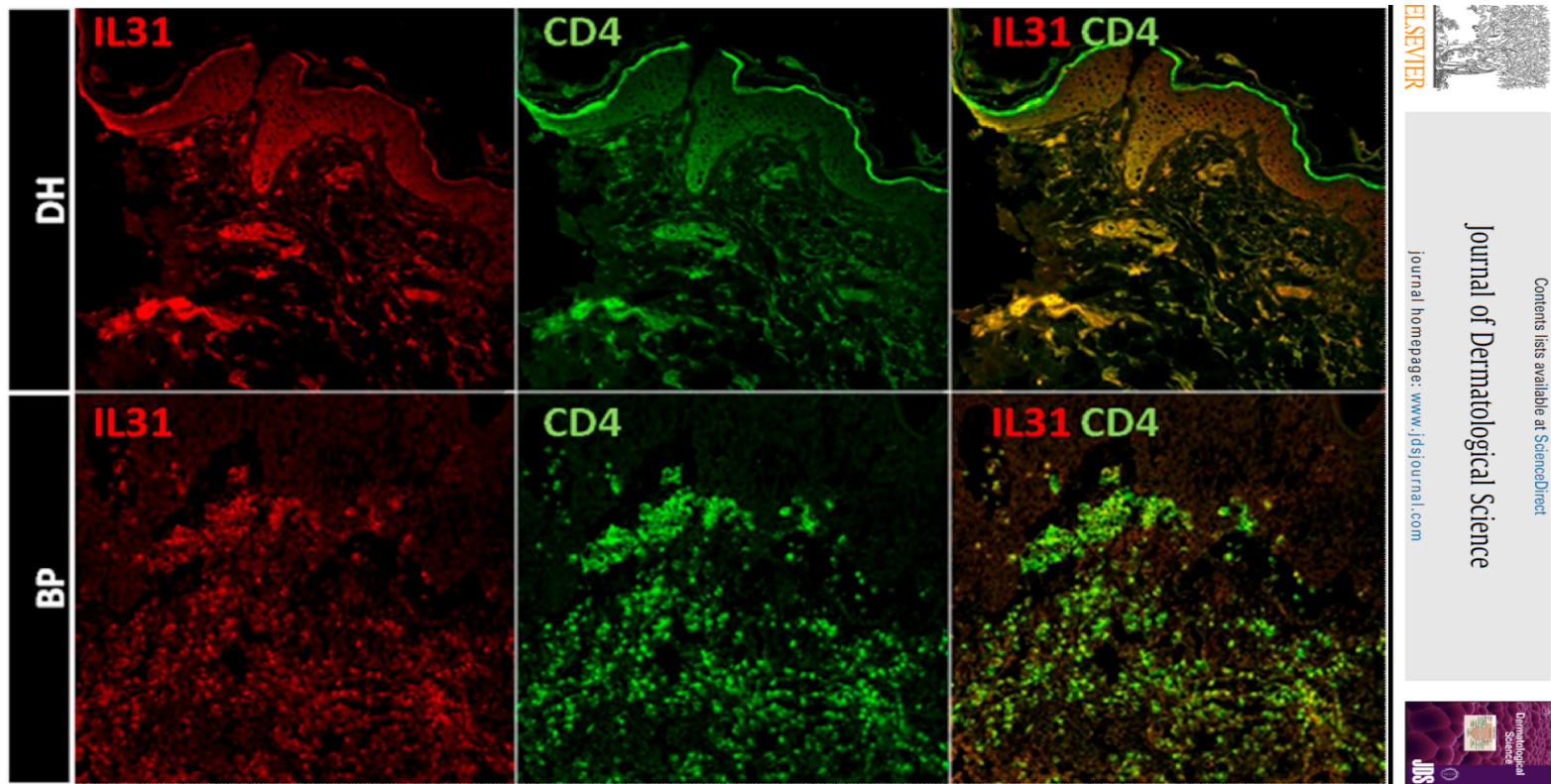


Fig. 2. Confocal microscopy of IL-31⁺ and CD4⁺ cells. Lesional skin specimens of DH and BP were stained for IL-31 (left) and CD4 (middle), and merged images are shown (right).

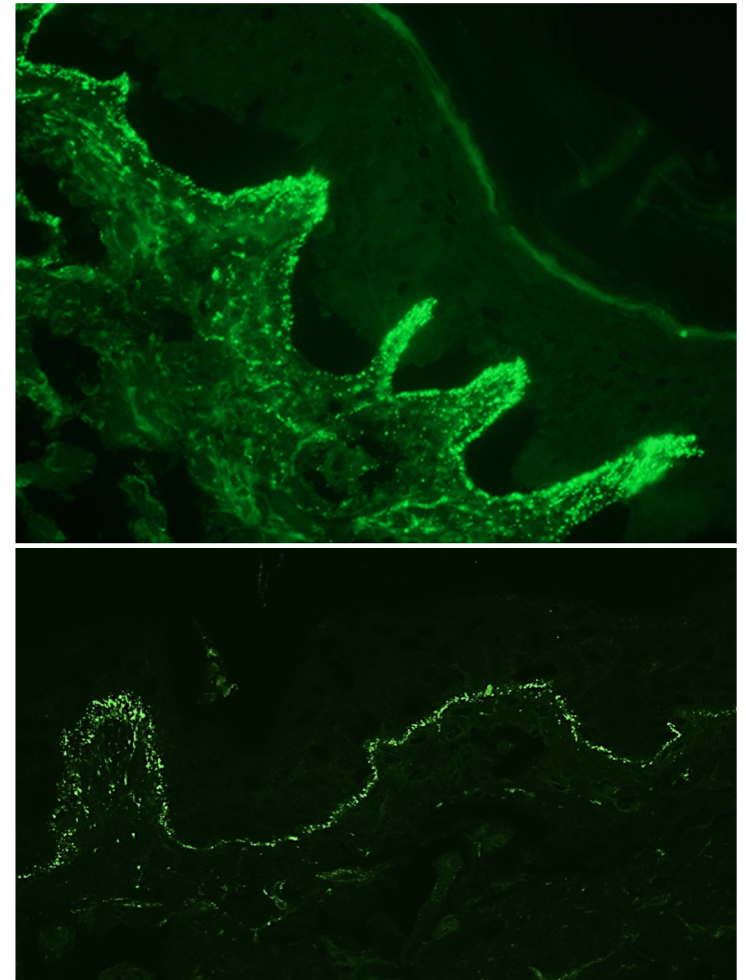
Boncianni D, Quintarelli L, Del Bianco E, Bianchi B, **Caproni M**. Serum levels and tissue expression of interleukin-31 in dermatitis herpetiformis and bullous pemphigoid. *J Dermatol Sci*. 2017;87(2):210-2.

Diagnosi

Major criteria
Compatible clinical manifestations
Perilesional IFD showing granular, microgranular or fibrillar IgA deposits at the tips of dermal papillae or at the DEJ or a combination of these patterns
Minor criteria
Compatible histology
Positive serological test of high value (tTG, eTG or EMA)
CD-compatible duodenal biopsy
Compatible HLA testing
Positive iodine patch test or oral iodine challenge
Response to dapsone (partial recovery in 1 week of 100 mg daily)
Response to a long term GFD
Görög A, Antiga E, Caproni M, Cianchini G, De D, Dmochowski M, Dolinsek J, Drenovska K, Feliciani C, Hervonen K, Lakos Jukic I, Kinyó Á, Koltai T, Korponay-Szabó I, Marzano AV, Patsatsi A, Rose C, Salmi T, Schmidt E, Setterfield J, Shahid M, Sitaru C, Uzun S, Valitutti F, Vassileva S, Yayli S, Sárdy M. S2k guidelines (consensus statement) for diagnosis and therapy of dermatitis herpetiformis initiated by the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol. 2021 Jun;35(6):1251-1277. doi: 10.1111/jdv.17183. PMID: 34004067.

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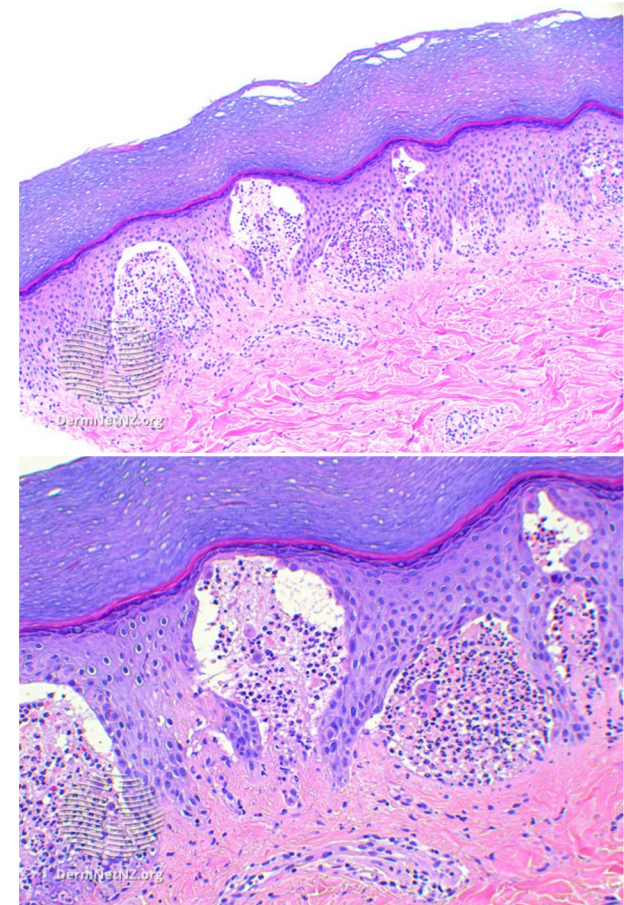
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Sierologia per:

- diagnosi se IFD non conclusiva;
- diagnosi differenziale;
- per monitorare aderenza alla GFD durante il follow-up

IgA anti tTG

IgA anti eTG

Ab anti EMA : test di conferma per ab anti tTG

Ab anti gliadina: non raccomandati

Görög A, Antiga E, Caproni M, Cianchini G, De D, Dmochowski M, Dolinsek J, Drenovska K, Feliciani C, Hervonen K, Lakos Jukic I, Kinyó Á, Koltai T, Korponay-Szabó I, Marzano AV, Patsatsi A, Rose C, Salmi T, Schmidt E, Setterfield J, Shahid M, Sitaru C, Uzun S, Valitutti F, Vassileva S, Yayli S, Sárdy M. S2k guidelines (consensus statement) for diagnosis and therapy of dermatitis herpetiformis initiated by the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol. 2021 Jun;35(6):1251-1277. doi: 10.1111/jdv.17183. PMID: 34004067.

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Biopsia duodenale raccomandata per valutare il grado di enteropatia. Nei bambini l'enteropatia può essere diagnosticata senza biopsia in caso di ab anti tTG 10 volte sopra il limite normale e di ab anti EMA positivi su di un secondo prelievo sanguigno.

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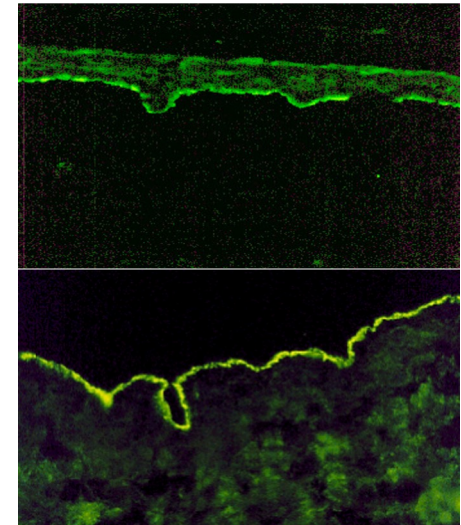
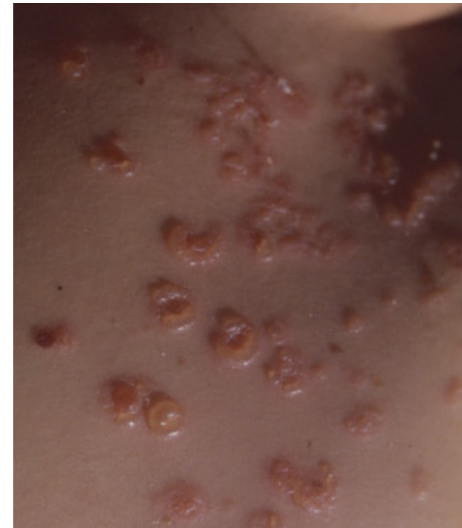
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HLA-DQ2/DQ8 testing ha un alto valore predittivo negativo (99%). In alcune popolazioni tuttavia potrebbero essere presenti altri polimorfismi.

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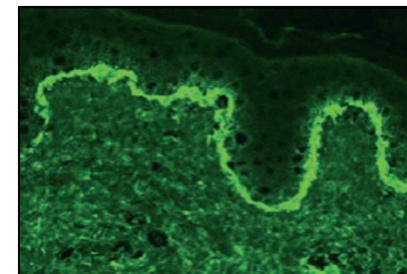
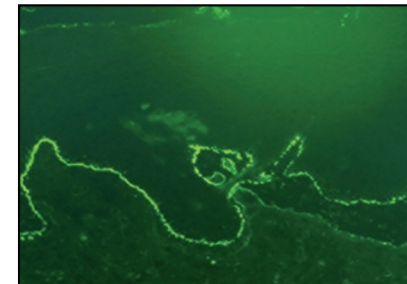
Diagnosi differenziali - DlgAI

Clinica	Istologia	Immunofluorescenza diretta	Screening per celiachia	Risposta a GFD
Bolle a disposizione arciforme, “ad orletto di perle”	Infiltrato neutrofilico	Deposito lineare predominante o esclusivo di IgA alla giunzione dermoepidermica	Negativo	Non dimostrata



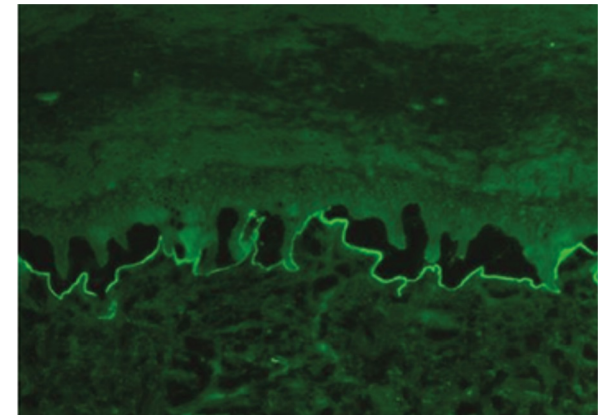
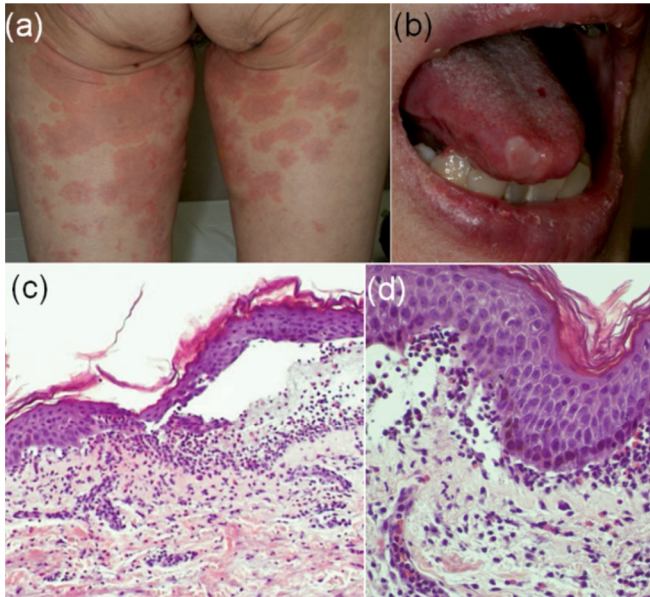
Diagnosi differenziali – Pemfigoide bolloso

Clinica	Istologia	Immunofluorescenza diretta	Screening per celiachia	Risposta a GFD
Bolle, vescicole o lesioni orticarioidi nell'anziano	Infiltrato eosinofilo	Deposito predominante o esclusivo di IgG alla giunzione dermoepidermica	Negativo	Non dimostrata



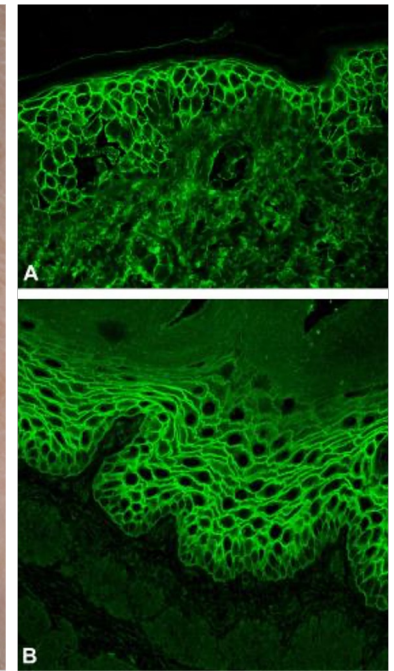
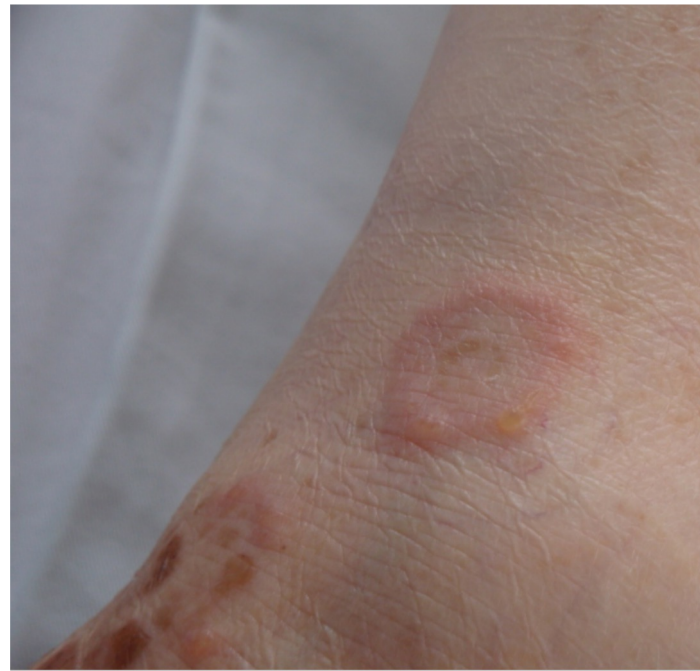
Diagnosi differenziali – Epidermolisi Bollosa Acquisita

Clinica	Istologia	Immunofluorescenza diretta	Screening per celiachia	Risposta a GFD
Lesioni vescico-bollose nei siti di trauma	Infiltrato misto	Deposito lineare di IgG o IgA alla giunzione dermoepidermica	Negativo	Non dimostrata



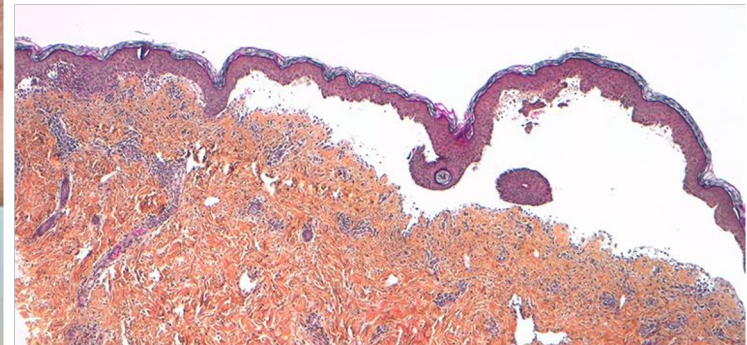
Diagnosi differenziali – Pemfigo erpetiforme

Clinica	Istologia	Immunofluorescenza diretta	Screening per celiachia	Risposta a GFD
Lesioni vescicolo-bollose con placche arcuate, orticarioidi e circinate	Acantolisi intraepidermica e spongiosi eosinofila	Depositi intraepidermici di IgG e C3 con pattern intercellulare	Negativo	Non dimostrata



Diagnosi differenziali – Lupus sistemico bolloso

Clinica	Istologia	Immunofluorescenza diretta	Screening per celiachia	Risposta a GFD
Da piccoli cluster di vescicole, larghe bolle tese	Dermatite dell'interfaccia con distacco dermo-epidermico	Depositi di IgG e IgA alla giunzione dermoepidermica	Negativo	Non dimostrata



Diagnosi differenziali – Dermatite atopica

Clinica	Istologia	Immunofluorescenza diretta	Screening per celiachia	Risposta a GFD
Eczema, papule e vescicole raggruppate	Spongiosi eosinofila	Non conclusiva	Negativo	Non dimostrata



Diagnosi differenziali - Scabbia

Clinica	Istologia	Immunofluorescenza diretta	Screening per celiachia	Risposta a GFD
Papule multiple eritematose ed escoriate	Infiltrato eosinofilo	Non conclusiva	Negativo	Non dimostrata



Diagnosi differenziali – Non C

Clinica	Istologia	Immunofluorescenza dire
Dermatite eczematosa, vescicole escoriate, dermatite psoriasiforme e orticaria-angioedema	Non specifica	80% dei casi: deposito granulare di C3 delle papille dermiche

- NCGS fa parte dei disordini gluten-related
- Diagnosi di esclusione (no chiari criteri sierologici o istopatologici)
- Sintomi GI che migliorano poco tempo dopo GFD
- Sintomi dermatologici: dermatosi non specifiche, pruriginose, in altri casi più eczematose o psoriasiformi
- IFD: nell'80% dei casi deposito granulare o microgranulare delle papille dermiche



Article

**Cutaneous Manifestations of Non-Celiac Gluten Sensitivity:
Clinical Histological and Immunopathological Features**

Veronica Bonciolini ^{1,*}, Beatrice Bianchi ¹, Elena Del Bianco ¹, Alice Verdelli ¹ and Marzia Caproni ²

¹ Department of Surgery and Translational Medicine, Section of Dermatology, University of Florence,

Non Celiac Gluten Sensitivity

Clinica	Istologia	Immunofluorescenza diretta	Screening per celiachia	Risposta a GFD
Dermatite eczematosa, vescicole escoriate, dermatite psoriasiforme e orticaria-angioedema	Non specifica	80% dei casi: deposito granulare di C3 all'apice delle papille dermiche	Negativo	Osservata

- NCGS fa parte dei disordini gluten-related
- Diagnosi di esclusione (no chiari criteri sierologici o istopatologici)
- Sintomi GI che migliorano poco tempo dopo GFD
- Sintomi dermatologici: dermatosi non specifiche, pruriginose, in alcuni casi simili a DH, in altri casi più eczematose o psoriasiformi
- IFD: nell'80% dei casi deposito granulare o microgranulare di C3 all'apice delle papille dermiche

CUTANEOUS GLUTEN SENSITIVITY

- Lesioni cutanee pruriginose
- C3 granulare all'apice delle papille
 - Risposta a GFD

Terapia

- **Dieta priva di glutine**
- **Dapsone** (previo dosaggio di G6PD)
Dose iniziale 25-50 mg/die, dose di mantenimento 100-200 mg/die.
- **Corticosteroidi topici**



TABLE 1 Demographic, clinical, serological and histological data of dermatitis herpetiformis (DH) patients with and without gastrointestinal (GI) symptoms at the time of DH diagnosis.

	GI symptoms (<i>n</i> = 91)		No GI symptoms (<i>n</i> = 131)		<i>p</i> -Value
	<i>n</i>	%	<i>n</i>	%	
Persistent gastrointestinal symptoms at follow-up	17	19	14	11	0.096

- 216 pazienti DH con dati di follow-up disponibili (Finlandia)
- Persistenza di sintomi gastrointestinali nel 14% dei pazienti dopo una mediana di follow-up di 25 anni
- Spesso pazienti fumatori e con una QoL inferiore alla popolazione senza sintomi persistenti
- La presenza di sintomi GI non correlava con durata o severità dei segni e sintomi cutanei, né con la loro risoluzione in corso di GFD

Laamanen A, Salmi T, Huhtala H, Reunala T, Hervonen K, Kaukinen K, Pasternack C. Gastrointestinal symptoms at diagnosis and during long-term gluten-free diet treatment in dermatitis herpetiformis patients. J Eur Acad Dermatol Venereol. 2023

Alternative al dapstone:

- **Sulfasalazina** (utile in aggiunta a dapstone se il pz non tollera monoterapia con dapstone ad alte dosi)
- **Colchicina** (attività anti neutrofilica)
- Ciclosporina
- Azatioprina
- Micofenolato



DH: ACKNOWLEDGEMENTS



Dipartimento di Scienze della Salute
Azienda USL Toscana Centro
Università degli Studi di Firenze

Emiliano Antiga
Beatrice Bianchi
Alberto Corrà
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Elena Mariotti
Elena Del Bianco

Roberto Maglie
Valentina Ruffo
Lavinia Quintarelli
Stefano Senatore
Alice Verdelli
Walter Volpi

A close-up photograph of a golden wheat field. The wheat stalks are in sharp focus in the foreground, showing their intricate structure and golden-brown color. The background is a soft, out-of-focus expanse of the same wheat field, creating a sense of depth. A semi-transparent white rectangular box is centered horizontally and vertically, containing the text "Thank you!" in a bold, black, sans-serif font.

Thank you!

Diagnosi differenziali – Non Celiac Gluten Sensitivity

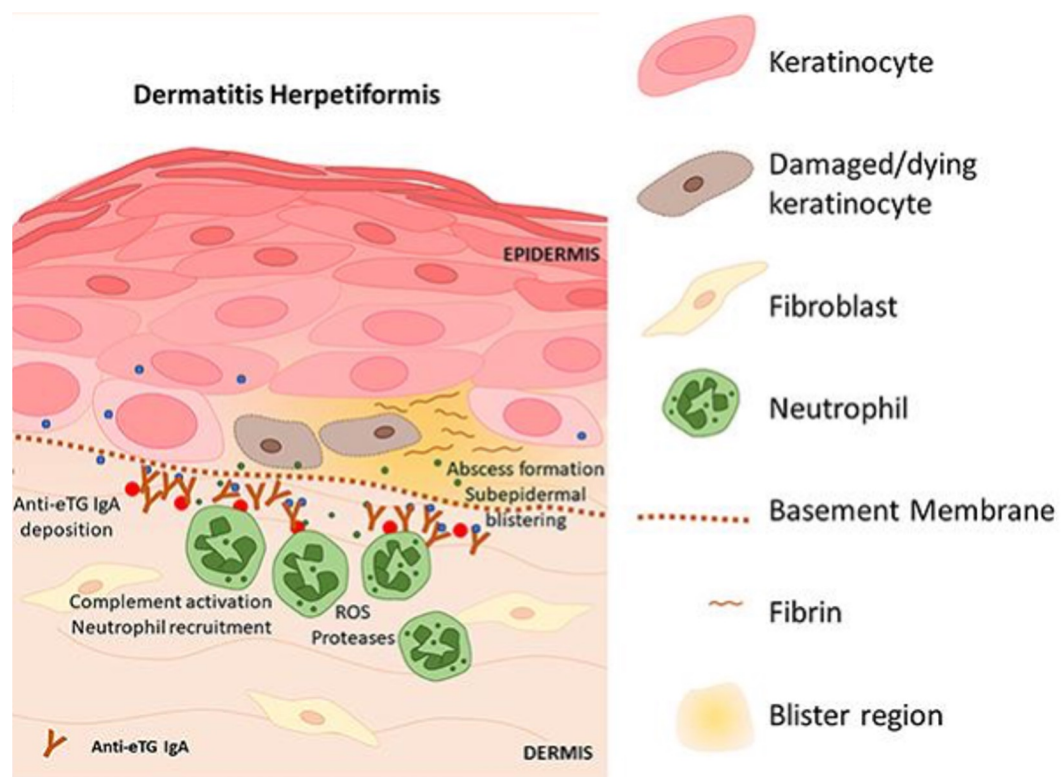
Clinica	Istologia	Immunofluorescenza diretta	Screening per celiachia	Risposta a GFD
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Immunità umorale

Anticorpi **IgA** anti transglutaminasi epidermica (TG3)

- Gli autoAb si formerebbero nell'intestino assieme agli autoanticorpi anti-TG2
- Epitope spreading?



> [J Immunol](#). 2011 Apr 1;186(7):4474–80. doi: 10.4049/jimmunol.1003273. Epub 2011 Feb 18.

Dermatitis herpetiformis sera or goat anti-transglutaminase-3 transferred to human skin-grafted mice mimics dermatitis herpetiformis immunopathology

John J Zone ¹, Linda A Schmidt, Ted B Taylor, Christopher M Hull, Michael C Sotiriou, Troy D Jaskowski, Harry R Hill, Laurence J Meyer

Affiliations + expand

PMID: 21335491 DOI: [10.4049/jimmunol.1003273](#)

> [Acta Derm Venereol](#). 2018 Mar 13;98(3):366–372. doi: 10.2340/00015555-2849.

Ex vivo Culture of Duodenal Biopsies from Patients with Dermatitis Herpetiformis Indicates that Transglutaminase 3 Antibody Production Occurs in the Gut

Minna Hietikko ¹, Kaisa Hervonen, Tuire Ilus, Teea Salmi, Heini Huhtala, Kaija Laurila, Tiina Rauhavirta, Timo Reunala, Katri Kaukinen, Katri Lindfors

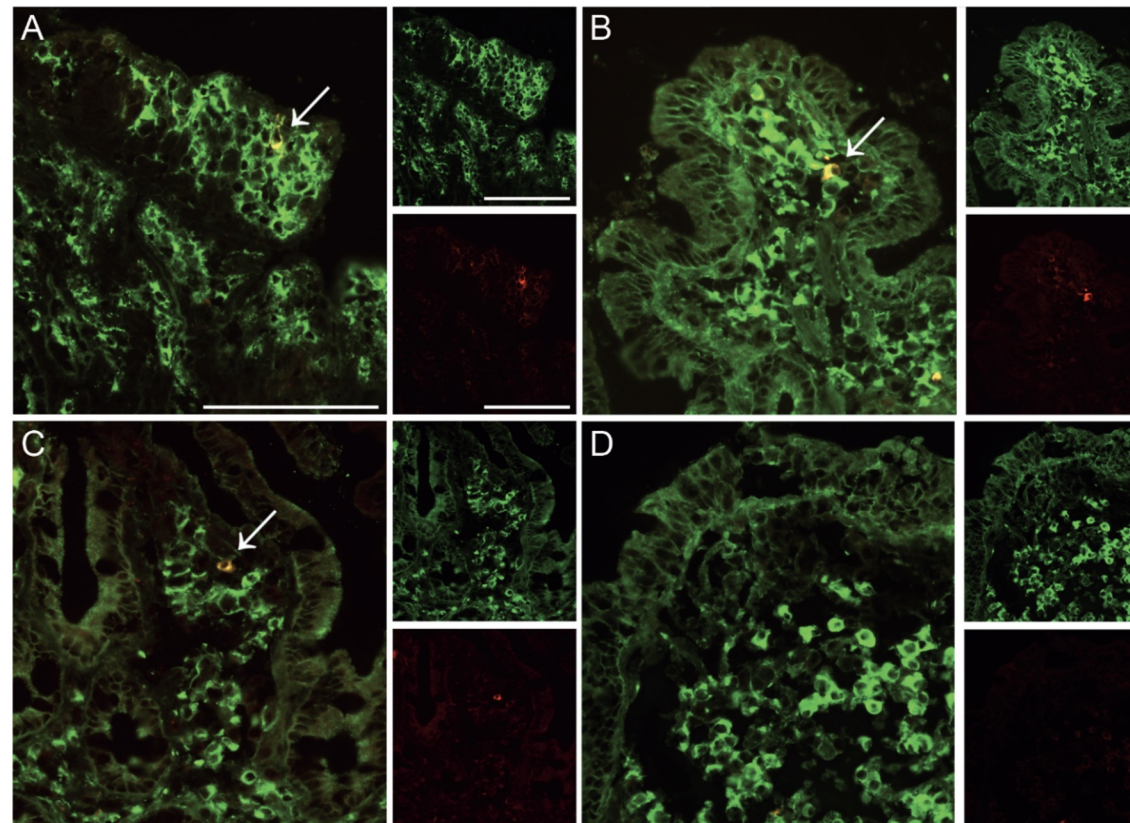
Affiliations + expand

PMID: 29182792 DOI: [10.2340/00015555-2849](#)

***Ex vivo* Culture of Duodenal Biopsies from Patients with Dermatitis Herpetiformis Indicates that Transglutaminase 3 Antibody Production Occurs in the Gut**

Minna HIETIKKO¹, Kaisa HERVONEN^{1,2}, Tuire ILUS^{1,3}, Teea SALMI^{1,2}, Heini HUHTALA⁴, Kaija LAURILA¹, Tiina RAUHAVIRTA¹, Timo REUNALA^{1,2}, Katri KAUKINEN^{1,5} and Katri LINDFORS¹

¹Coeliac Disease Research Center, Faculty of Medicine and Life Sciences and ⁴Faculty of Social Sciences, University of Tampere, Departments of ²Dermatology, ³Gastroenterology and Alimentary Tract Surgery, and ⁵Internal Medicine, Tampere University Hospital, Tampere, Finland



Perché nell'intestino vengono prodotti autoanticorpi e plasmacellule specifiche per un antigene cutaneo?

ARTICLE



<https://doi.org/10.1038/s41467-021-27743-1>

OPEN

Transglutaminase 3 crosslinks the secreted gel-forming mucus component Mucin-2 and stabilizes the colonic mucus layer

Jack D. A. Sharpen ¹, Brendan Dolan ¹, Elisabeth E. L. Nyström¹, George M. H. Birchenough ¹,
Liisa Arike ¹, Beatriz Martinez-Abad ¹, Malin E. V. Johansson ¹, Gunnar C. Hansson ¹ &
Christian V. Recktenwald ¹✉

RESEARCH ARTICLE

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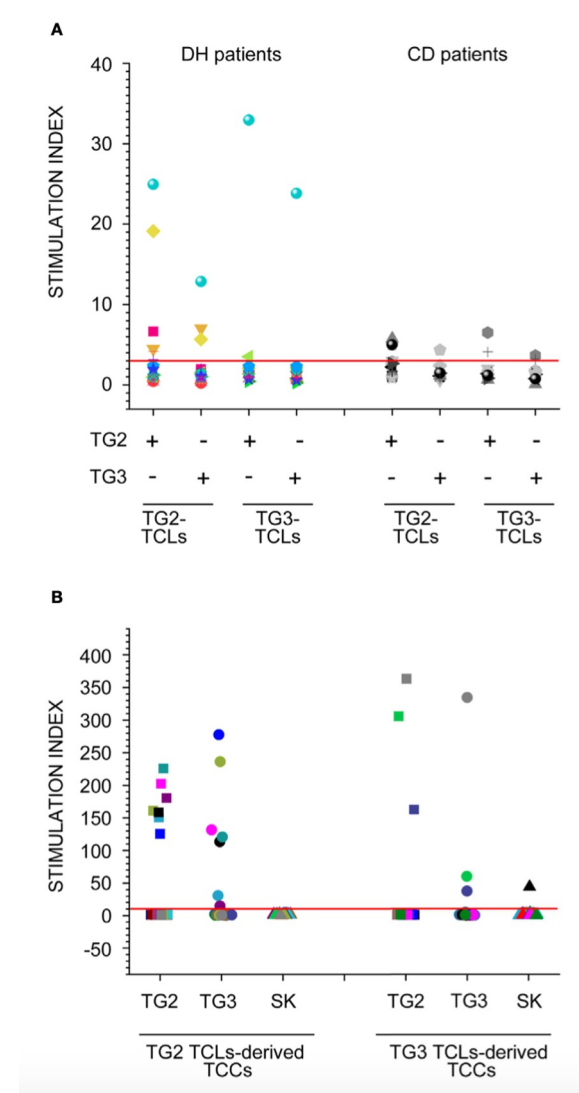
Separate Gut Plasma Cell Populations Produce Auto-Antibodies against Transglutaminase 2 and Transglutaminase 3 in Dermatitis Herpetiformis

Saykat Das, Jorunn Stamnaes, Esko Kemppainen, Kaisa Hervonen, Knut E. A. Lundin, Naveen Parmar, Frode L. Jahnsen, Jørgen Jahnsen, Katri Lindfors, Teea Salmi, Rasmus Iversen, and Ludvig M. Sollid**

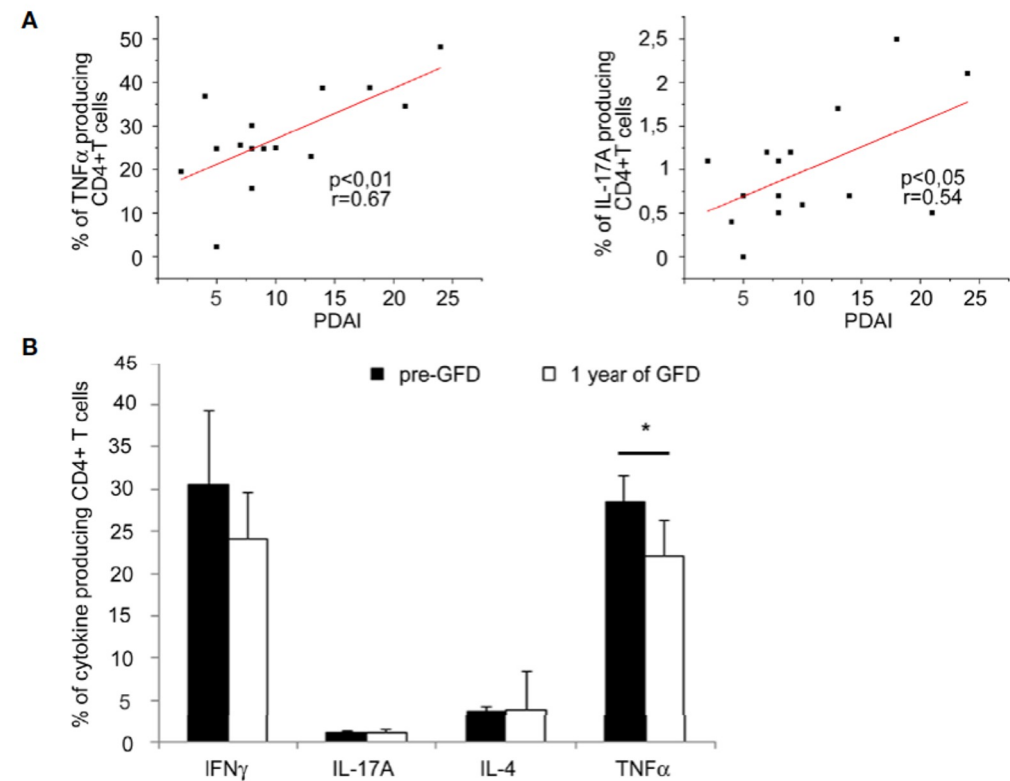
Immunità cellulare

- Garioch et al individuano la presenza di cell T CD4+ nelle lesioni di DH
- Ridotta funzionalità immunosoppressiva dei T reg Foxp3+ nella pelle DH rispetto a controlli sani (Antiga et al. 2015)
- Esistenza di una **risposta T cellulare crociata** verso le due isoforme di transglutaminasi sia nei pazienti CD che nei pazienti DH.

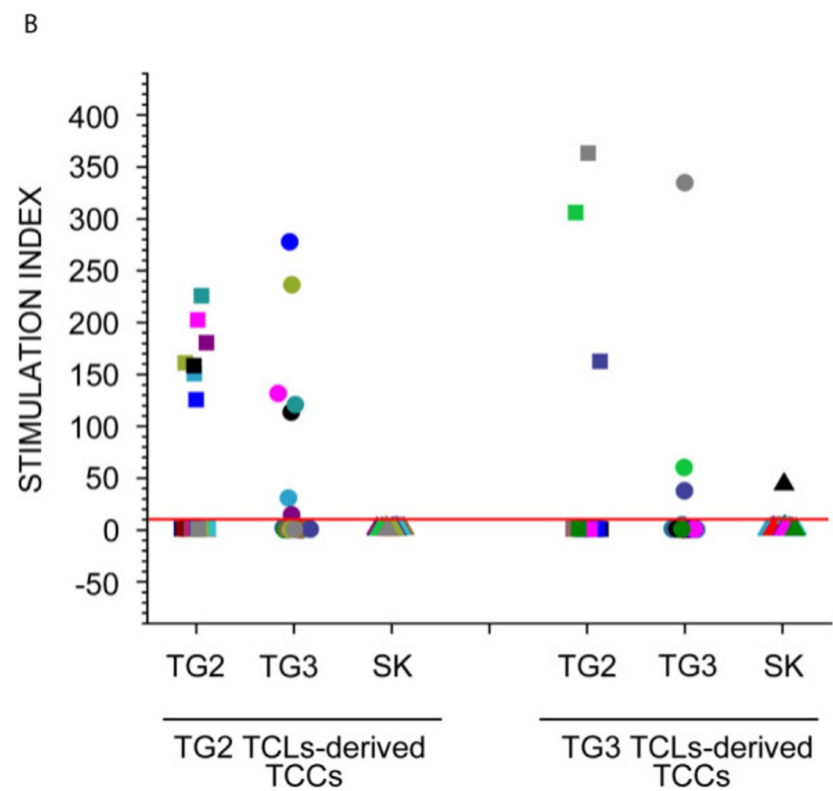
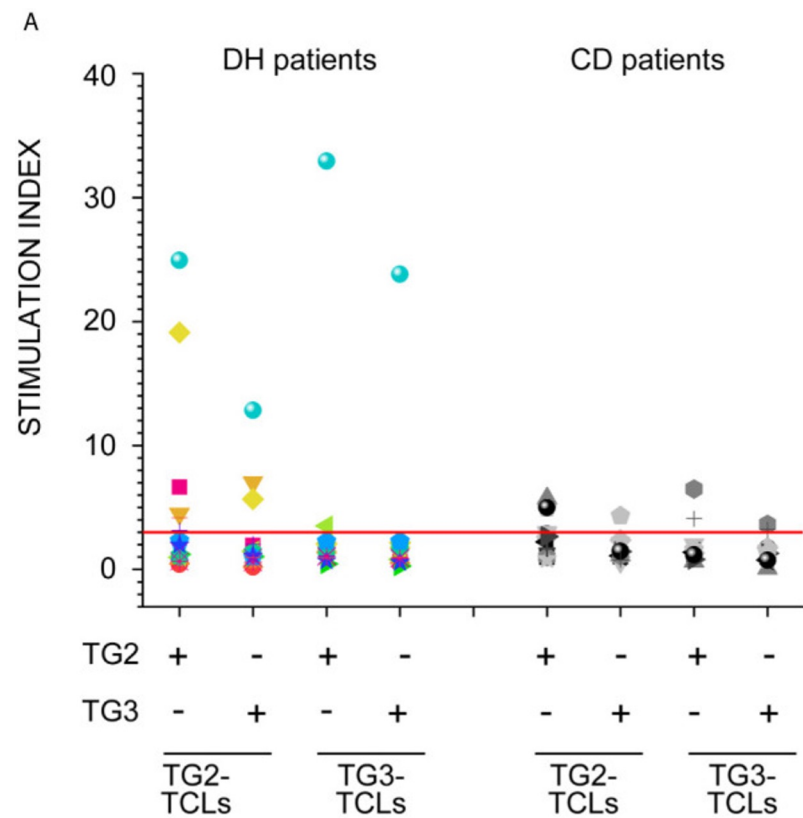
Caproni M, Capone M, Rossi MC et al. T Cell Response Toward Tissue-and Epidermal-Transglutaminases in Coeliac Disease Patients Developing Dermatitis Herpetiformis. Front Immunol. 2021 Apr 20;12:645143. doi: 10.3389/fimmu.2021.645143. PMID: 33959126; PMCID: PMC8093623.



- Nella **cute** di pazienti DH ci sono più linfociti T produttori TNF α rispetto alla cute di pazienti con solo CD.
- Linfociti T **circolanti** produttori TNF α e IL-17A correlano positivamente con score di gravità di malattia (misurato mediante score PDAI) e diminuiscono dopo dieta priva di glutine



Caproni M, Capone M, Rossi MC et al. T Cell Response Toward Tissue-and Epidermal-Transglutaminases in Coeliac Disease Patients Developing Dermatitis Herpetiformis. Front Immunol. 2021 Apr 20;12:645143. doi: 10.3389/fimmu.2021.645143. PMID: 33959126; PMCID: PMC8093623.



Fattori genetici predisponenti

Ingestione di **glutine**
±
Fattori aggravanti

AUTOIMMUNITA' vs eTG

Autoanticorpi IgA

Cellule T autoreattive



Prurito

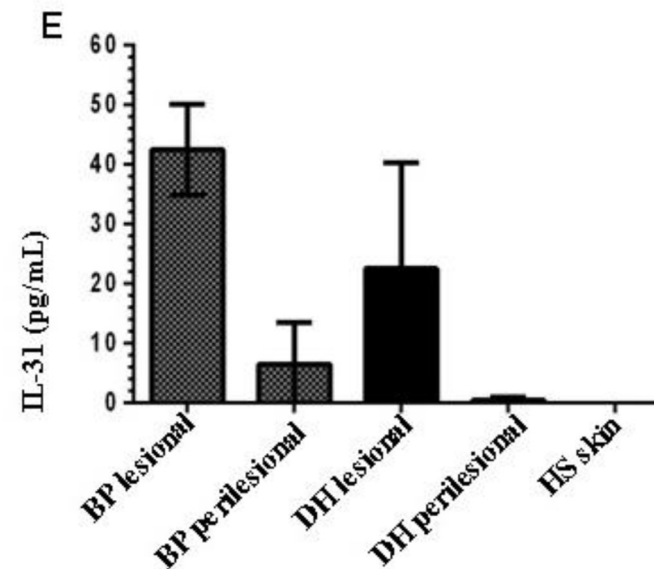
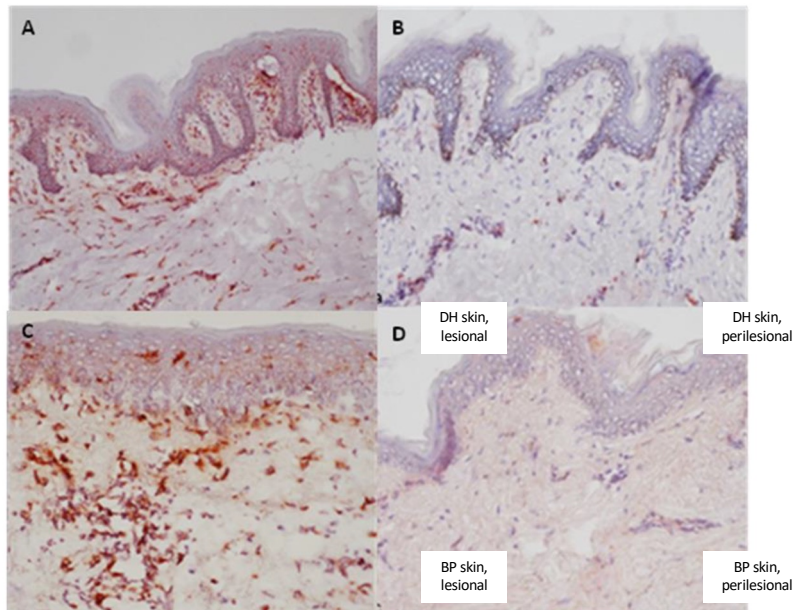
> [J Dermatol Sci.](#) 2017 Aug;87(2):210-212. doi: 10.1016/j.jdermsci.2017.04.008. Epub 2017 Apr 22.

Serum levels and tissue expression of interleukin-31 in dermatitis herpetiformis and bullous pemphigoid

Diletta Bonciani ¹, Lavinia Quintarelli ², Elena Del Bianco ², Beatrice Bianchi ², Marzia Caproni ²

Affiliations + expand

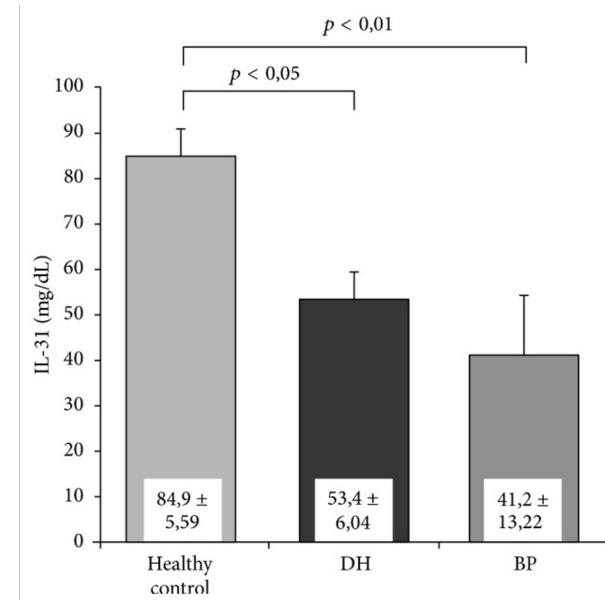
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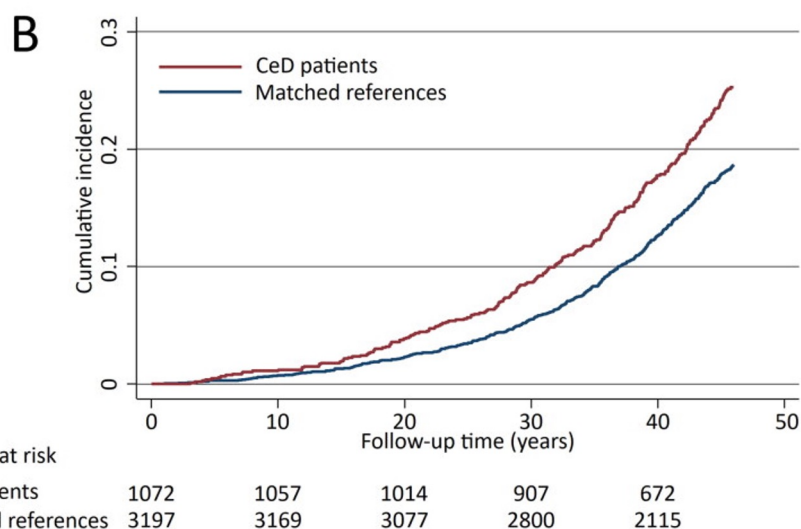
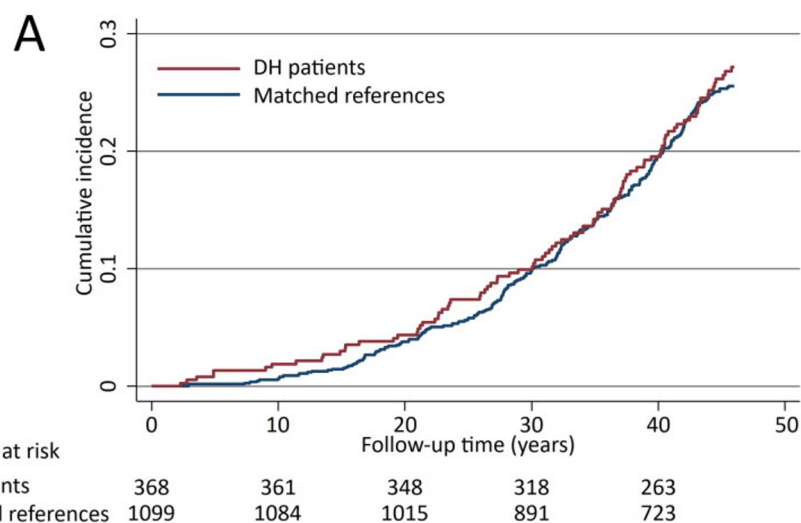


> [Biomed Res Int](#). 2017;2017:5965492. doi: 10.1155/2017/5965492. Epub 2017 Jul 20.

The Role of Intereukin-31 in Pathogenesis of Itch and Its Intensity in a Course of Bullous Pemphigoid and Dermatitis Herpetiformis

Lilianna Kulczycka-Siennicka ¹, Anna Cynkier ¹, Elżbieta Waszczykowska ¹, Anna Woźniacka ¹, Agnieszka Żebrowska ¹





Incidenza di eventi cardiovascolari

confronto tra popolazioni con DH/CD e popolazione generale (age- and sex-matched)

- No differenze significative tra pazienti DH e popolazione generale
- Rischio CV aumentato in pazienti CD, soprattutto malattia coronarica e malattia aterosclerotica delle valvole

Ruolo dell'inflammatione sistemica in CD?

Evidenze non confermate da altri studi

(Jhannesdottir SA, Erichsen R, Horváth-Puhó E, Schmidt M, Sørensen HT. Coeliac disease and risk of venous thromboembolism: a nationwide population-based case-control study. Br J Haematol. 2012)

ORIGINAL ARTICLE

OPEN ACCESS



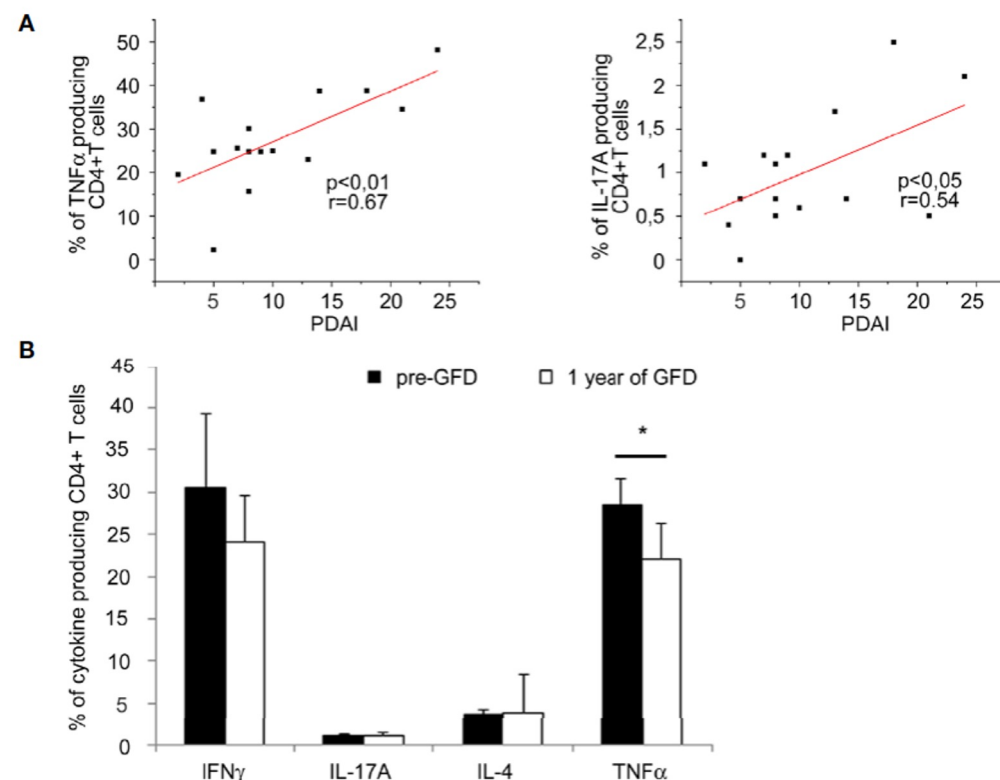
Risk of vascular diseases in patients with dermatitis herpetiformis and coeliac disease: a long-term cohort study

Noora Nilsson^{a,b}, Joonas Leivo^c, Pekka Collin^d, Inka Koskinen^{a,e}, Katri Kaukinen^{a,f}, Heini Huhtala^g , Johanna Palmio^h, Timo Reunala^a, Kaisa Hervonen^{a,b}, Teea Salmi^{a,b} and Camilla Pasternack^a

- Nella cute di pazienti DH la frequenza di linfociti T produttori $\text{TNF}\alpha$ è risultata significativamente più elevata rispetto alla cute di pazienti con CD
- Linfociti T circolanti produttori $\text{TNF}\alpha$ e IL-17A correlano positivamente con score di gravità di malattia (misurato mediante score PDAI) e diminuiscono dopo dieta priva di glutine

T Cell Response Toward Tissue- and Epidermal-Transglutaminases in Coeliac Disease Patients Developing Dermatitis Herpetiformis

[Marzia Caproni](#)¹, [Manuela Capone](#)², [Maria Caterina Rossi](#)², [Veronica Santarlaschi](#)², [Laura Maggi](#)², [Alessio Mazzoni](#)², [Beatrice Rossettini](#)², [Daniela Renzi](#)³, [Lavinia Quintarelli](#)¹, [Beatrice Bianchi](#)⁴, [Alessandra Ninci](#)⁵, [Gabriele Lami](#)³, [Antonio Calabrò](#)³, [Lorenzo Cosmi](#)², [Francesco Annunziato](#)², [Francesco Liotta](#)² Front Immunol. 2021 Apr 20;12:645143. doi: 10.3389/fimmu.2021.645143. PMID: 33959126; PMCID: PMC8093623



Caproni M, Capone M, Rossi MC et al. T Cell Response Toward Tissue- and Epidermal-Transglutaminases in Coeliac Disease Patients Developing Dermatitis Herpetiformis. Front Immunol. 2021 Apr 20;12:645143. doi: 10.3389/fimmu.2021.645143. PMID: 33959126; PMCID: PMC8093623.

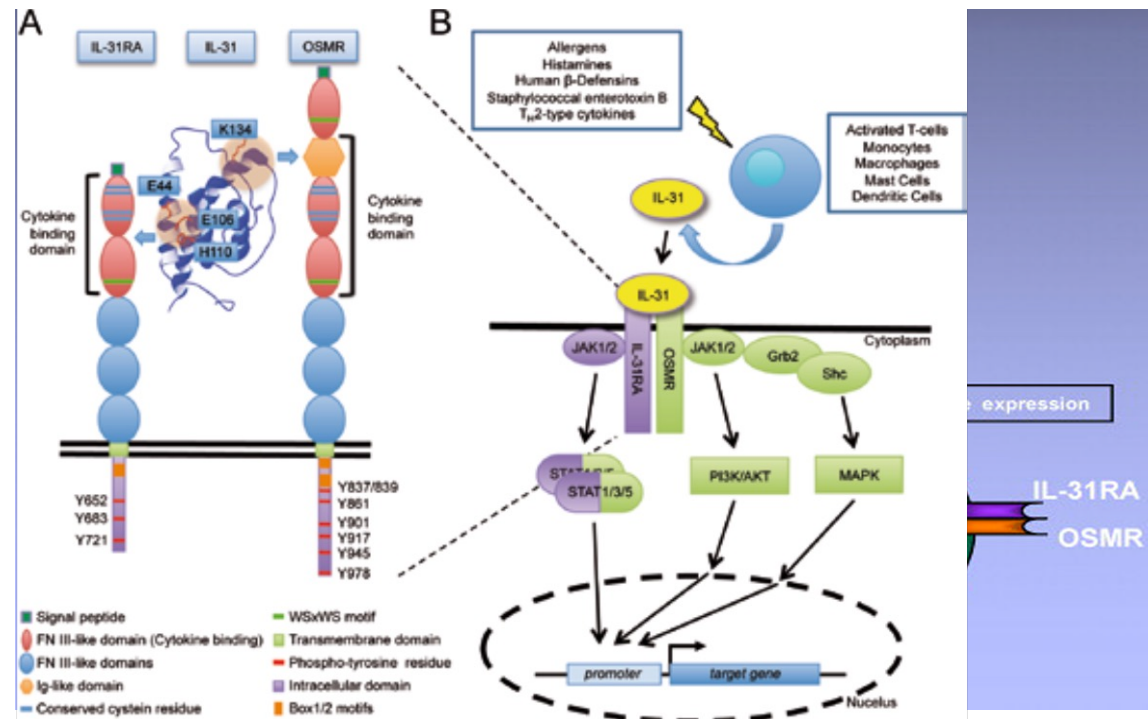
Clinica: prurito

-
- Pruritus is the leading symptom of DH and its absence is a strong argument against the diagnosis of DH
 - Usually very severe → scratching lesions
 - 12-24 h before the development of skin lesions: burning, stinging or drilling sensation



The pathogenesis of pruritus in DH

- Different pathways are involved in the pruritus of DH, including neurogenic inflammation, mechanical itch dysesthesias and release of inflammatory cytokines.
- Among inflammatory cytokines involved in pruritogenesis, IL-31 has gained a major interest
- IL-31 belongs to the cytokine family of IL-6. IL-31 interacts with a heterodimeric receptor, which comprises the IL-31 receptor A (IL-31RA) and the oncostatin M receptor and is expressed on various immune cells including T cells, keratinocytes, dendritic cells, eosinophils, basophils, macrophages and dorsal root ganglia
- IL-31 seems to be particularly implicated in pruritic dermatoses related to a prevalent Th2 type inflammation



The Role of Interleukin-31 in Pathogenesis of Itch and Its Intensity in a Course of Bullous Pemphigoid and Dermatitis Herpetiformis

Lilianna Kulczycka-Siennicka ¹, Anna Cynkier ¹, Elżbieta Waszczykowska ¹, Anna Woźniacka ¹, Agnieszka Żebrowska ¹

A recent study by our group demonstrated that IL-31 was found elevated in DH serum and significantly over-expressed in the skin, where it co-localized with IL-31RA

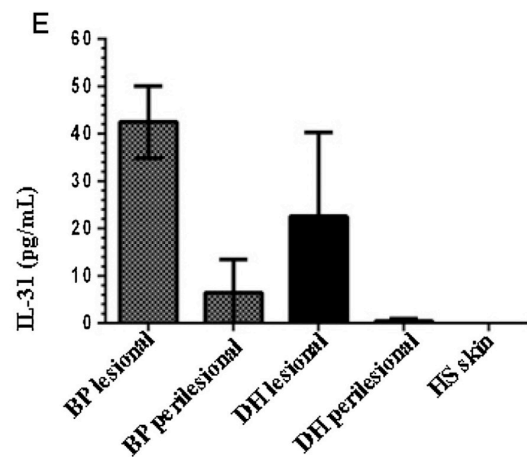
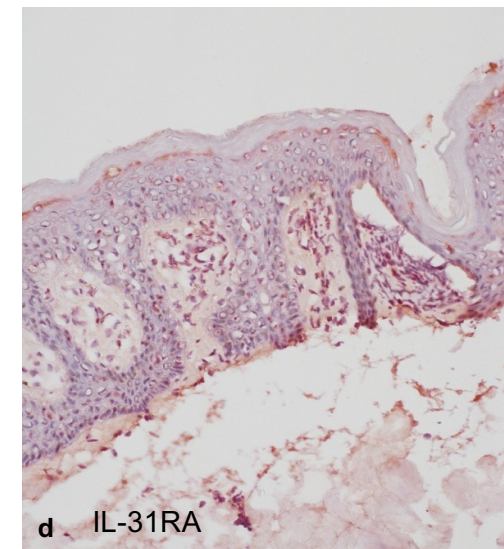
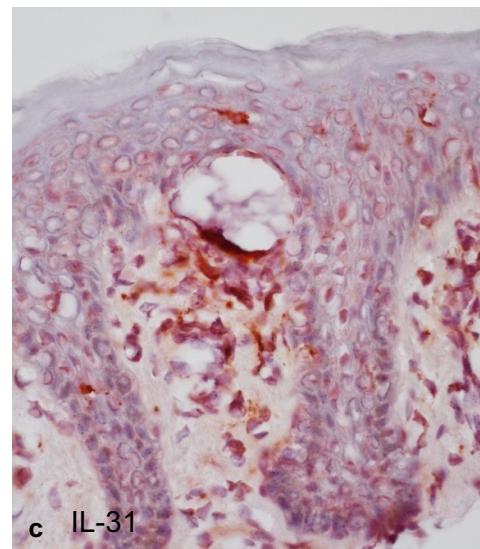
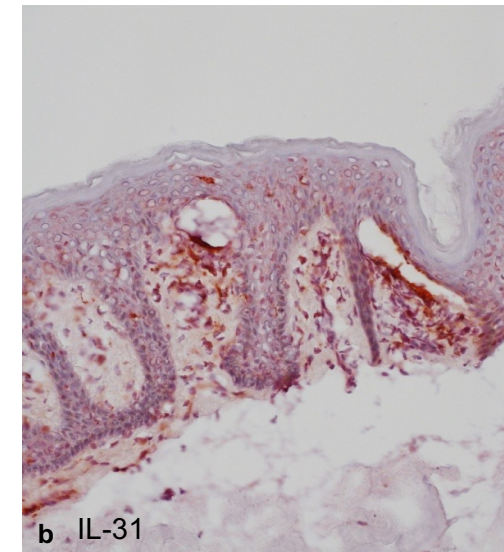
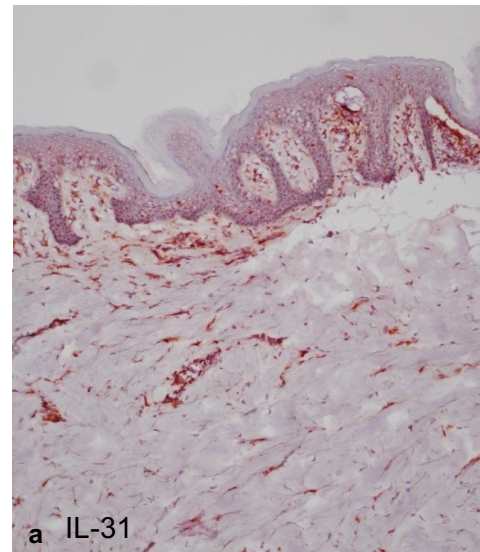


Fig. 1. Representative immunoreactivity for IL-31. A: DH lesional skin; B: DH perilesional skin; C: BP lesional skin; and D: BP perilesional skin. E: Mean $\pm$ SD immunofluorescence intensity of anti-IL-31 staining of the lesional and perilesional skin of BP, and DH, and HS skin.

LESIONAL DH



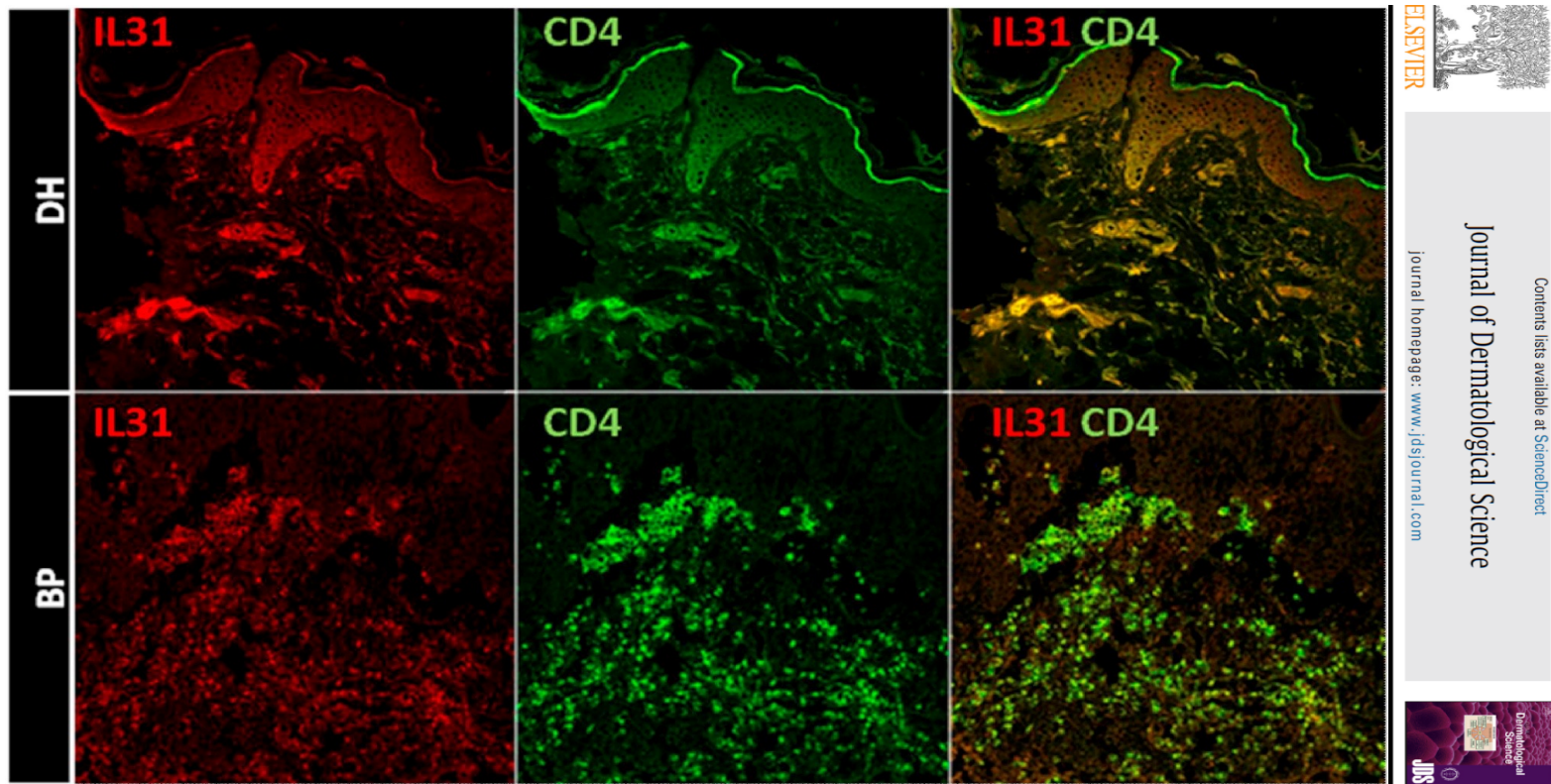


Fig. 2. Confocal microscopy of IL-31⁺ and CD4⁺ cells. Lesional skin specimens of DH and BP were stained for IL-31 (left) and CD4 (middle), and merged images are shown (right).

Boncianni D, Quintarelli L, Del Bianco E, Bianchi B, **Caproni M**. Serum levels and tissue expression of interleukin-31 in dermatitis herpetiformis and bullous pemphigoid. *J Dermatol Sci*. 2017;87(2):210-2.