

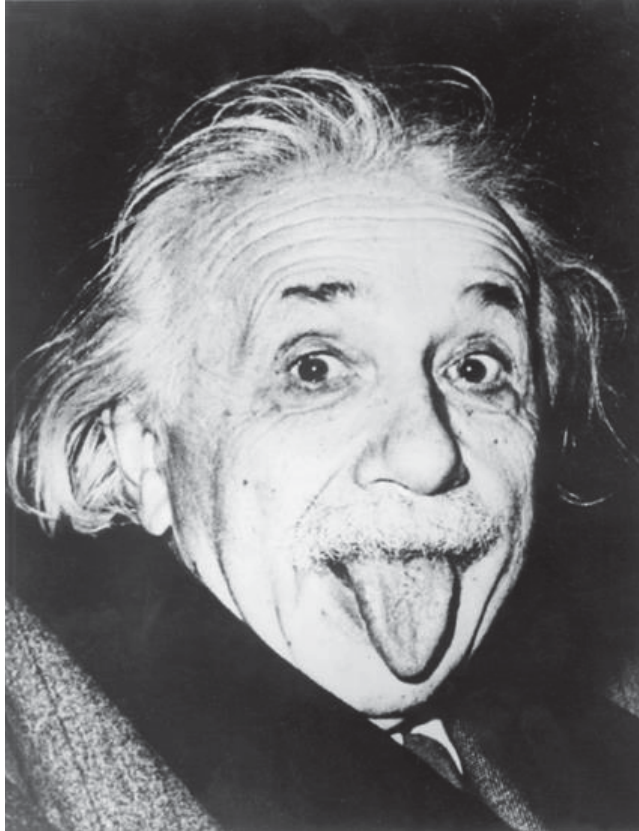


16th Summer Academy of Dermatopathology, Graz 2024

**Bullous dermatoses: How to diagnose
the common and rare diseases**

Christian Rose

Dermatopathology Lübeck



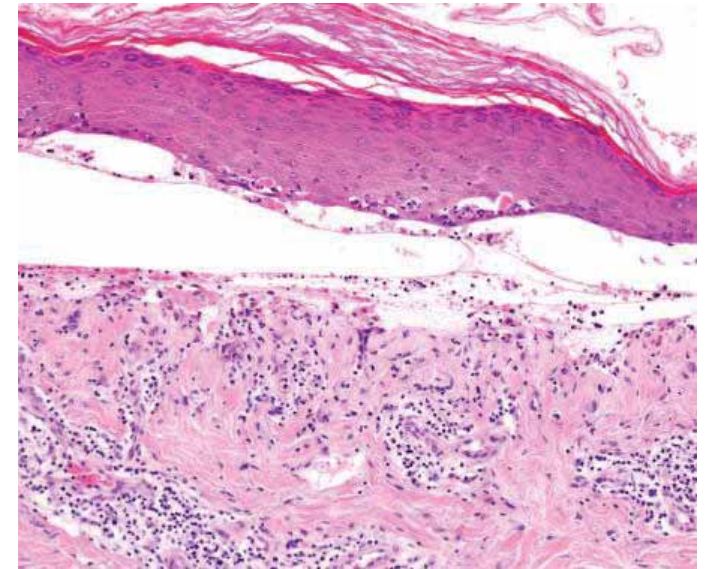
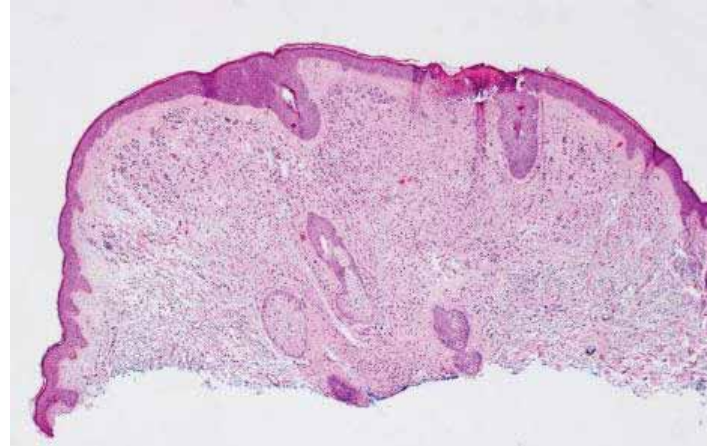
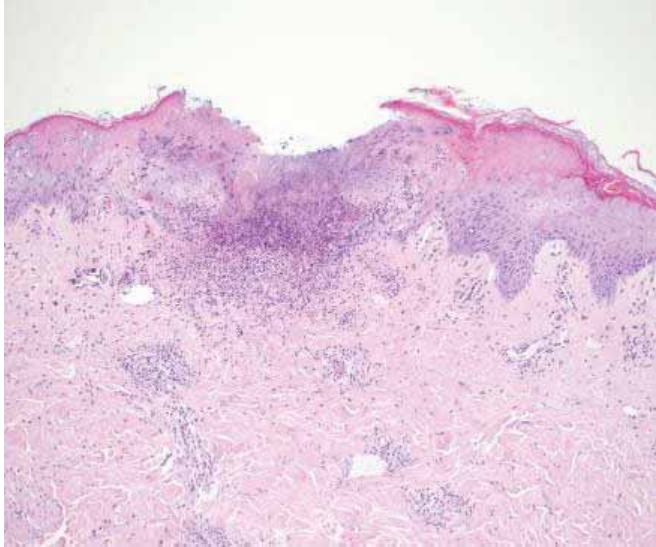
„Everything should be made as simple as possible, but not simpler.“

Albert Einstein



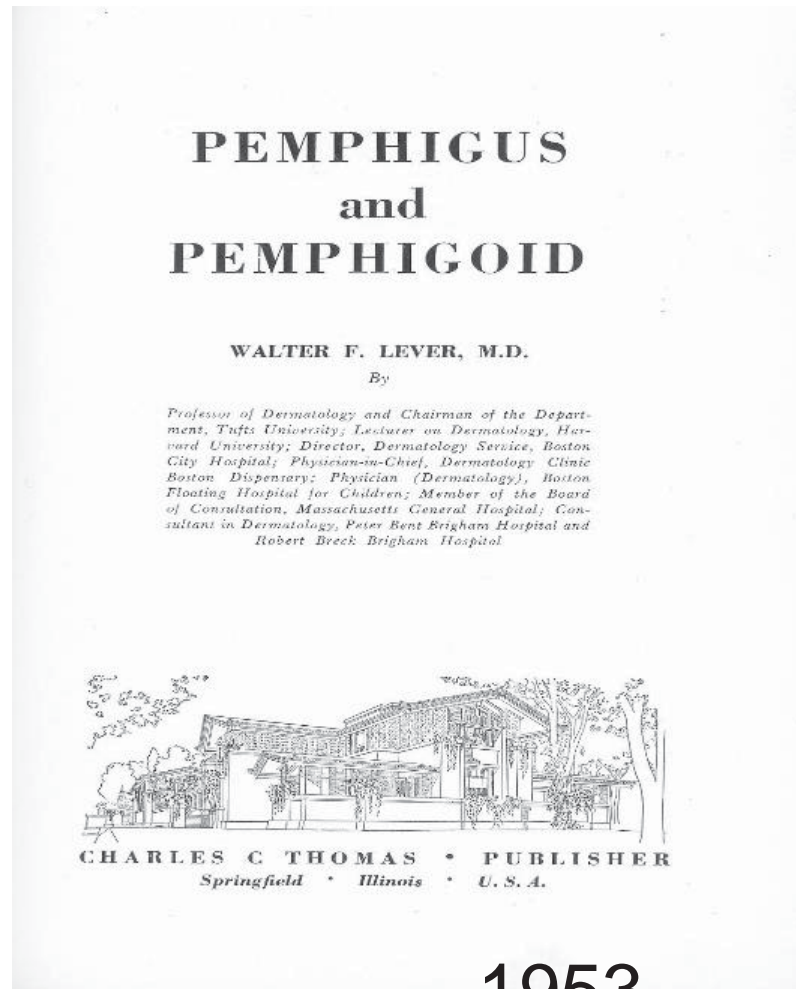
“Yoo-hoo! Oh, yoo-hoo! ...
I think I’m getting a blister.”

Do we have a blister?

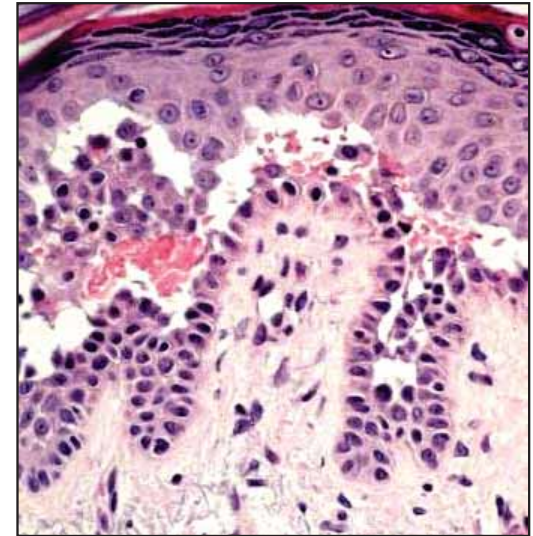




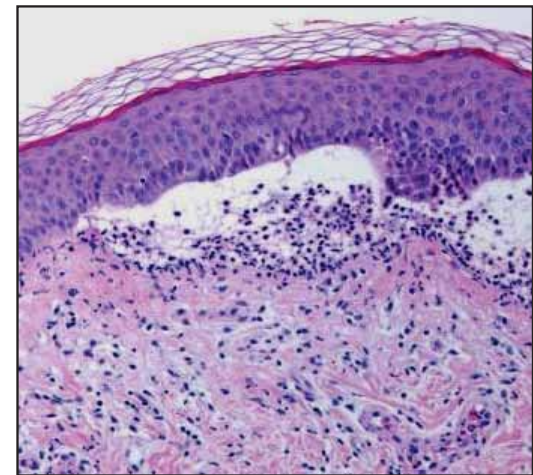
(1909 - 1993)



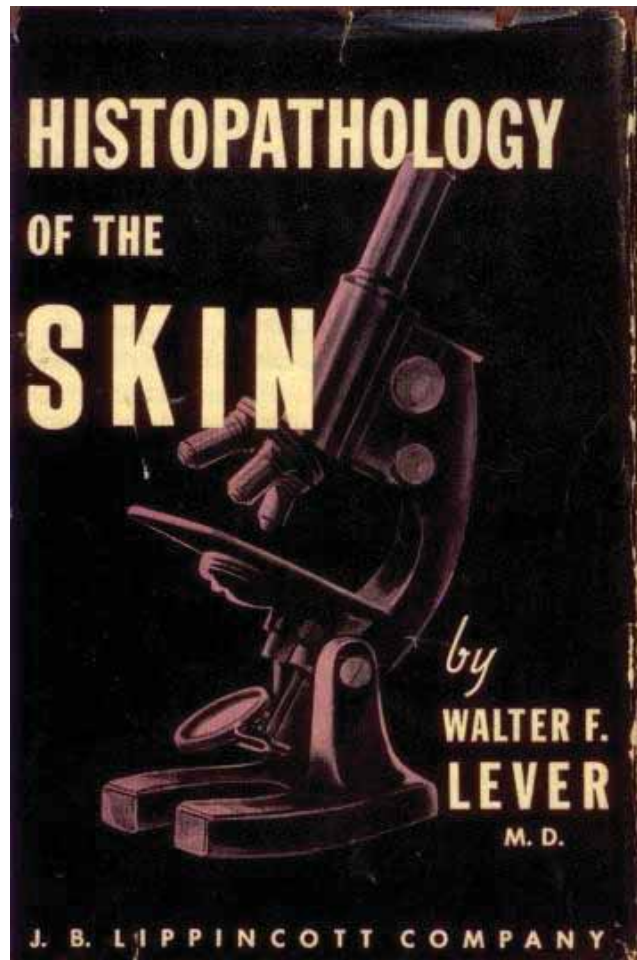
1953



Pemphigus



Pemphigoid



1948

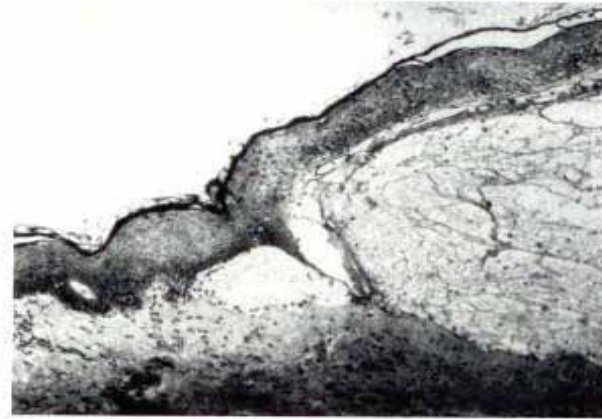


FIG. 3. Pemphigus vulgaris: Fig. 23 in the first edition.

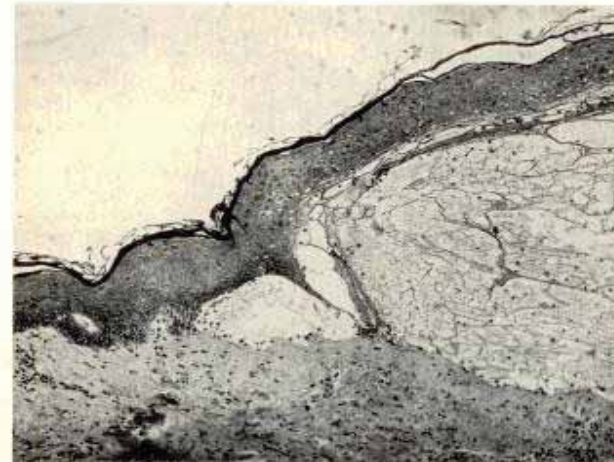
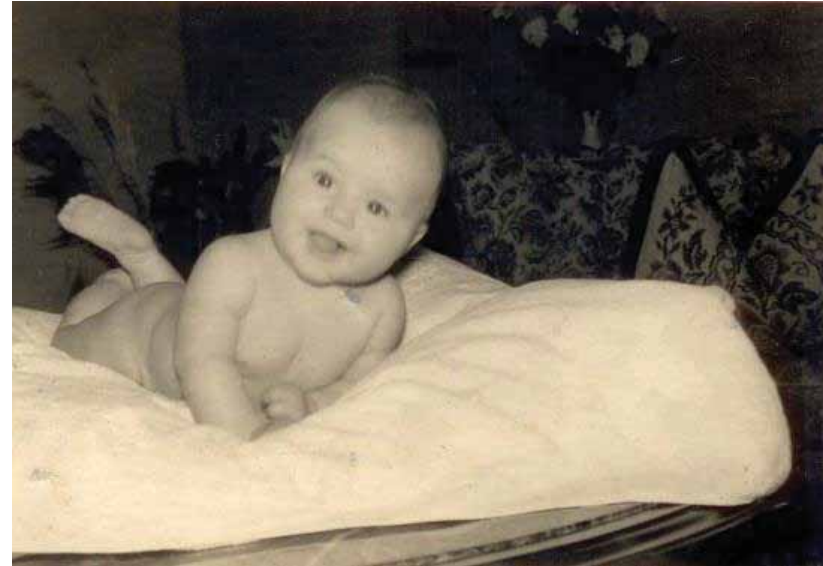


Abb. 35. Bullöses Pemphigoid. Eine große subepidermale Blase wird gezeigt. Auf der linken Seite kann man beobachten, wie die angesammelte Blasenflüssigkeit die unversehrte Epidermis von dem Corium abhebt. Die Blase enthält ein Fibrinnetz, aber nur wenige entzündliche Zellen. Das obere Corium zeigt Ödem mit sehr geringem entzündlichem Infiltrat. (x 100)

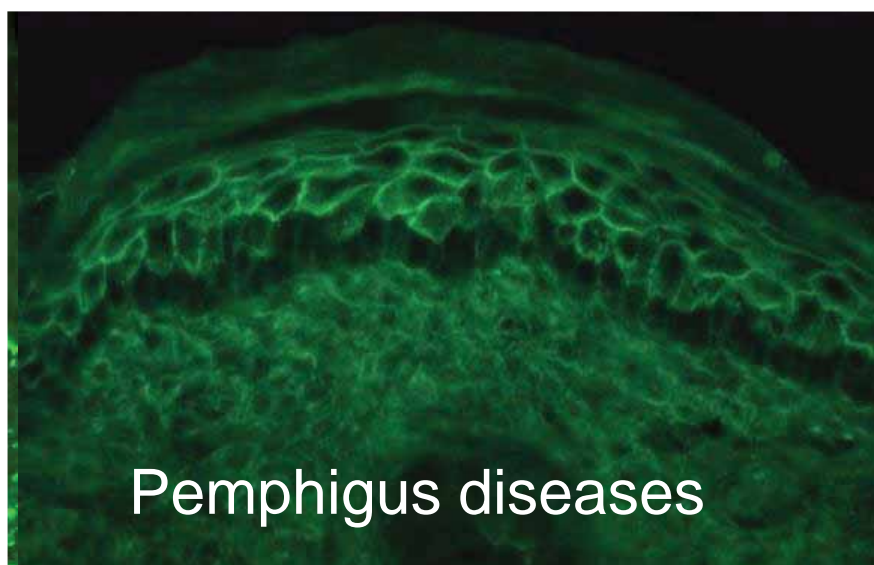
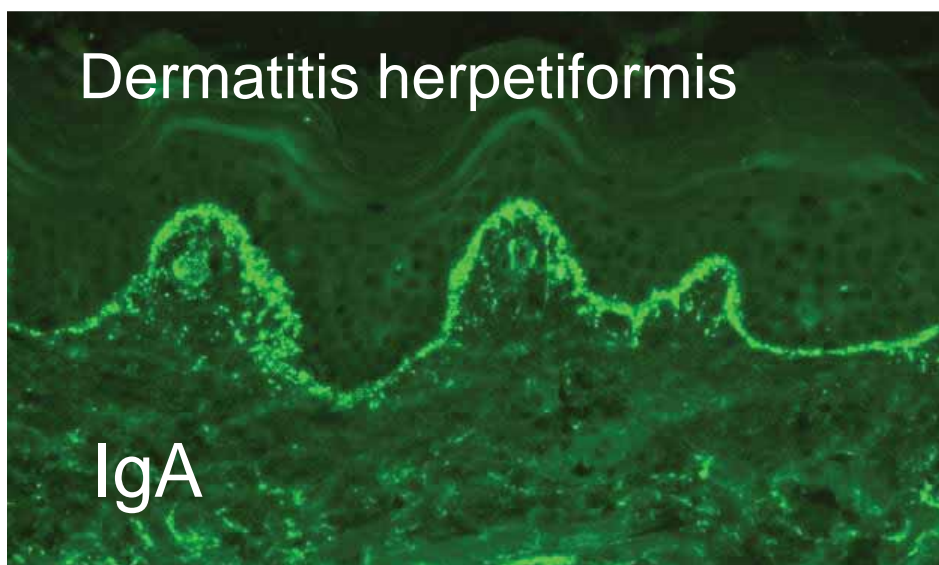
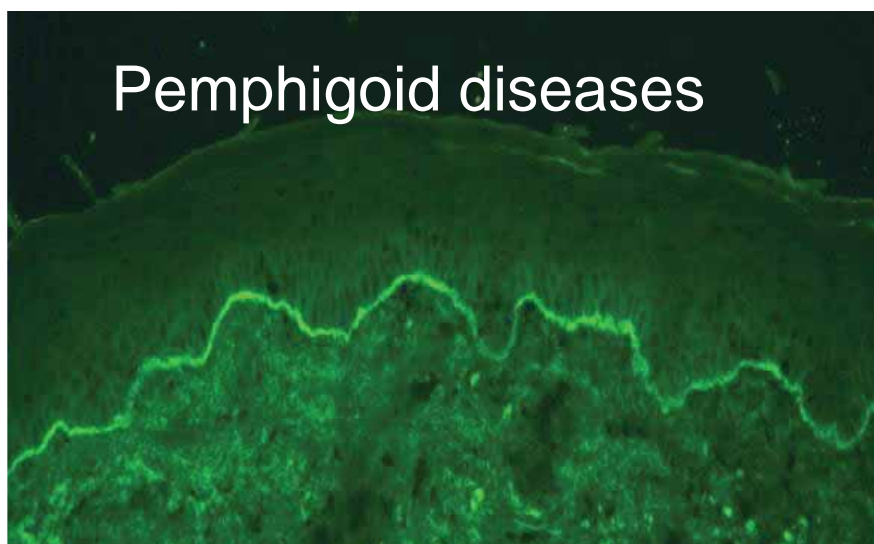
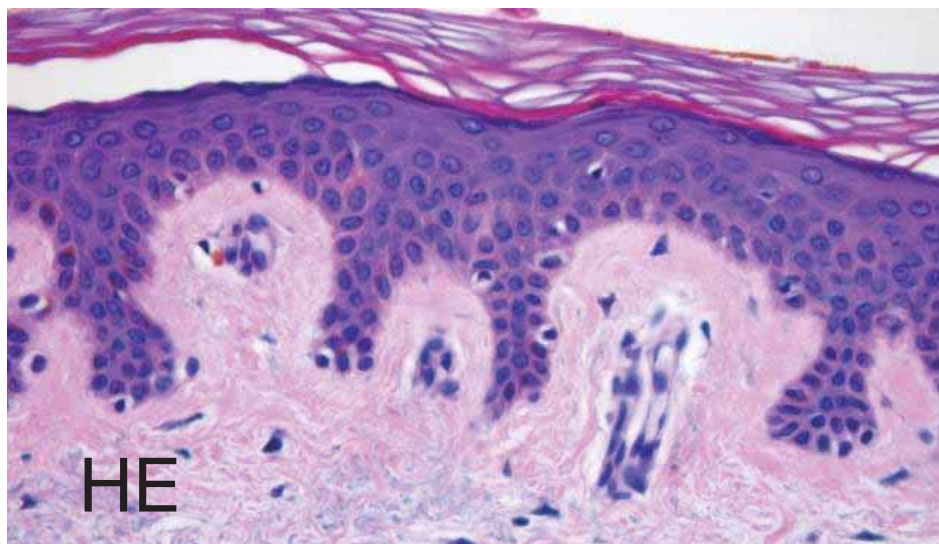


Beutner EH, Jordan RE

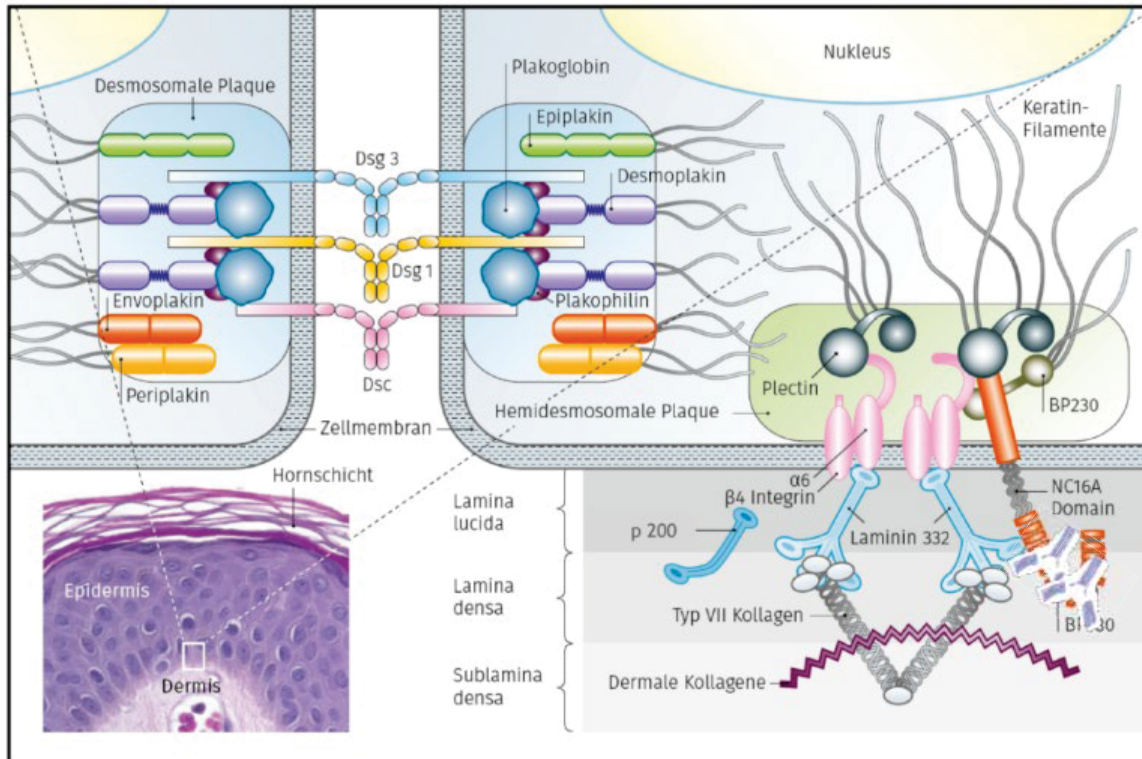
Demonstration of skin antibodies in sera of pemphigus vulgaris patients by indirect immunofluorescent staining

Proc Soc Exp Biol Med 1964; 117: 505-510

Direct immunofluorescence is gold standard



Target antigens of bullous autoimmune dermatoses



Van Beek et al, Dt. Aerzt Int 2021

Pemphigus diseases

- Pemphigus foliaceus
- Pemphigus vulgaris
- Paraneoplastic pemphigus
- IgA pemphigus

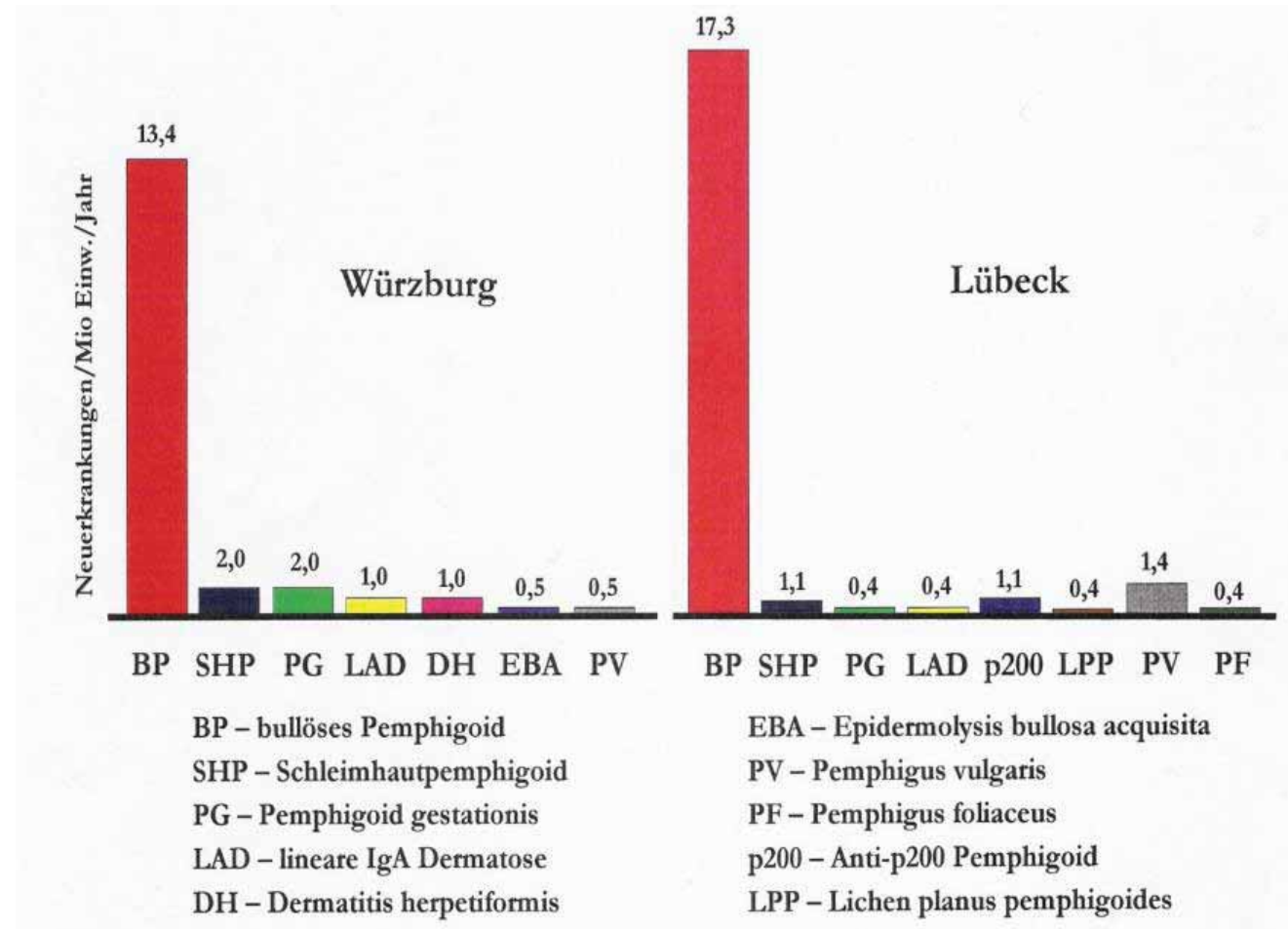
Pemphigoid diseases

- Bullous pemphigoid
- Mucous membrane pemphigoid
- Linear IgA disease
- Pemphigoid gestationis
- Anti-p200 pemphigoid

Epidermolysis bullosa acquisita

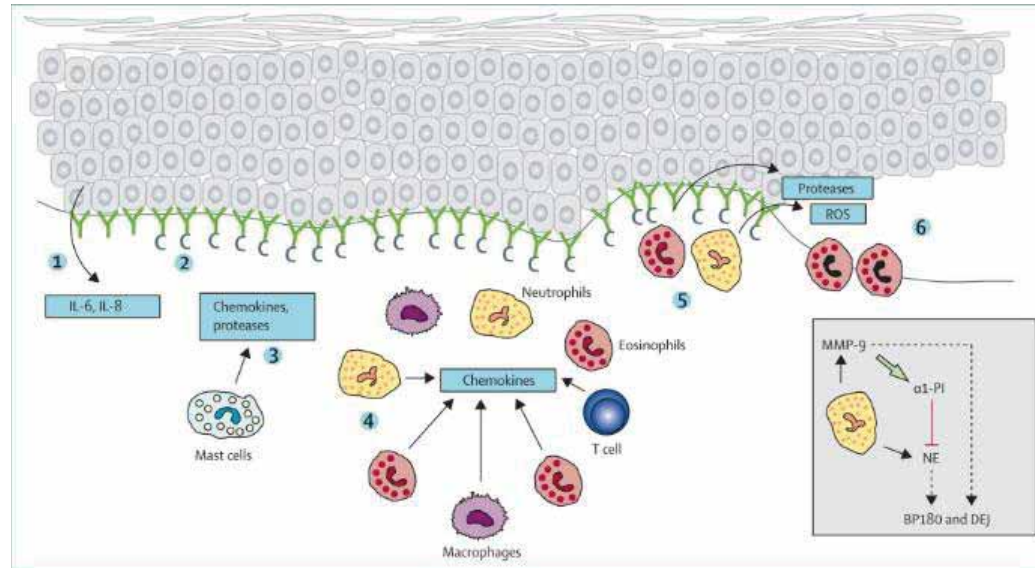
Dermatitis herpetiformis

Frequency of bullous autoimmune dermatoses

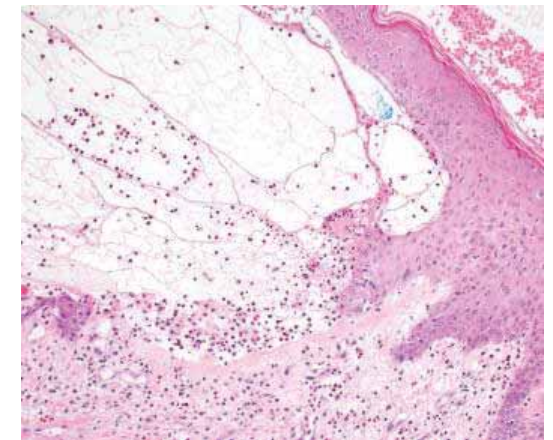
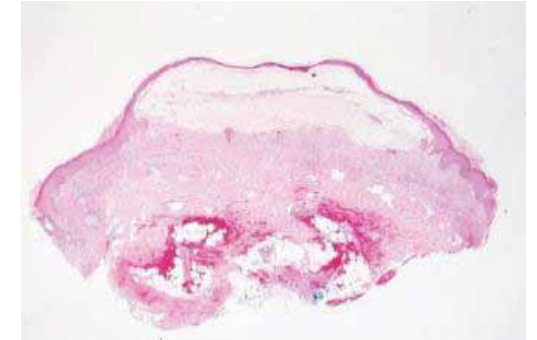
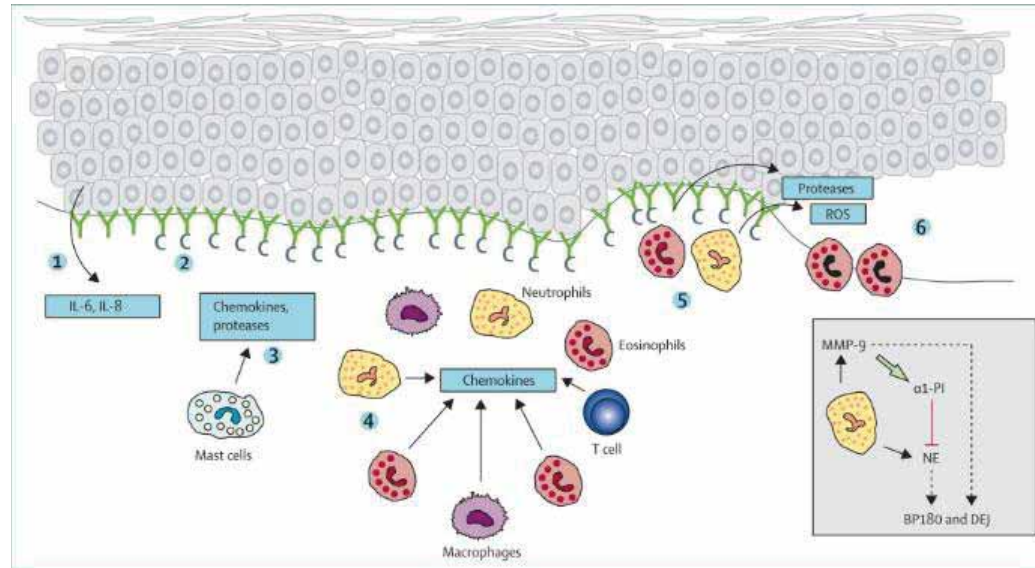


Bullous pemphigoid

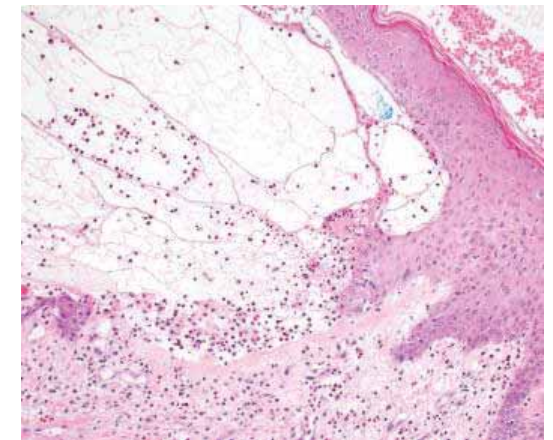
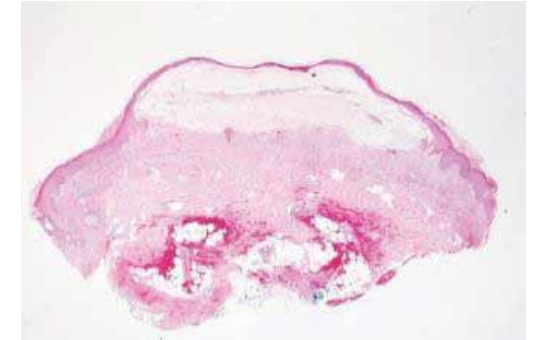
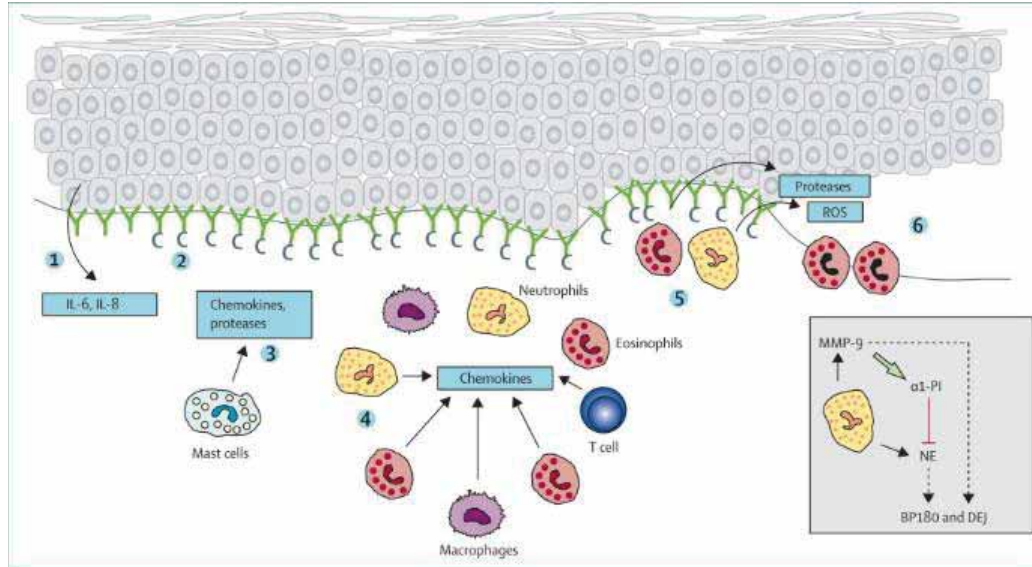
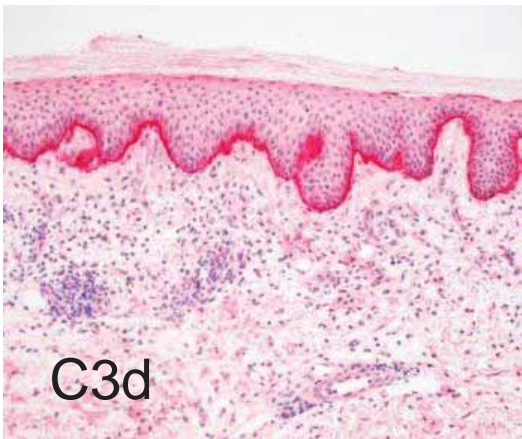
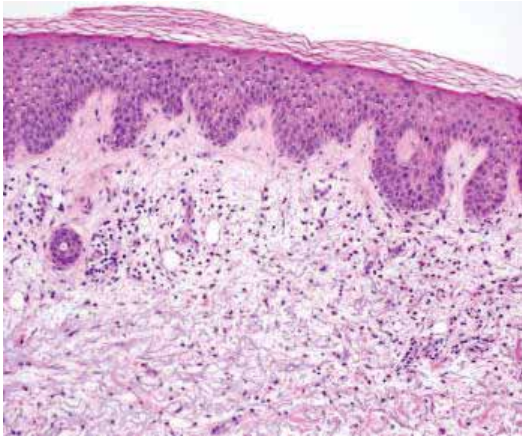




Schmidt et Zillikens, *Pemphigoid diseases*, Lancet 2013

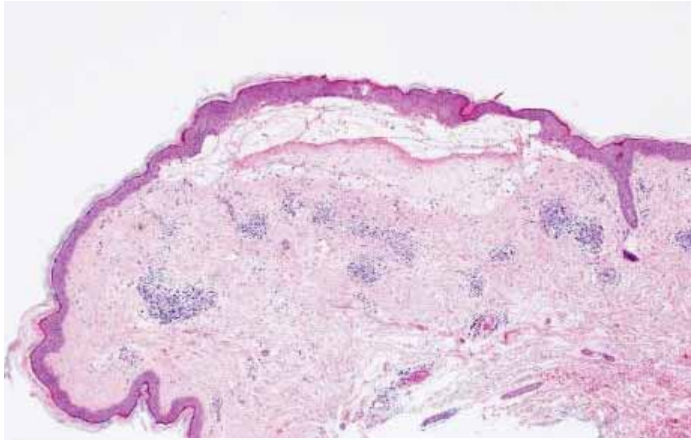


Schmidt et Zillikens, *Pemphigoid diseases*, Lancet 2013

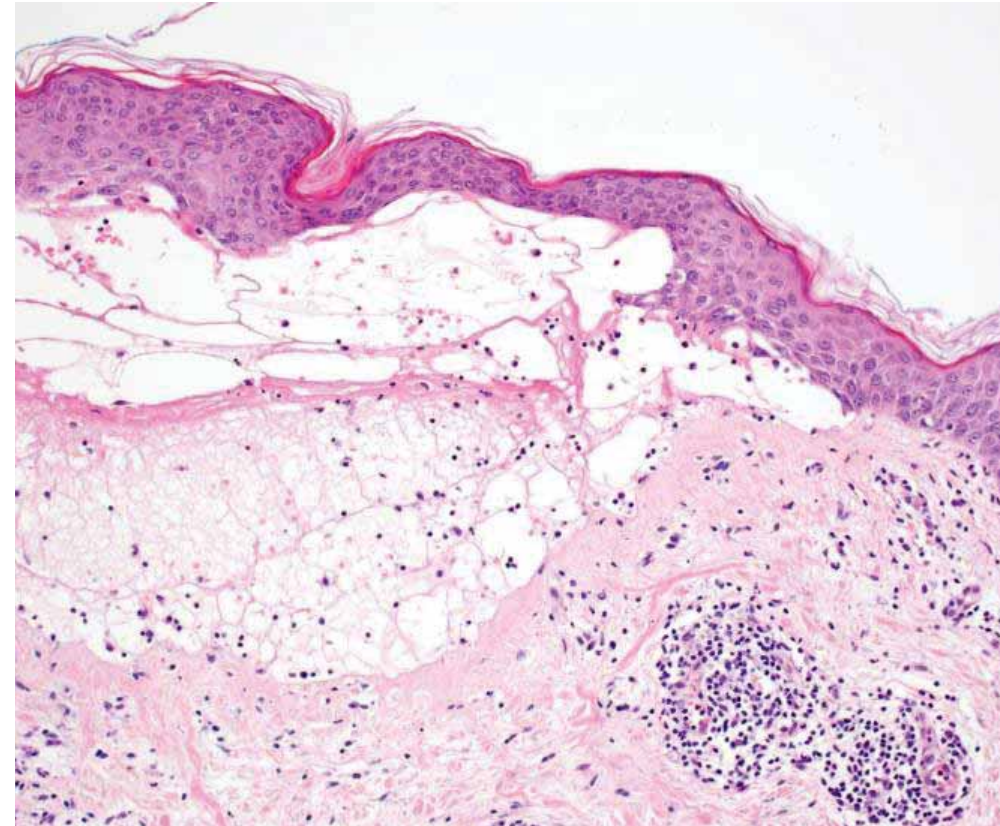
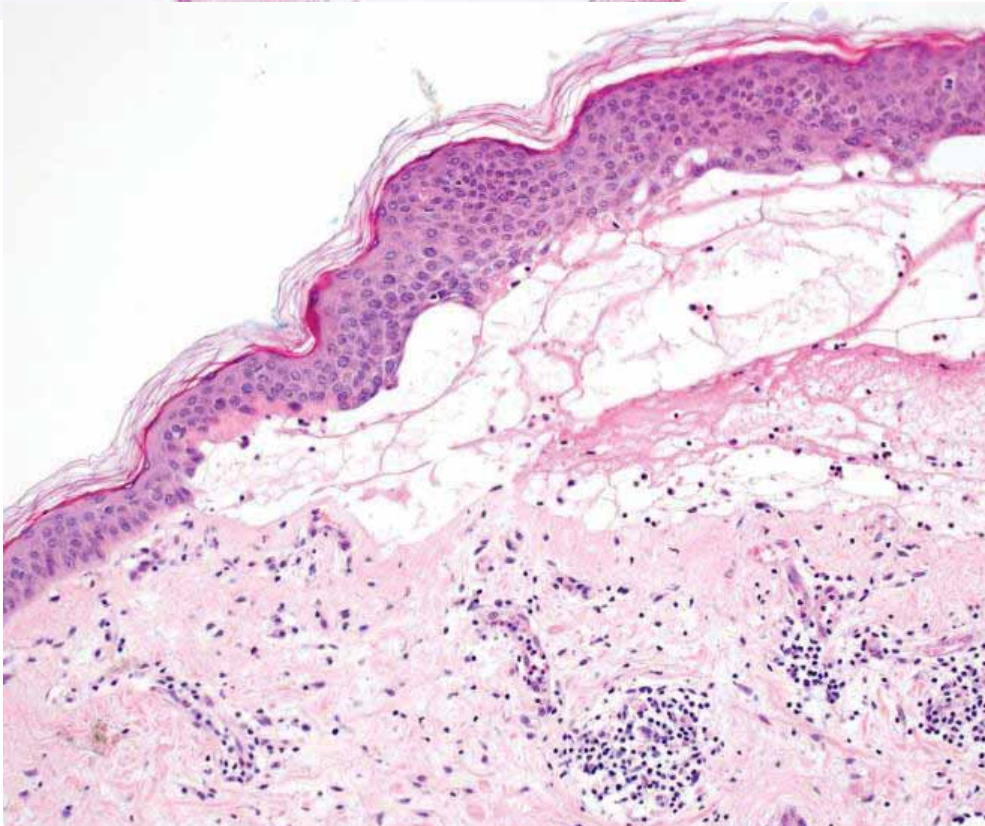


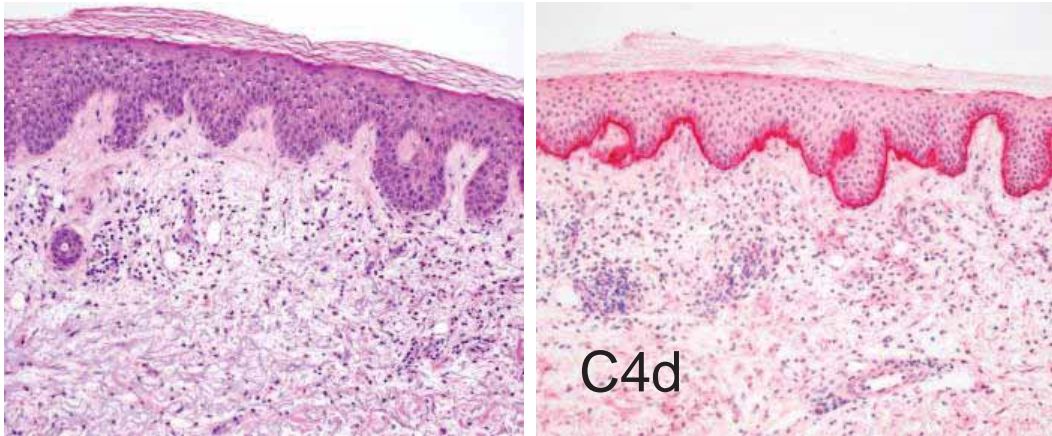
Schmidt et Zillikens, *Pemphigoid diseases*, Lancet 2013





Poor cell-type bullous pemphigod





C4d immunohistochemical stain is a sensitive method to confirm immunoreactant deposition in formalin-fixed paraffin-embedded tissue in bullous pemphigoid

Background: Bullous pemphigoid (BP) is characterized clinically by the onset of pruritic urticarial plaques, vesicles and bullae in a predominantly elderly population. While the diagnosis may be

Wells Chandler, MD¹, John Zone, MD² and Scott Florell, MD²

Accepted: 5 May 2018

DOI: 10.1111/jop.12732

ORIGINAL ARTICLE

WILEY *Journal of Oral Pathology & Medicine*

Immunohistochemical diagnosis of mucous membrane pemphigoid

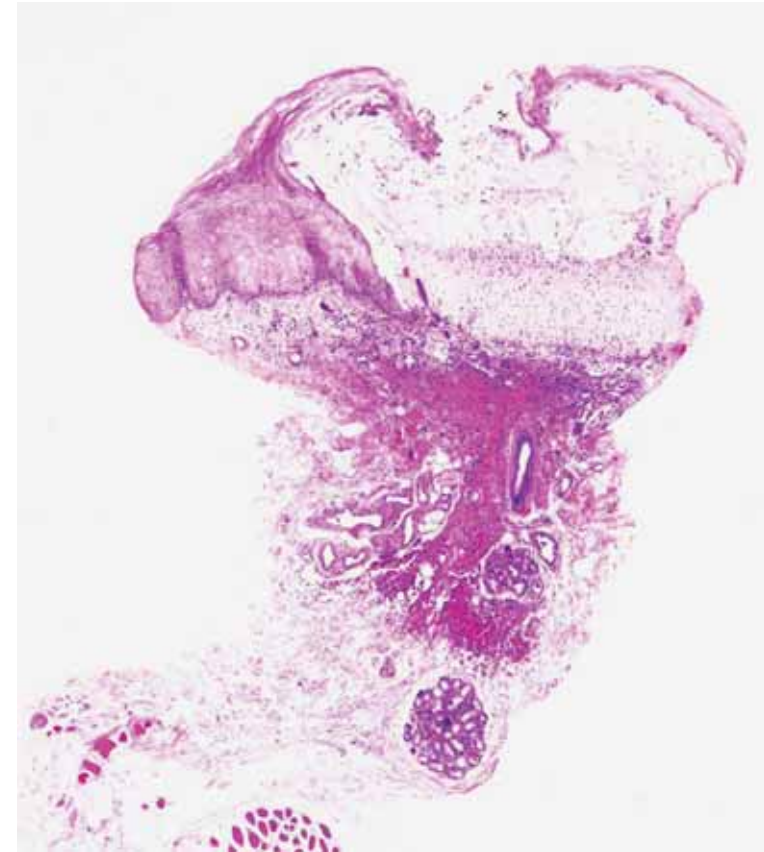
Iakov Shimanovich¹ | Julia Marie Nitz¹ | Mareike Witte¹ | Detlef Zillikens¹ | Christian Rose^{1,2}

Application of C4d Immunohistochemistry on Routinely Processed Tissue Sections for the Diagnosis of Autoimmune Bullous Dermatoses

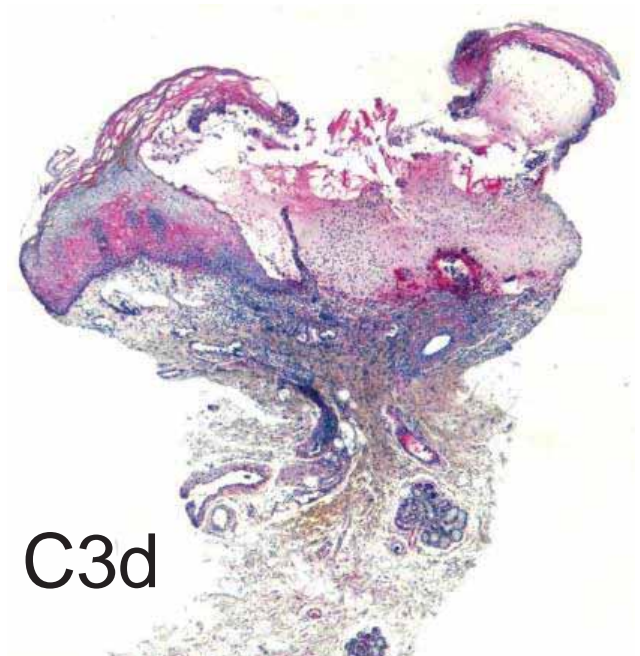
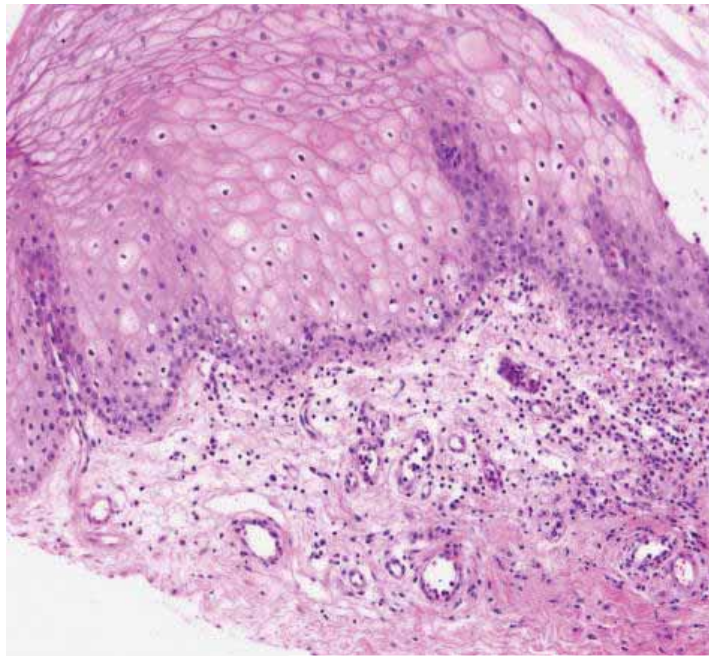
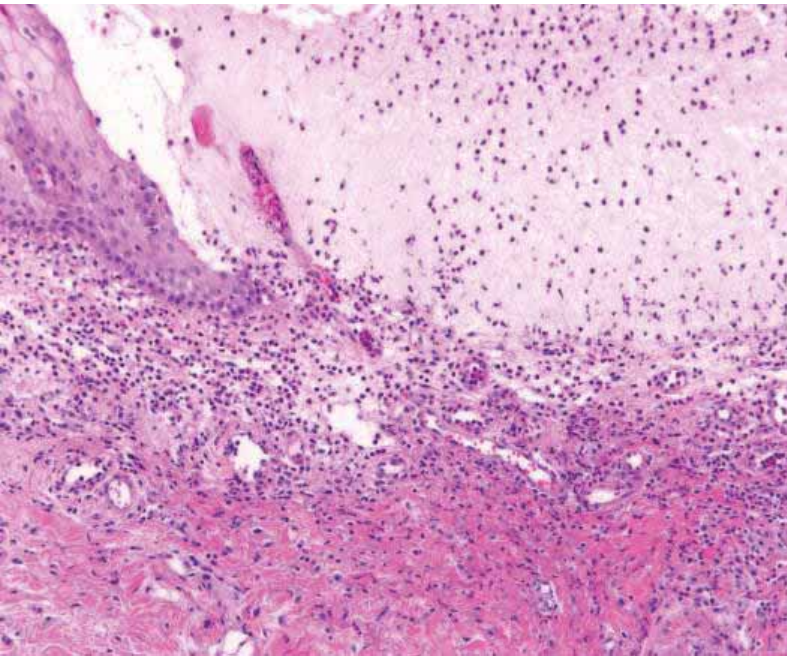
Axel P. Villani, MD,*† Brigitte Chouvet, MD,*† and Jean Kanitakis, MD*†

The use of C3d and C4d immunohistochemistry on formalin-fixed tissue as a diagnostic adjunct in the assessment of inflammatory skin disease

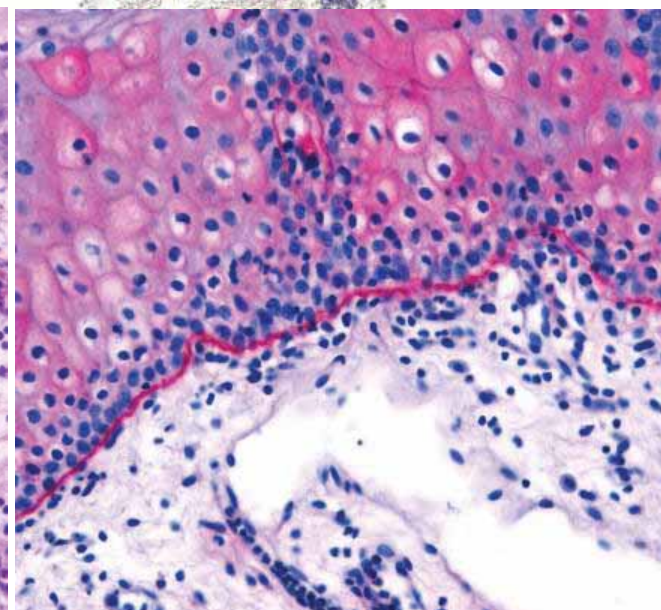
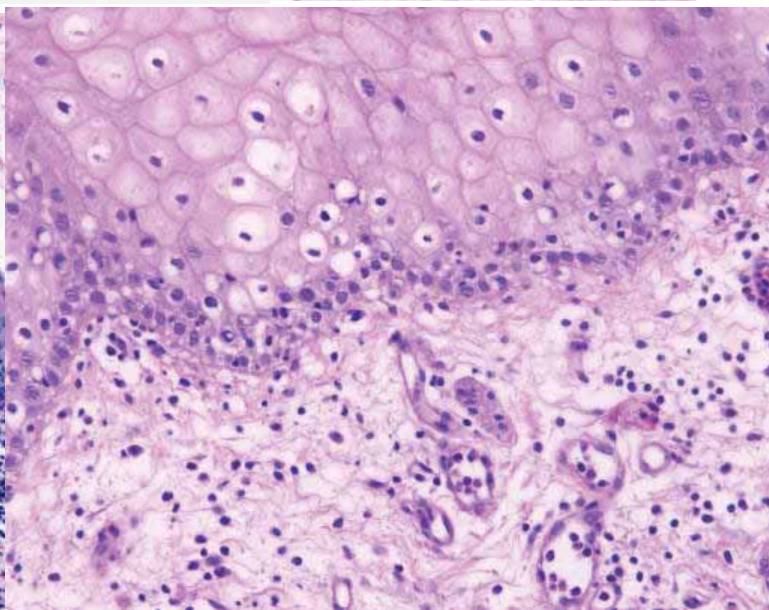
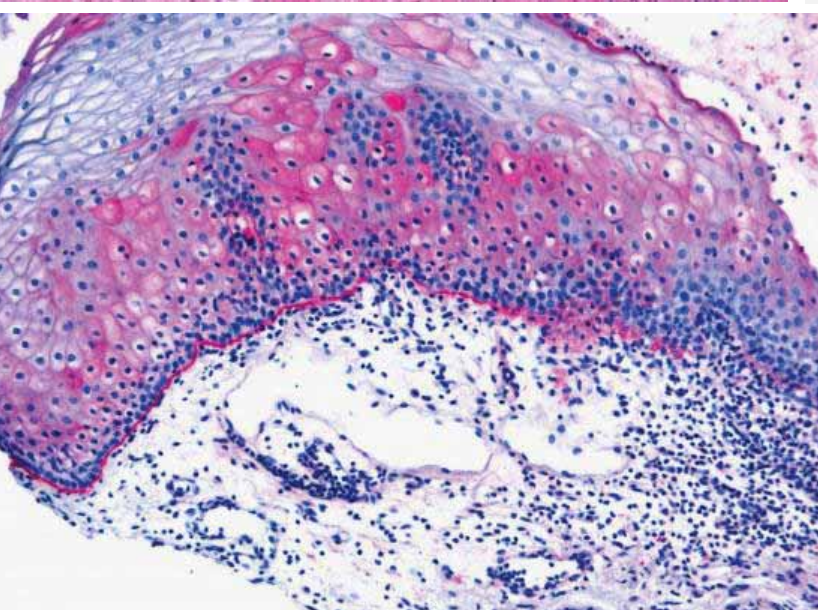
Cynthia M. Magro, MD, and Molly E. Dyrsen, MD
New York, New York



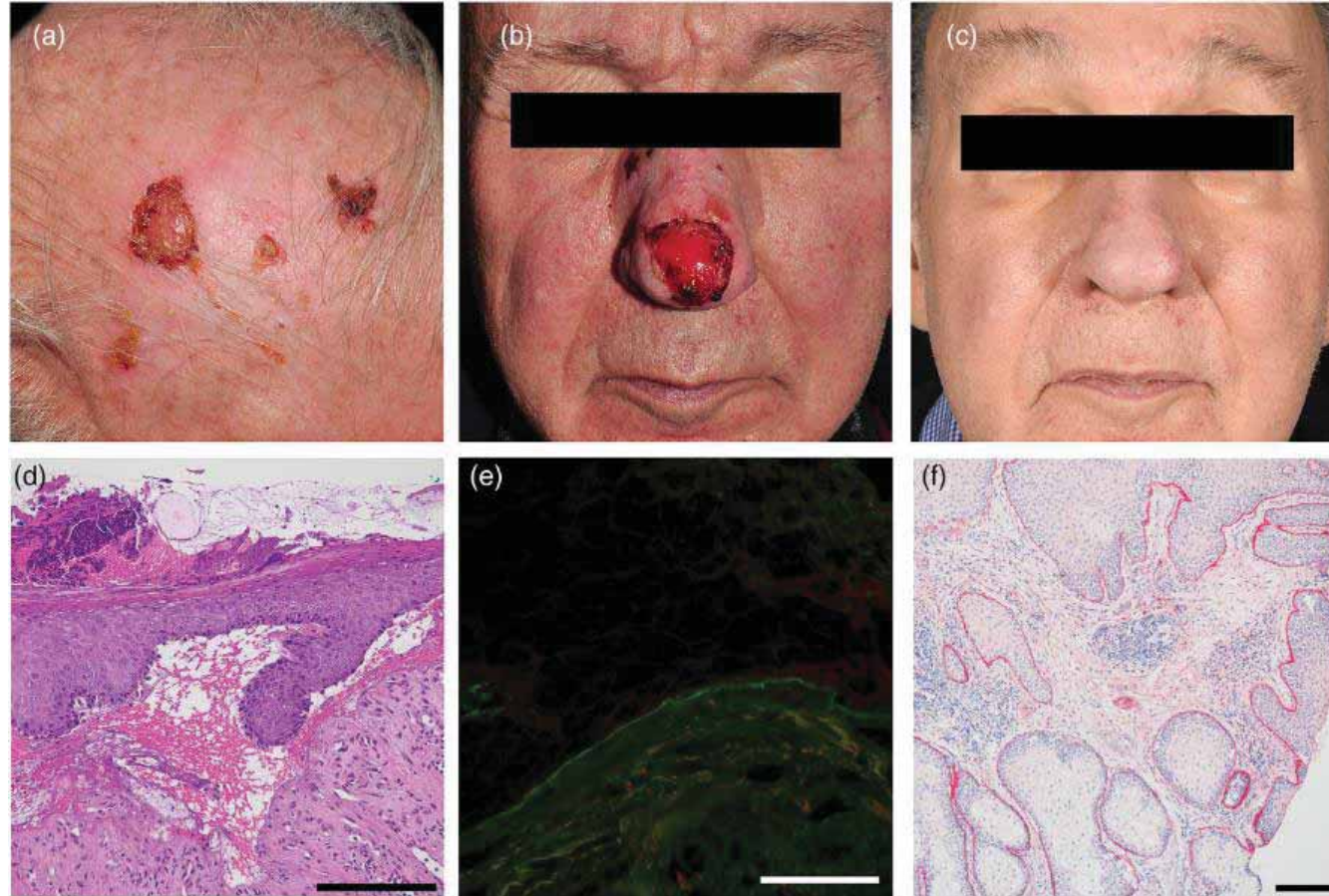
67 y, male



C3d

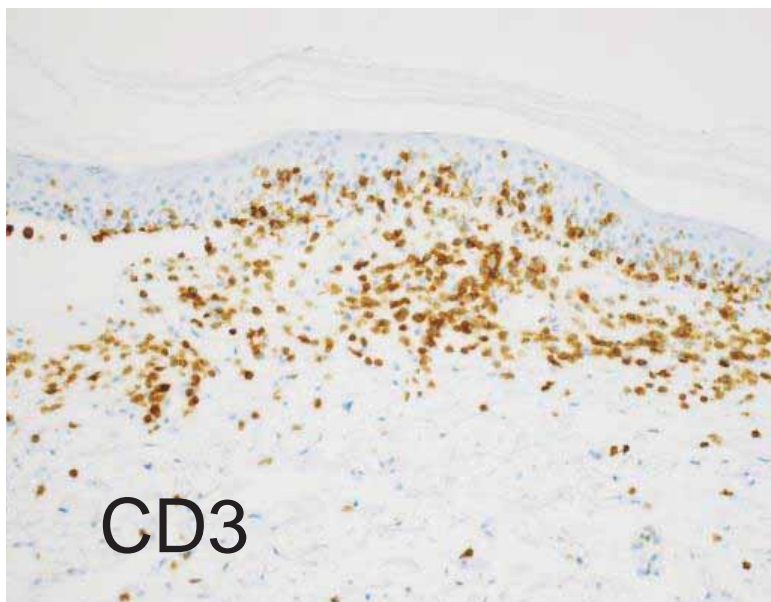
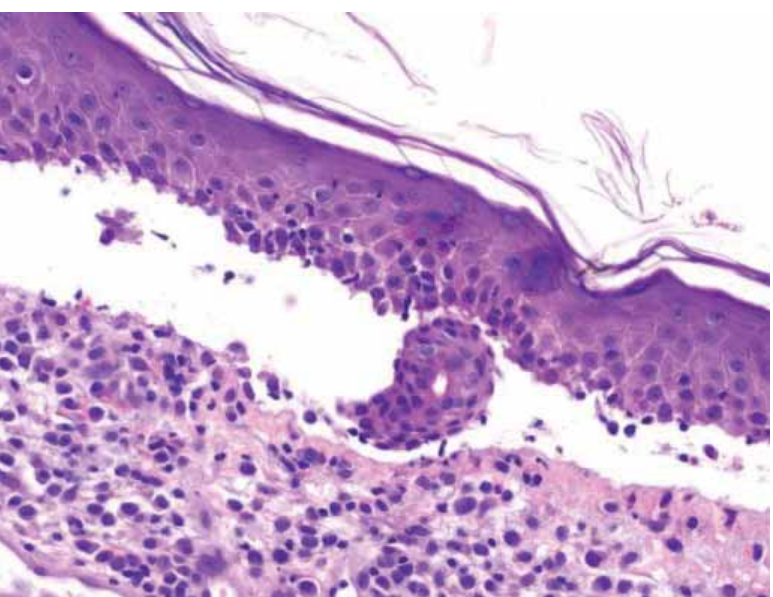
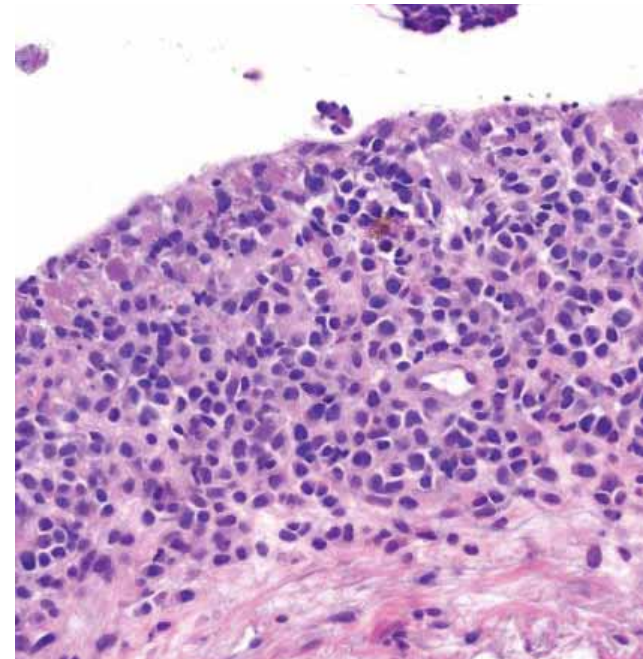
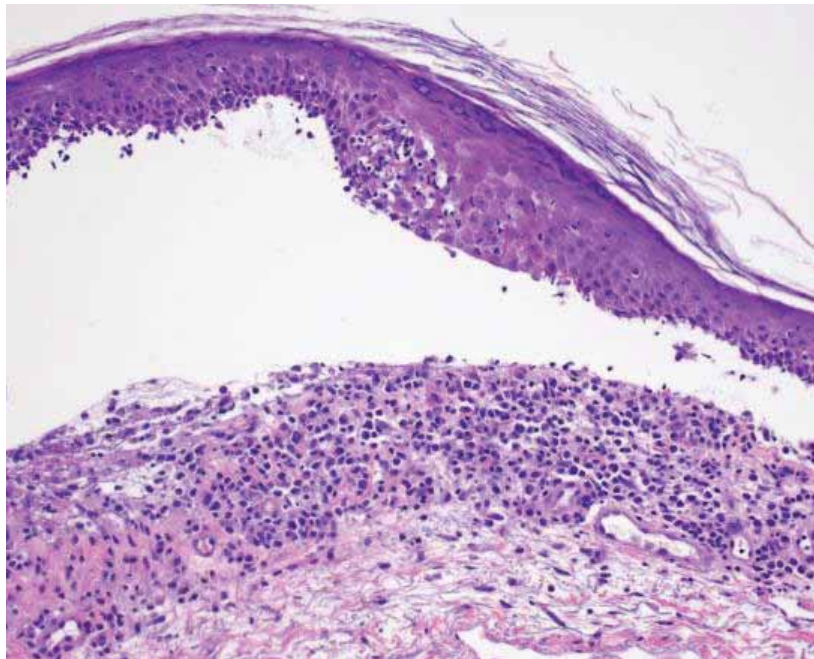
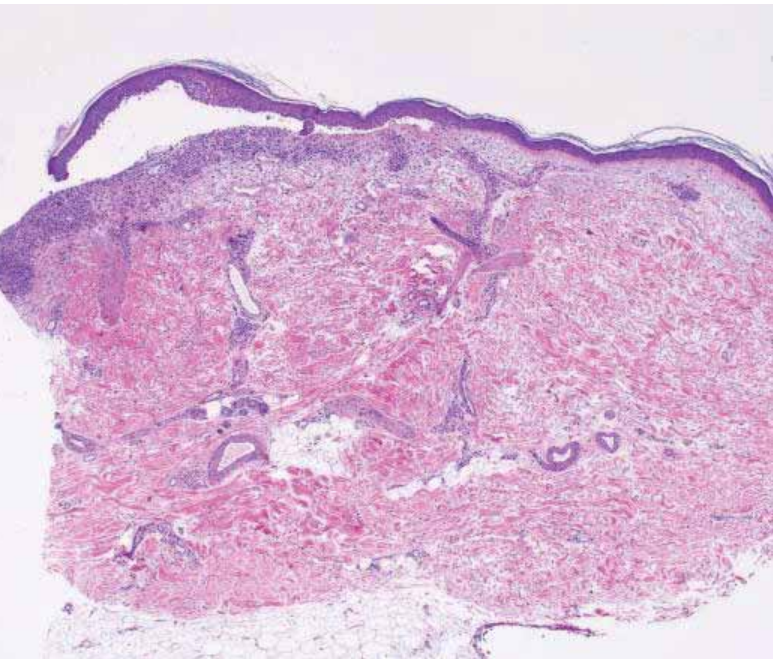


Facets of pemphigoid: Localized scarring Brunsting-Perry pemphigoid

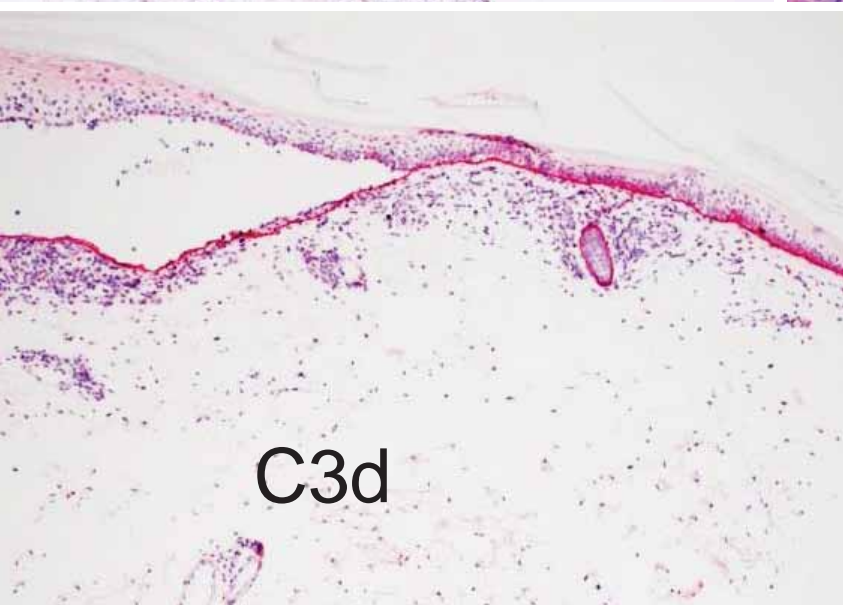
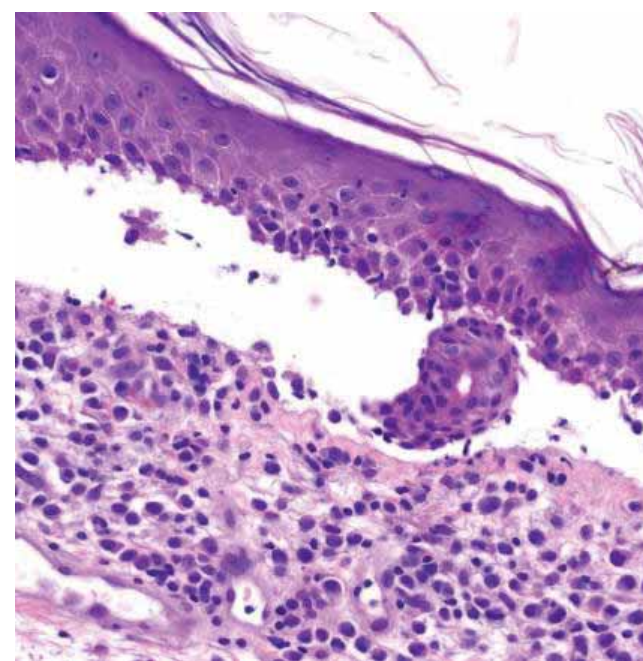
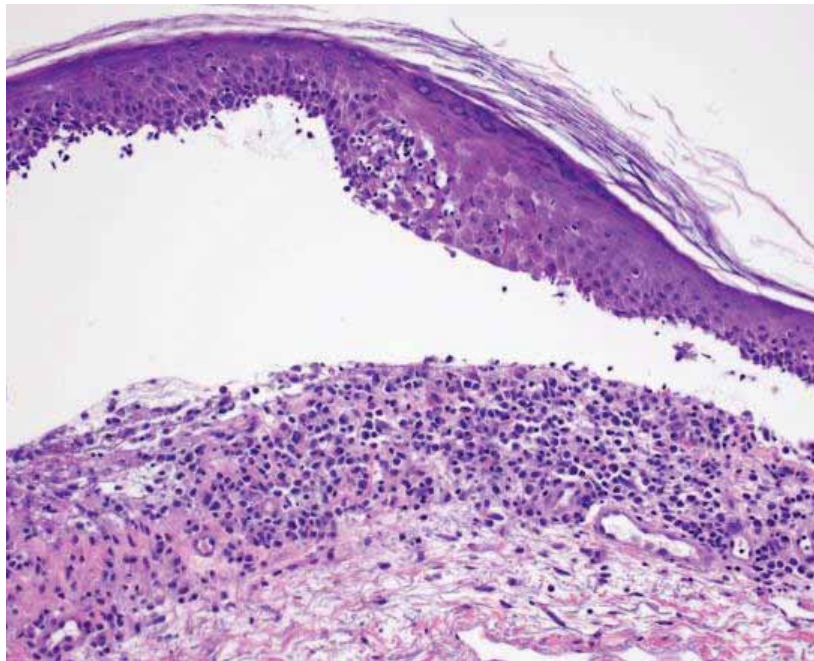
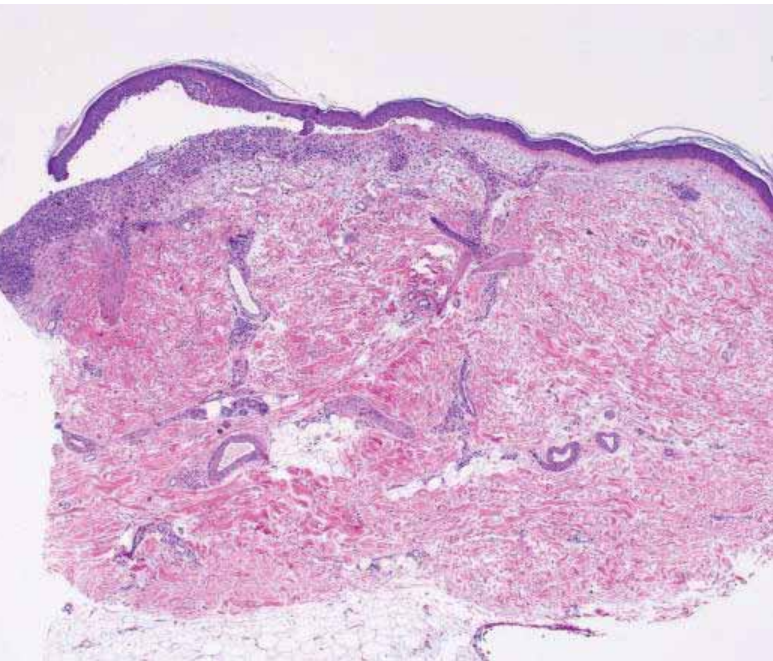


80 y, male

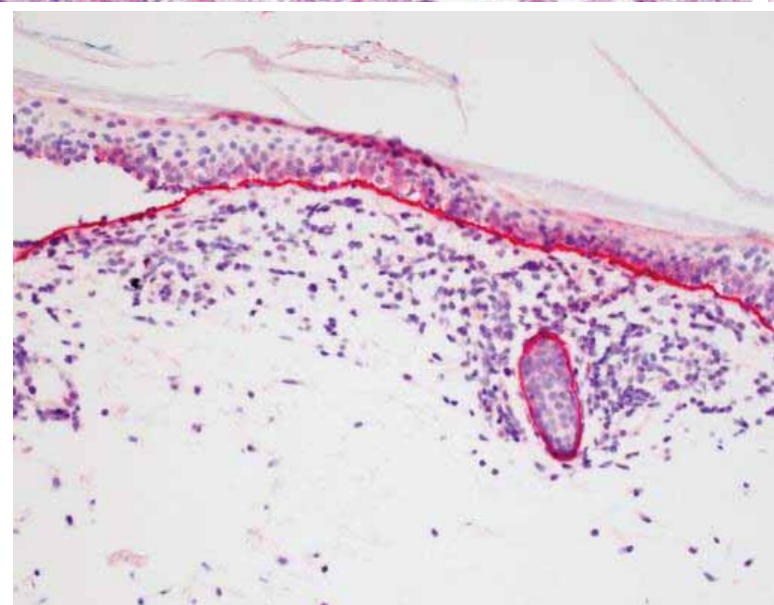
Lennartz JC, Bohne AS, Kaeding M, Rose C, Boch K, Schmidt, E, Weidinger S, Hammers CM. JDDG 2024, 22, 844-6



72 y, male
known MF for years,
erosions under
therapy with
mogamulizumab



C3d

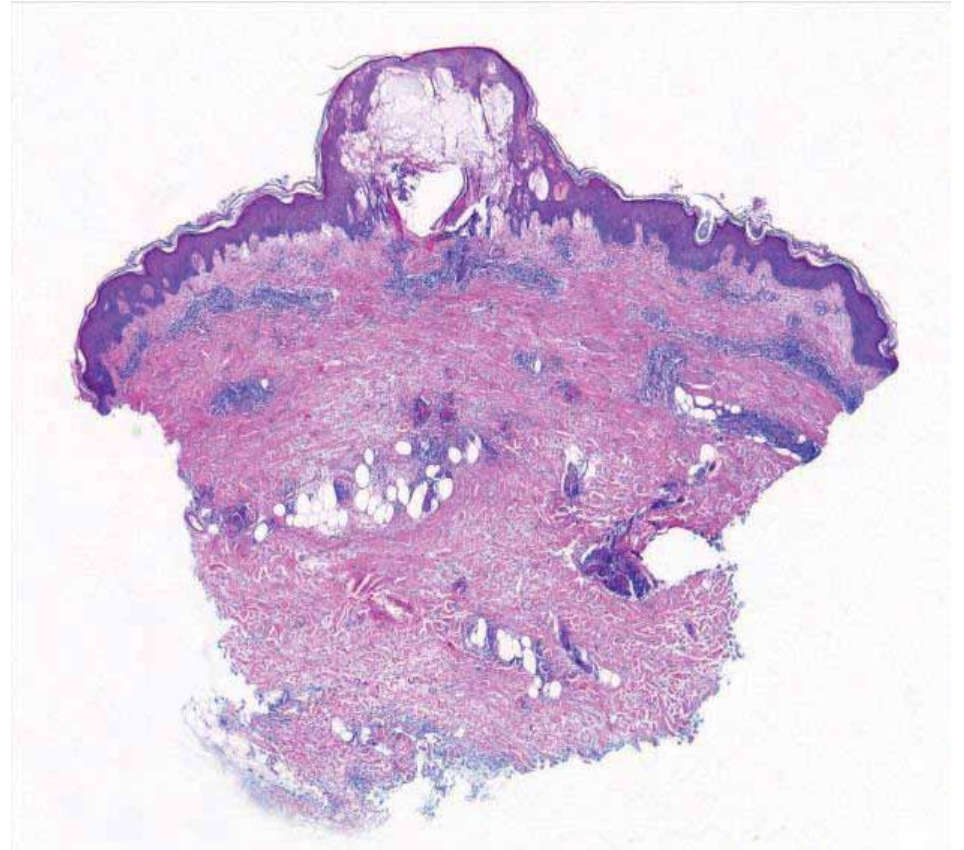


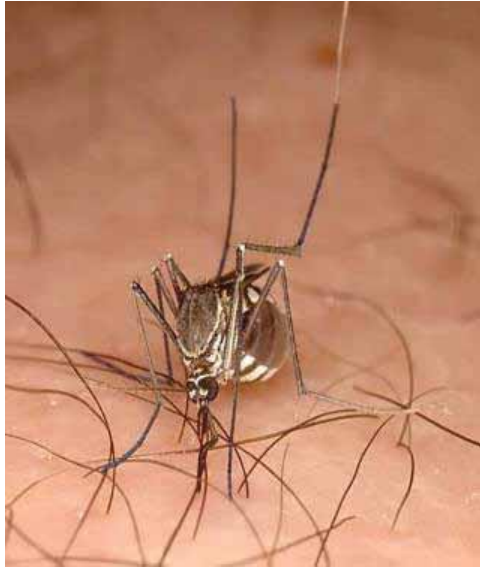
DIF: C3 positive
BP180: 1972 U/ml

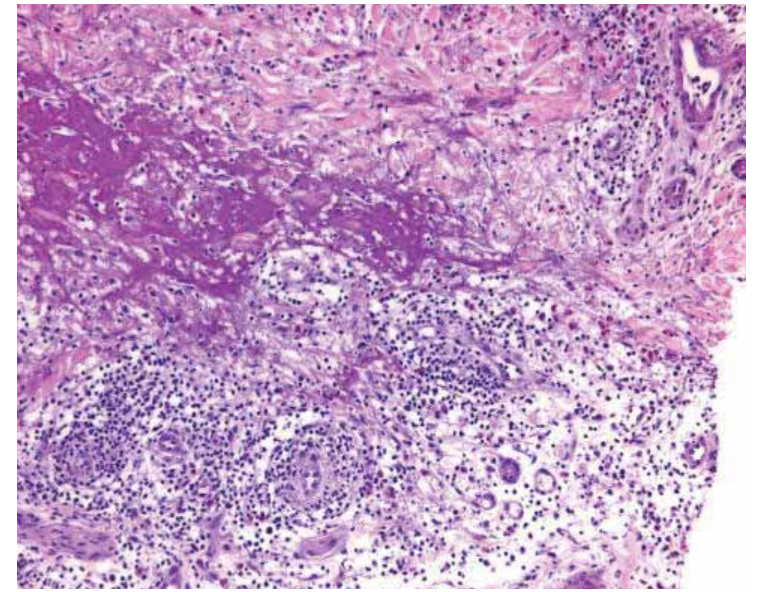
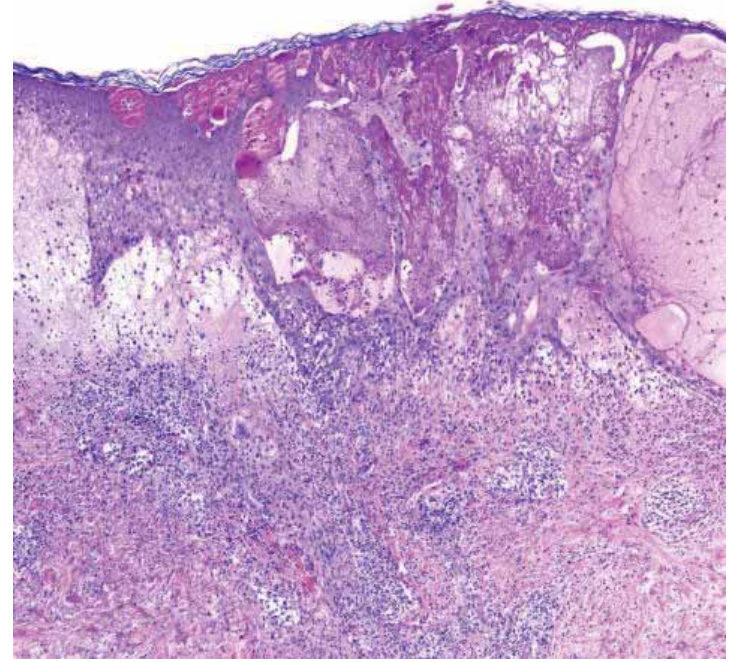
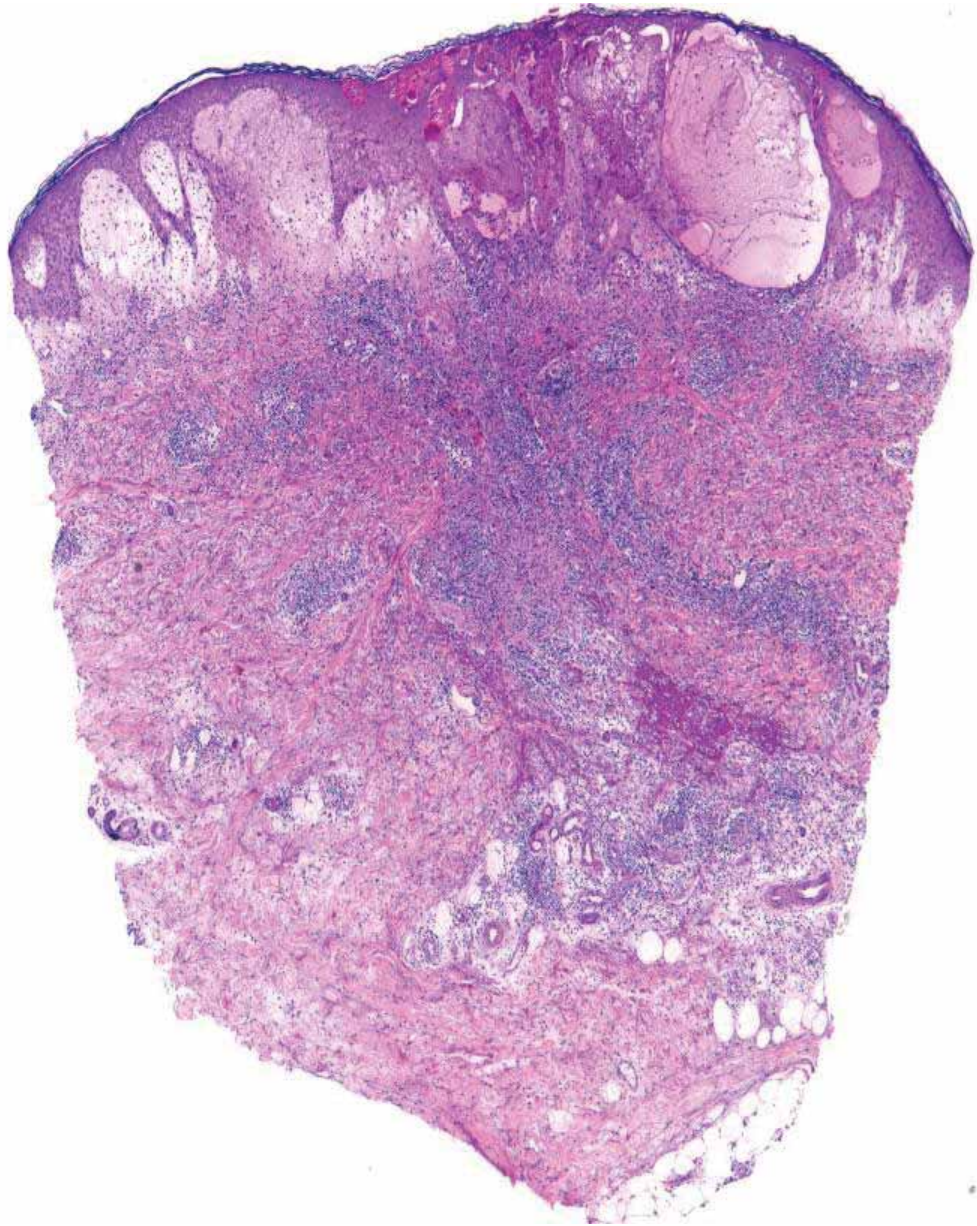


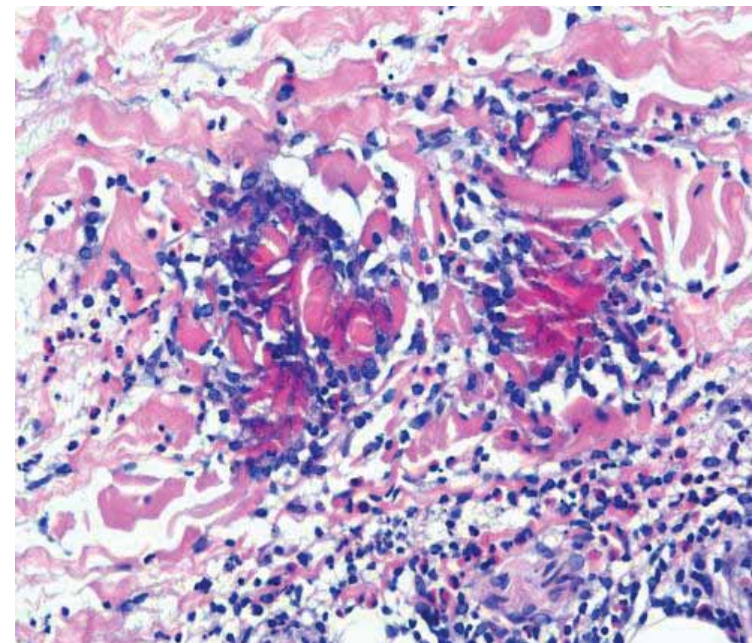
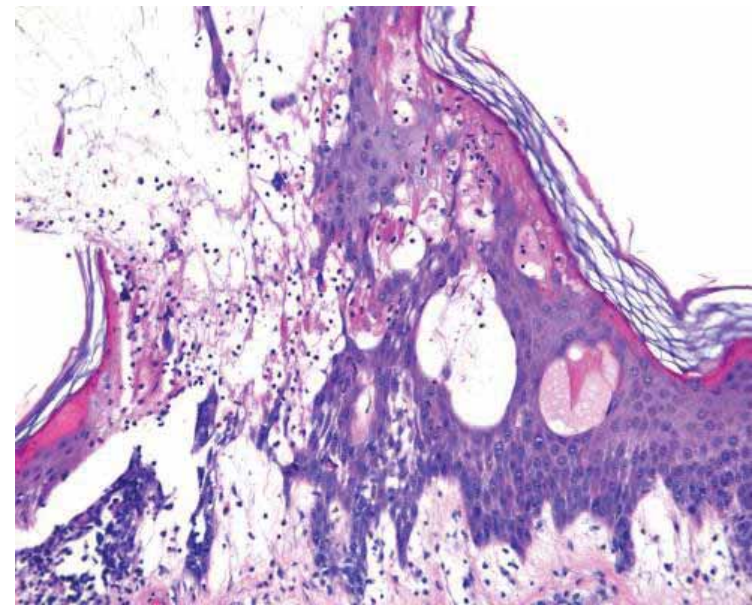
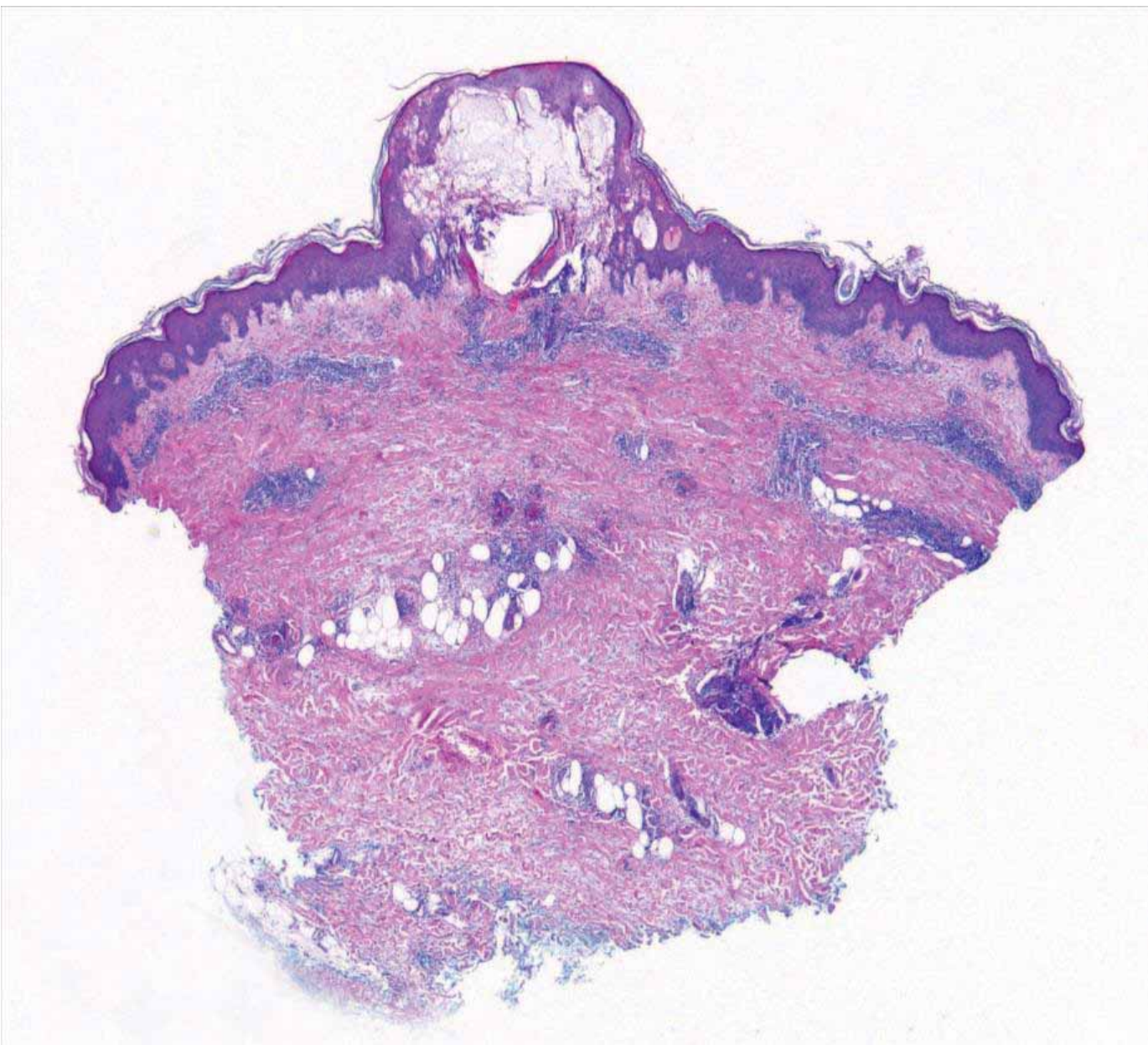
Emergence of bullous pemphigoid under treatment of mycosis fungoides with mogamulizumab

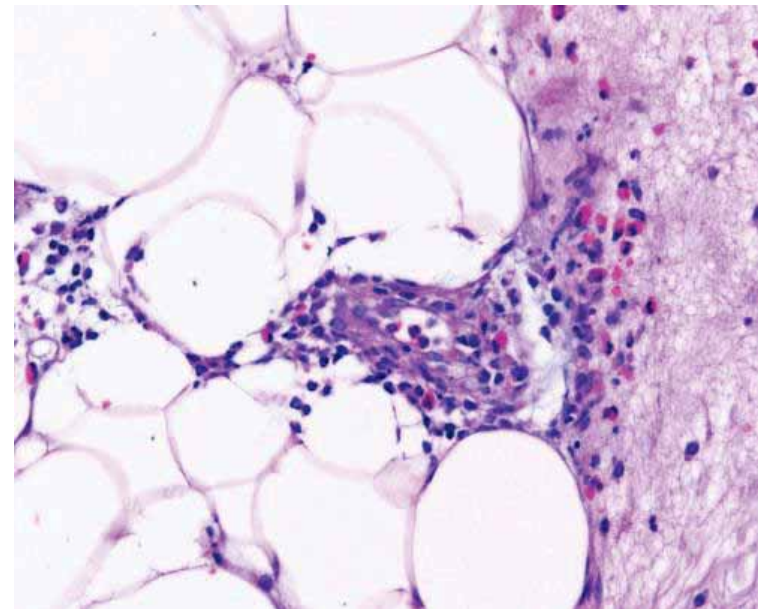
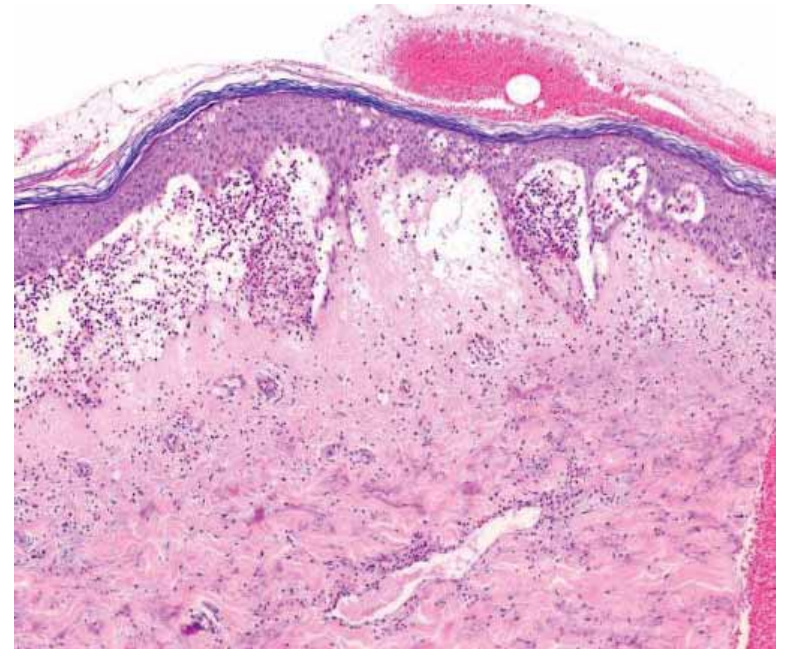
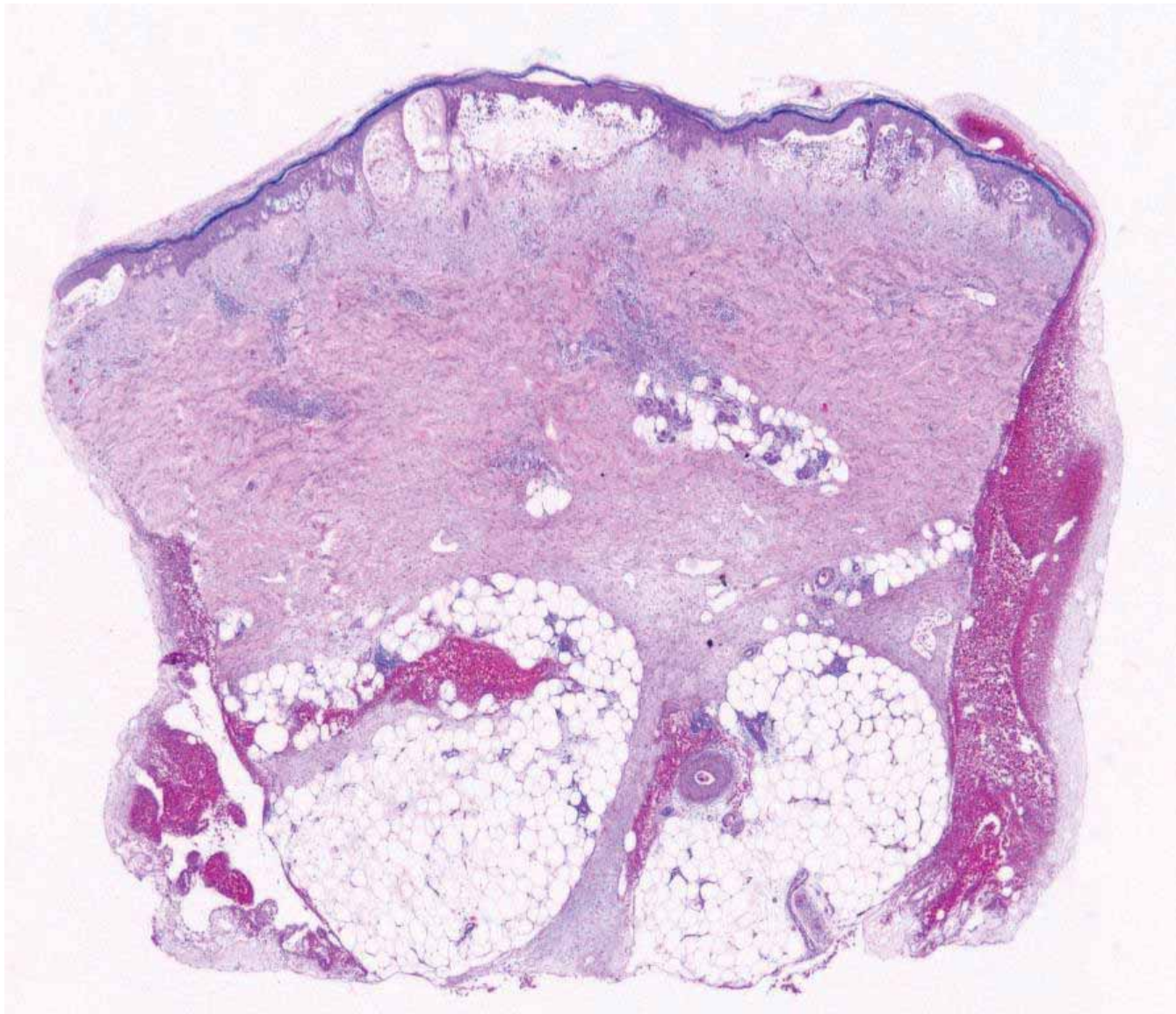
Uleer DU et al., in press

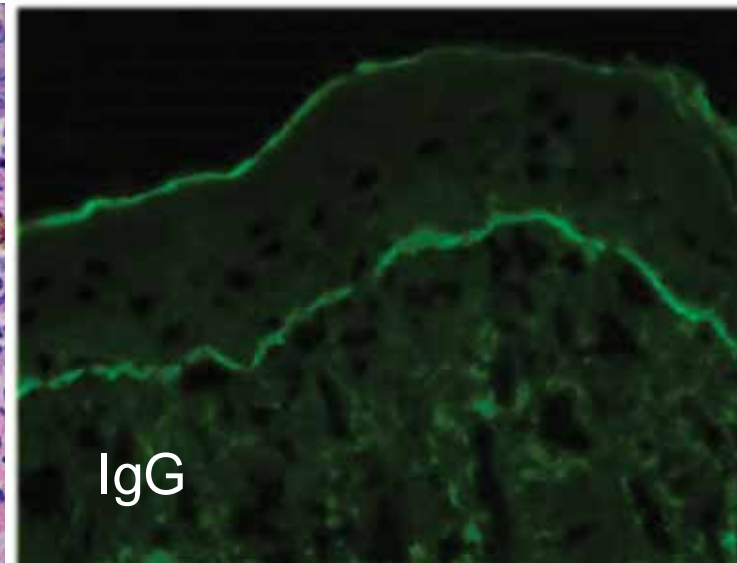
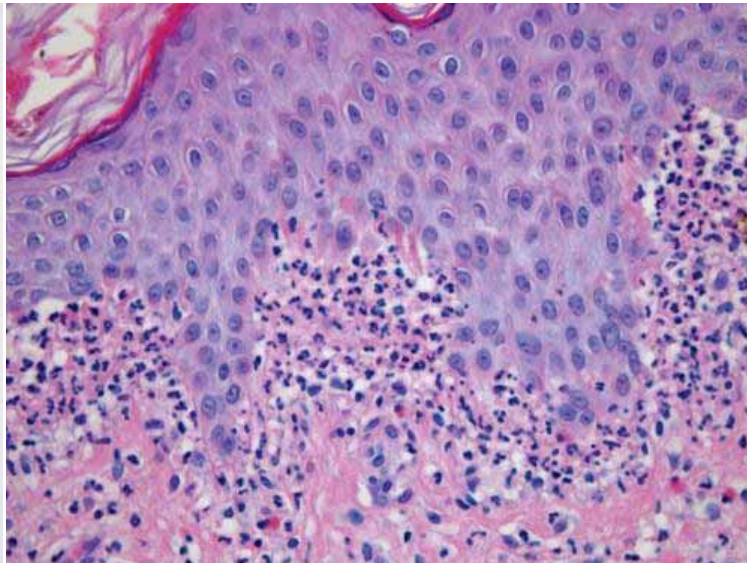
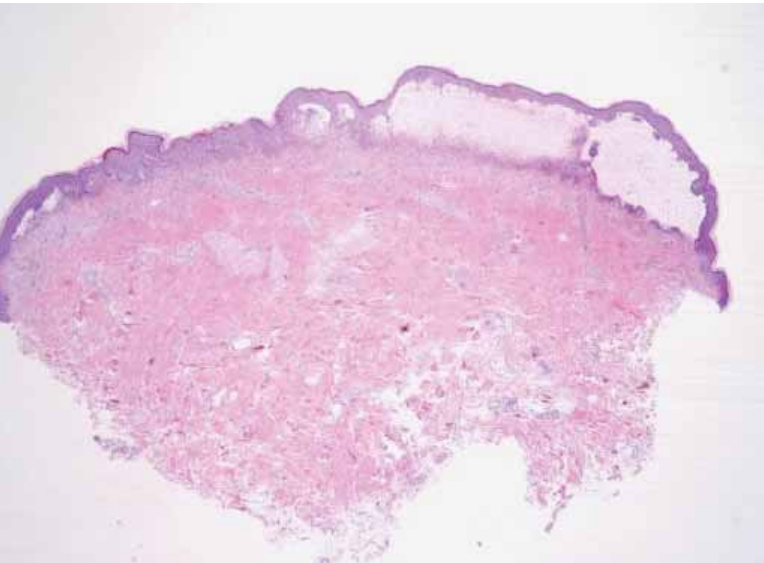






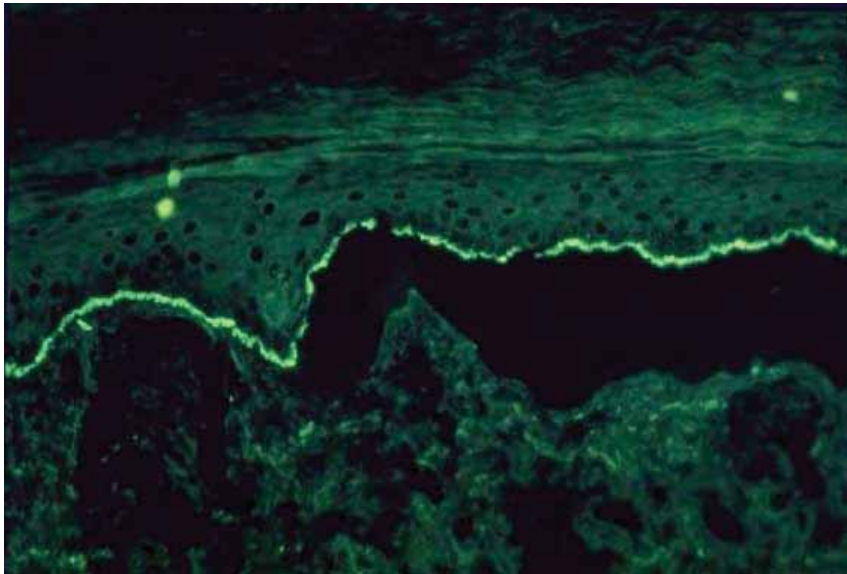






Indirect immunofluorescence on salt-split human skin

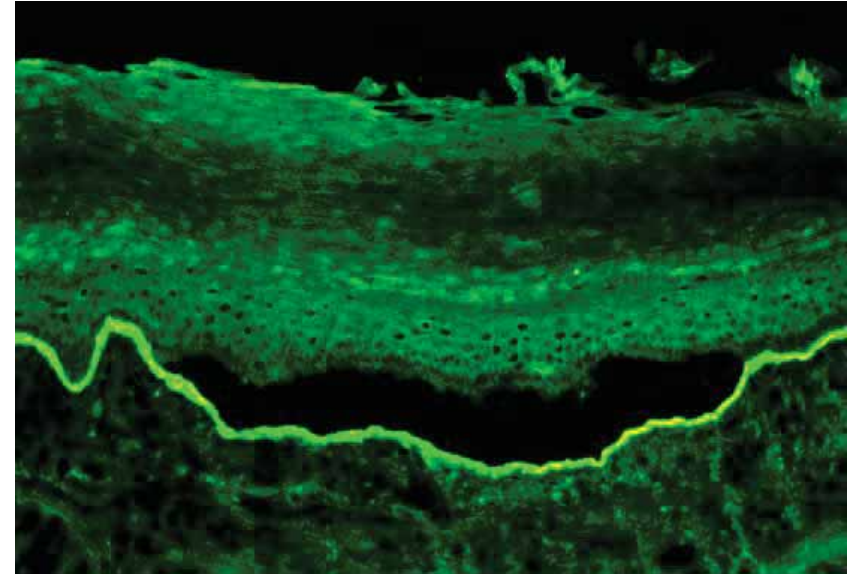
Epidermale binding



Antibodies to

BP180
BP230
Plektin
beta 4 integrin

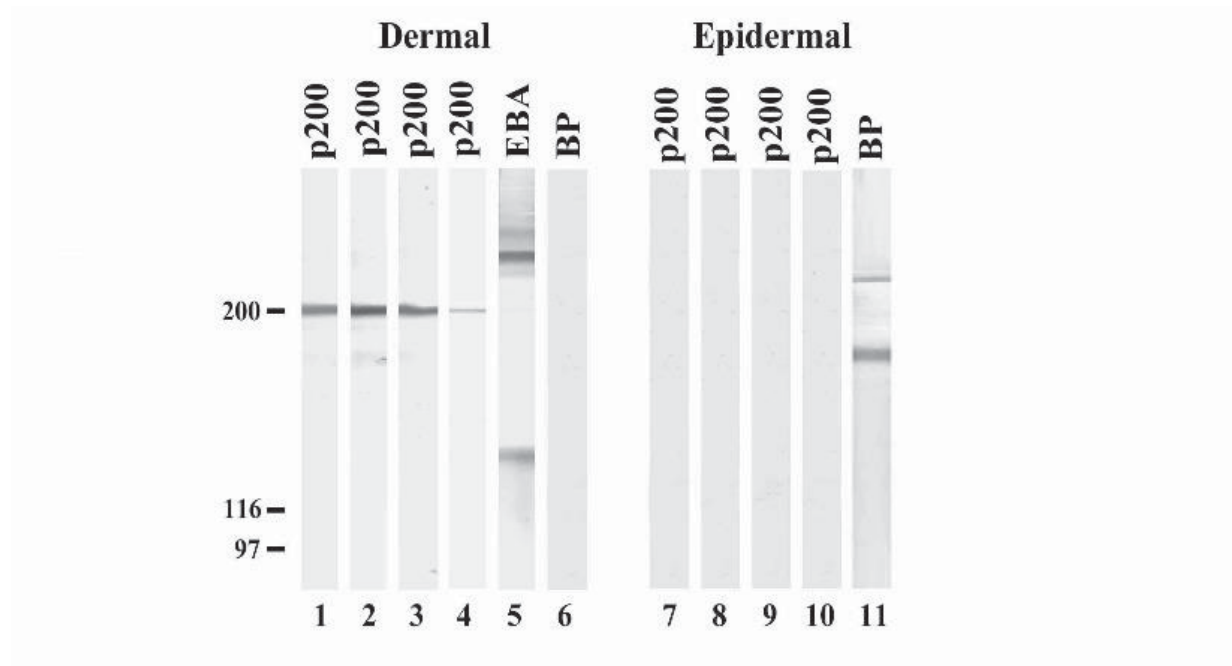
Dermal binding

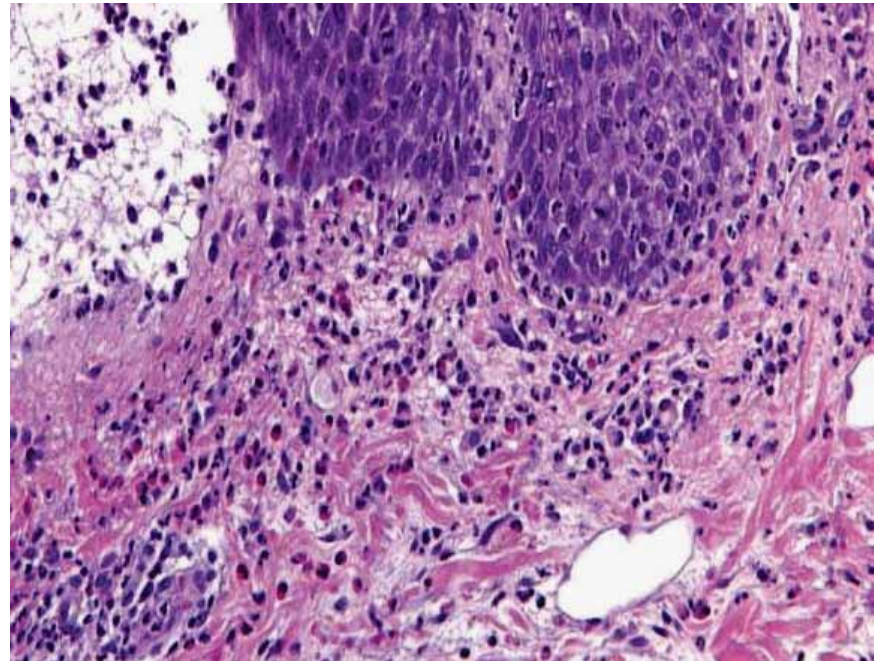
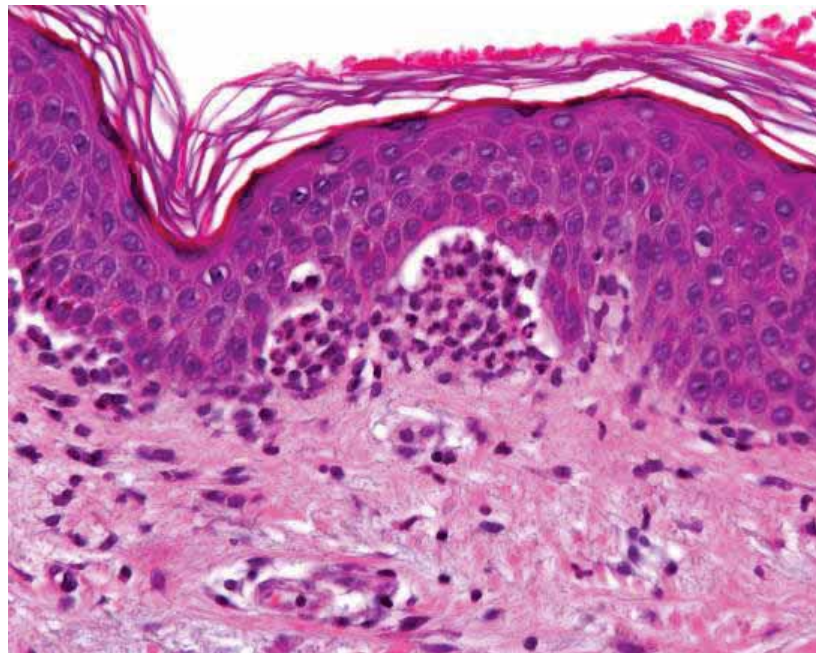
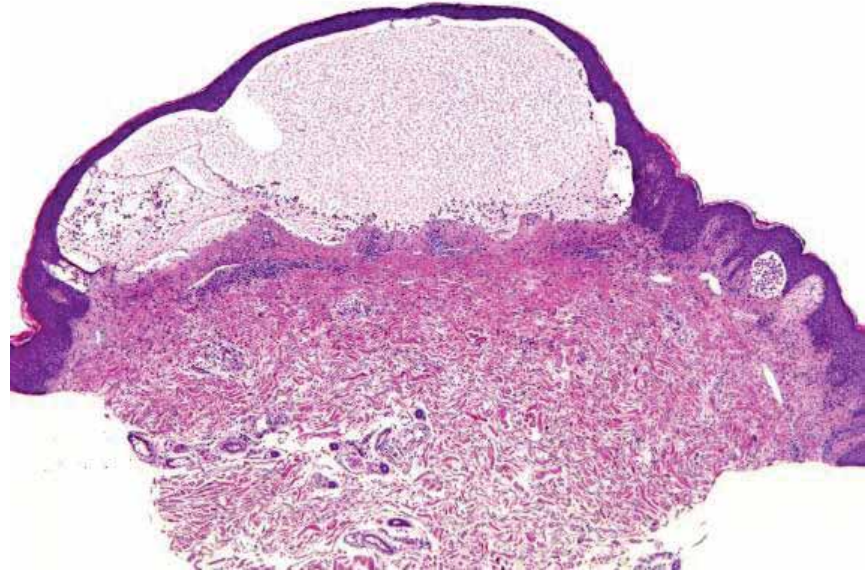
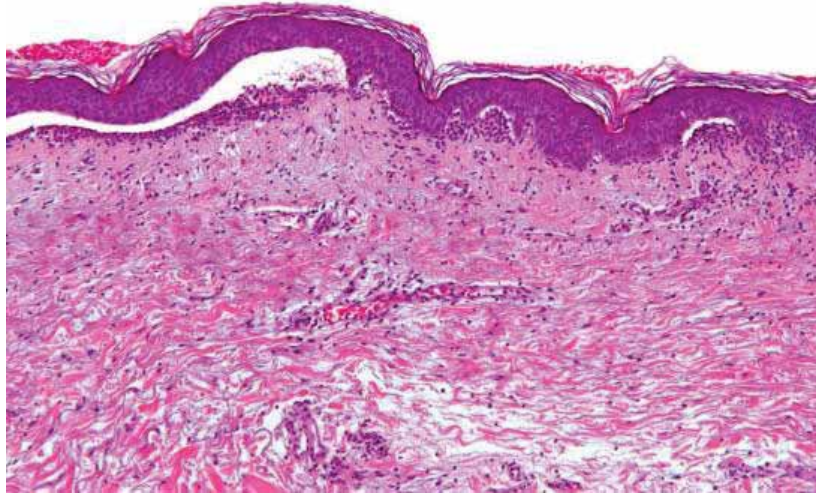


Antibodies to

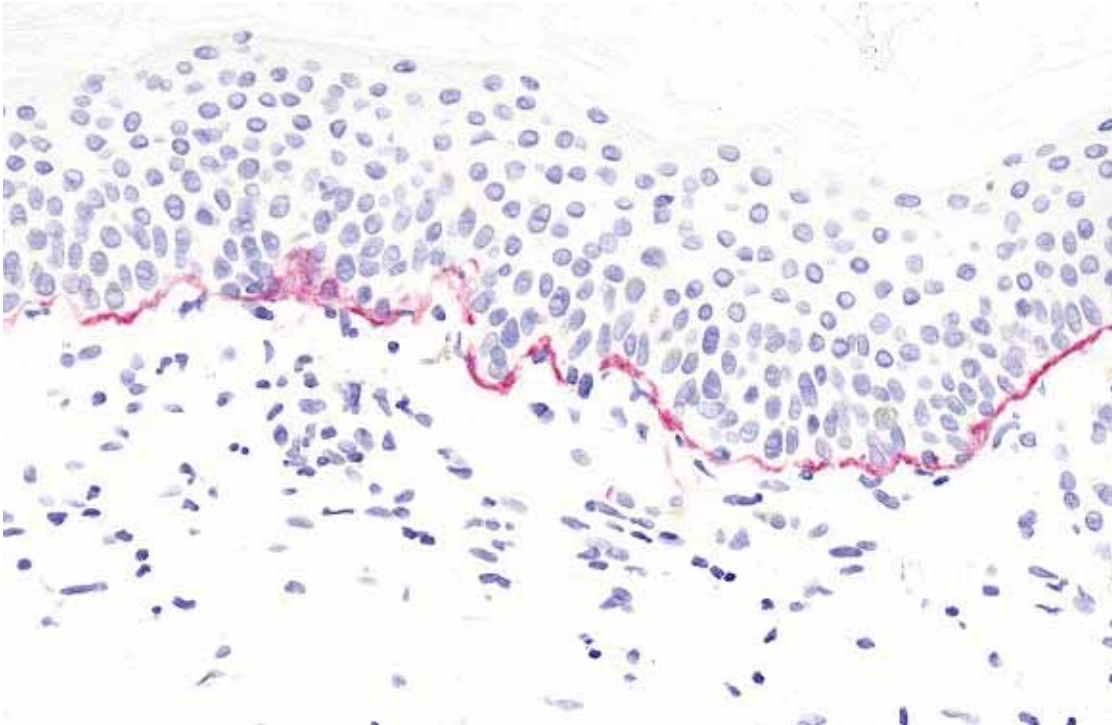
Laminin 5 und 6
p200
type VII collagen

Immunoblot on extract of human dermis





C4d staining as a diagnostic marker in anti-p200 pemphigoid



- 15 positiv (60%)
- 6 negativ (24%)
- 4 negativ,
with split formation (16%)

Anti-laminin gamma-1 pemphigoid

Teruki Dainichi^a, Sadamu Kurono^{b,1}, Bungo Ohyama^a, Norito Ishii^{a,c}, Noriko Sanzen^d, Maria Hayashi^d, Chisei Shimono^d, Yukimasa Taniguchi^d, Hiroshi Koga^a, Tadashi Karashima^a, Shinichiro Yasumoto^a, Detlef Zillikens^e, Kiyotoshi Sekiguchi^d, and Takashi Hashimoto^{a,2}

PNAS 2009, 106: 2800-5

Anti-laminin gamma-1 pemphigoid

Teruki Dainichi², Sadamu Kurono^{b,1}, Bungo Ohyama², Norito Ishii^{a,c}, Noriko Sanzen^d, Maria Hayashi^d, Chisei Shimono^d, Yukimasa Taniguchi^d, Hiroshi Koga², Tadashi Karashima², Shinichiro Yasumoto², Detlef Zillikens^c, Kiyotoshi Sekiguchi^d, and Takashi Hashimoto^{a,2}

PNAS 2009, 106: 2800-5

Laminin $\beta 4$ is a constituent of the cutaneous basement membrane zone and additional autoantigen of anti-p200 pemphigoid



Stephanie Goletz, PhD,^a Manuela Pigors, PhD,^a Tina Rastegar Lari, MD,^a Christoph M. Hammers, MD, PhD,^{a,b} Yao Wang, MSc,^c Shirin Emtenani, PhD,^a Monique Aumailley, MD,^d Maike M. Holtsche, MD,^b Felix H. Stang, MD,^c Imke Weyers, MD,^f Inke R. König, PhD,^g Cristina Has, MD,^c Christiane Radzimski, PhD,^h Lars Komorowski, PhD,^h Detlef Zillikens, MD,^b and Enno Schmidt, MD, PhD^{a,b}

J Am Acad Dermatol 2024; 90: 790-7



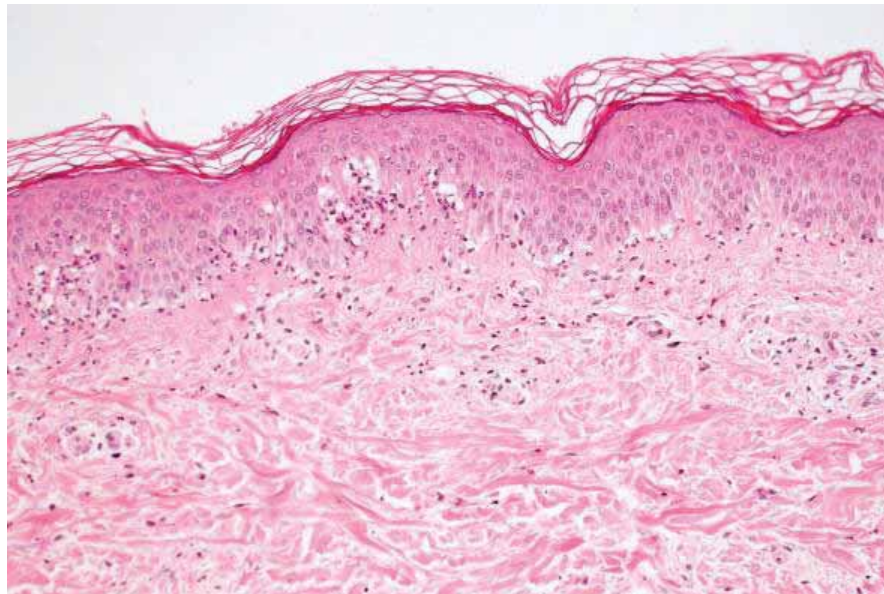
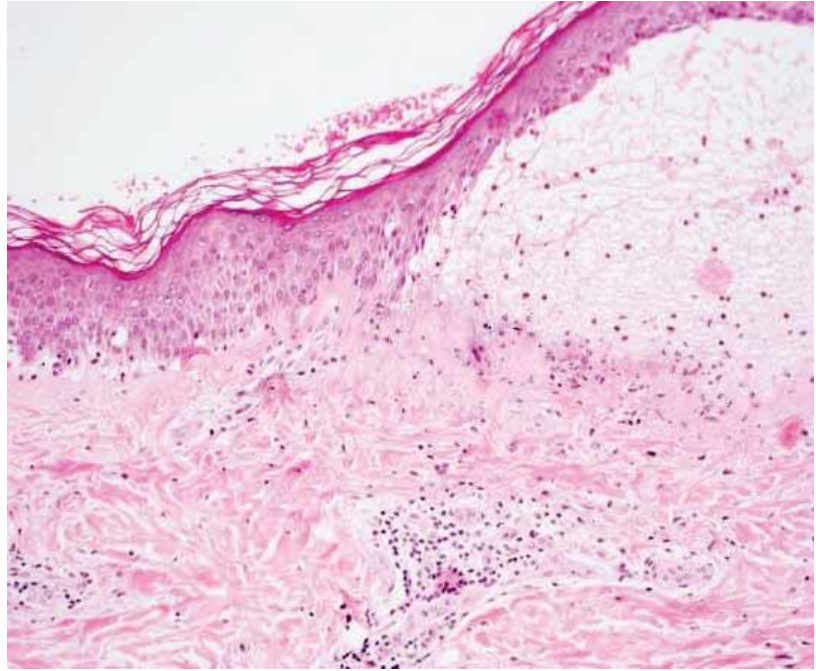
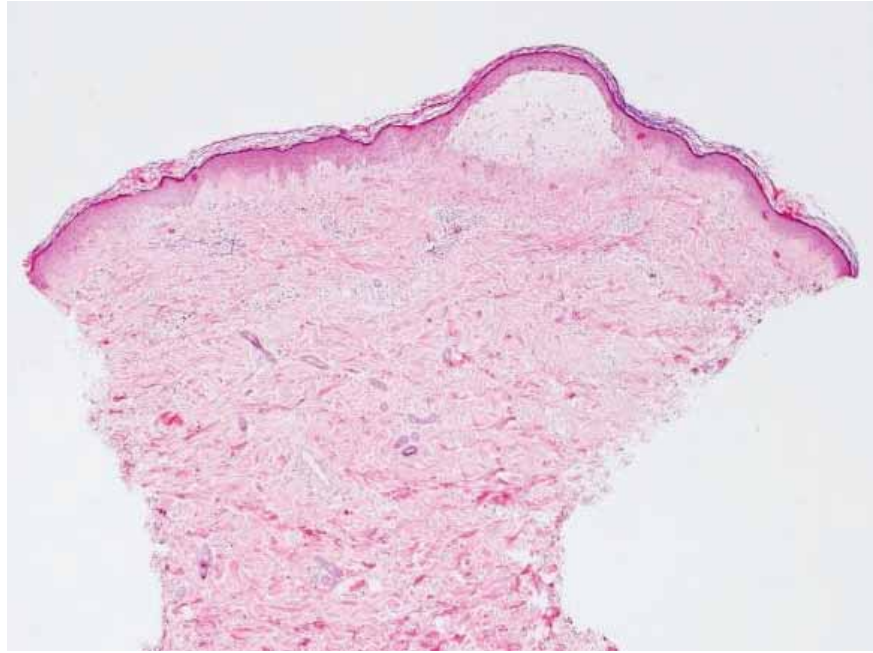
Detlef Zillikens
1958 - 2022

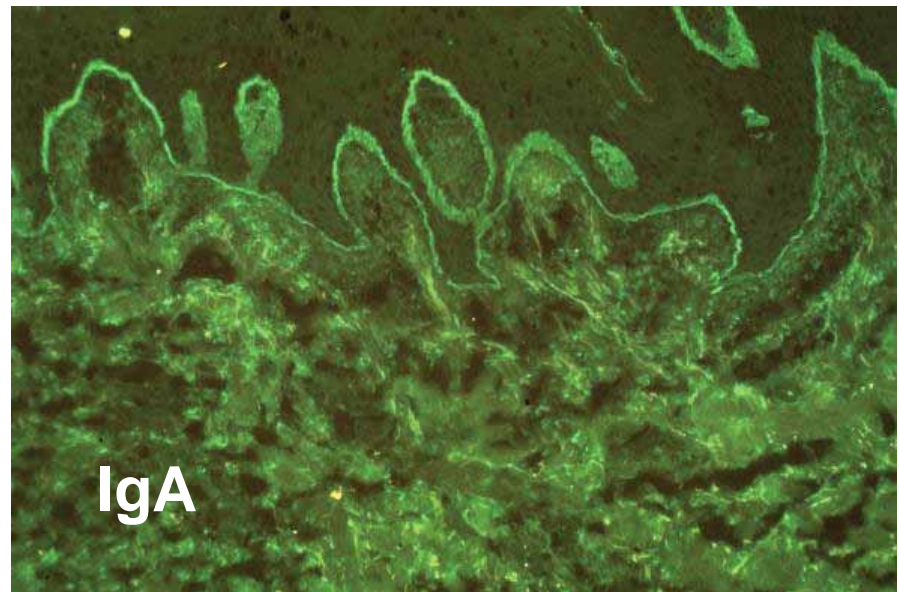
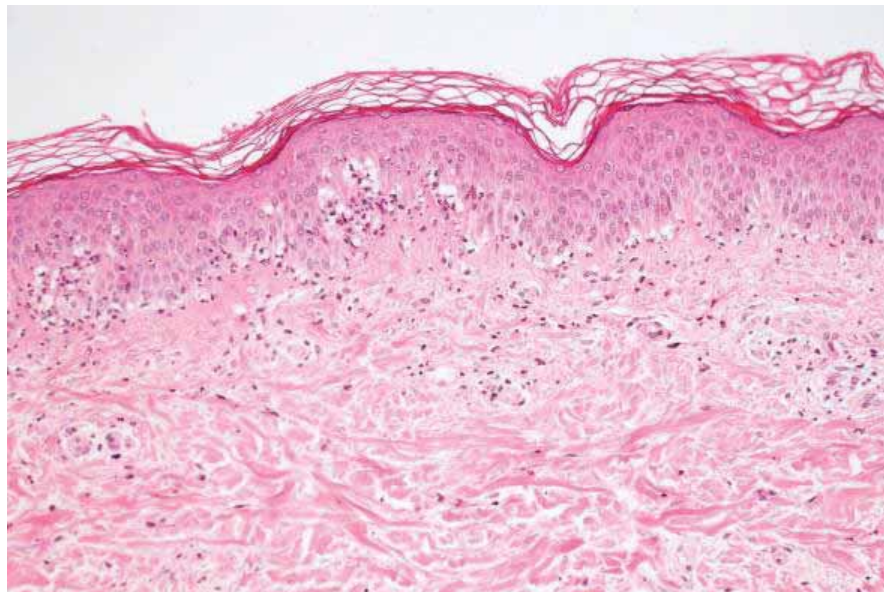
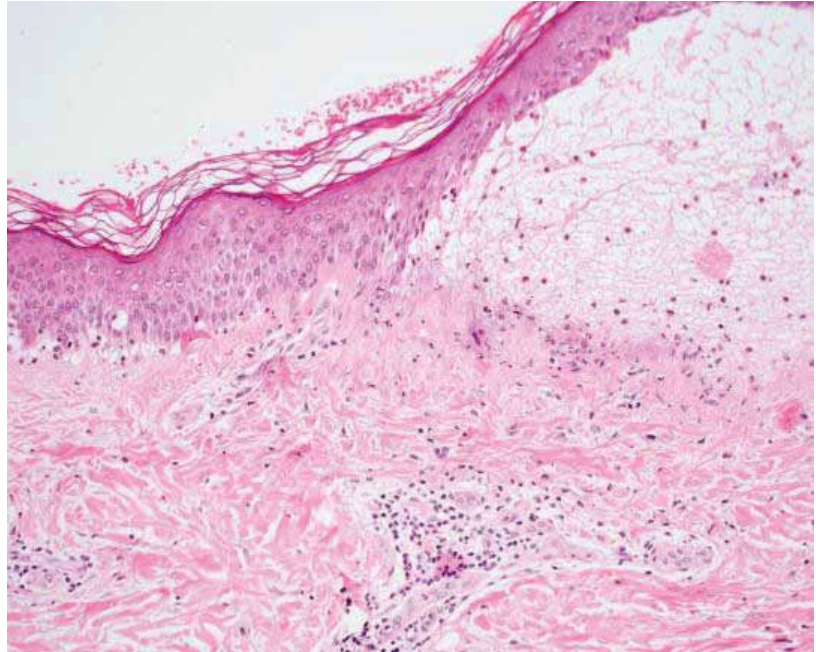
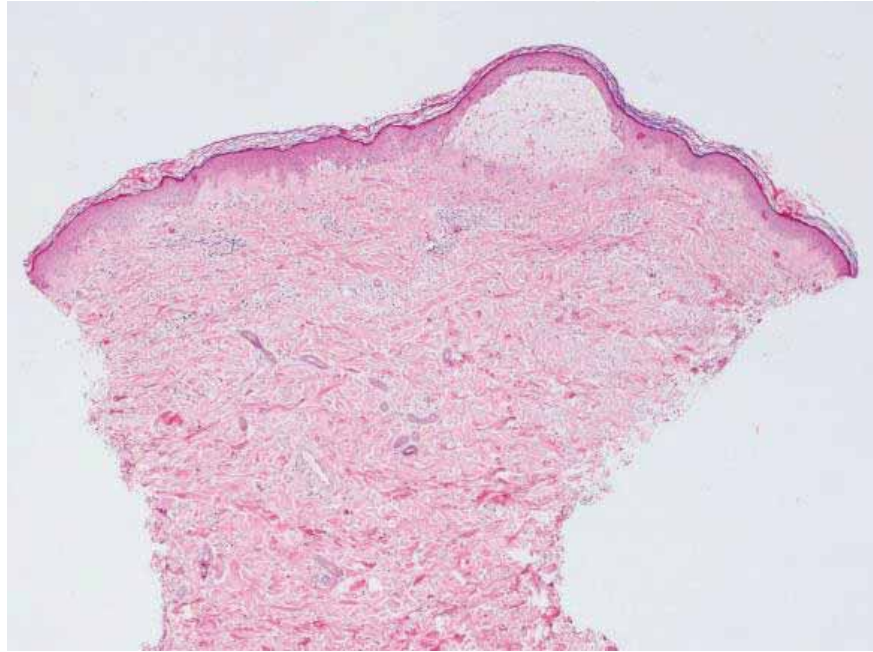
A life for autoimmune blistering
diseases: in memoriam Detlef Zillikens
Hundt JE et al. *Frontiers in Immunology*
2023

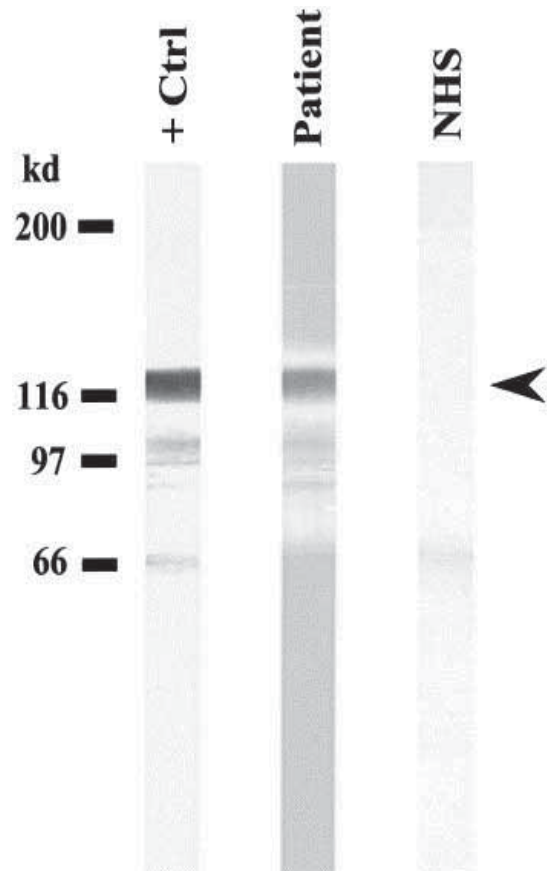


74 y, male

The night before discharge from the internal medicine ward, circumscribed perianal skin lesions.







Localized linear IgA disease induced by ampicillin/sulbactam

Iakov Shimanovich, MD, Christian Rose, MD, Cassian Sitaru, MD,
Eva-B. Bröcker, MD, and Detlef Zillikens, MD
Würzburg, Germany

J Am Acad Dermatol 2004; 51: 95-8

Linear IgA disease



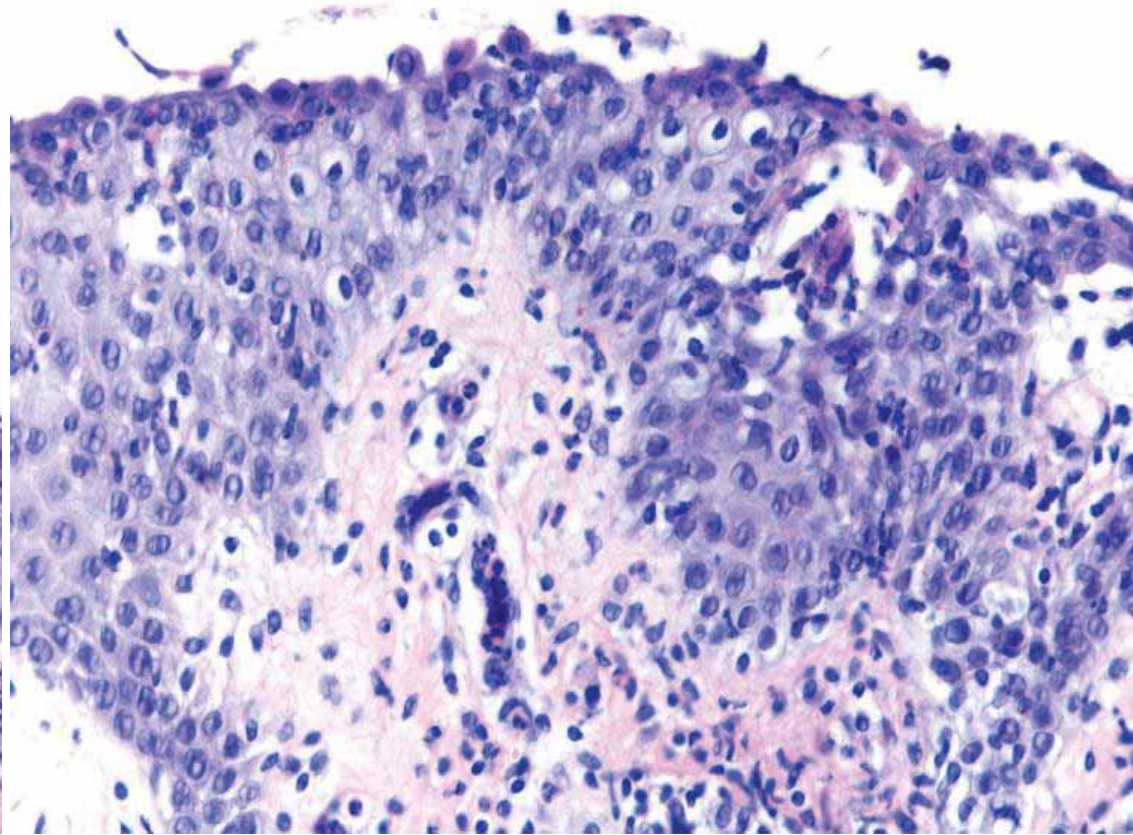
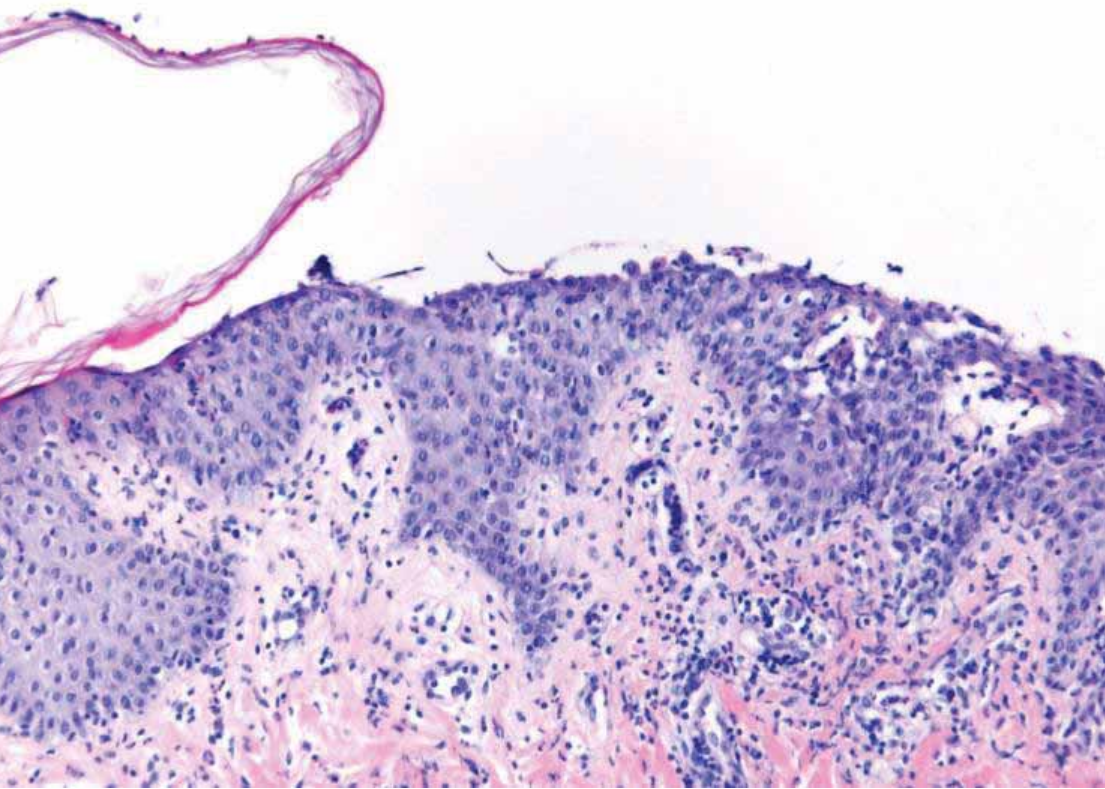
Linear IgA disease





6 y, girl

Courtesy B. Zelger

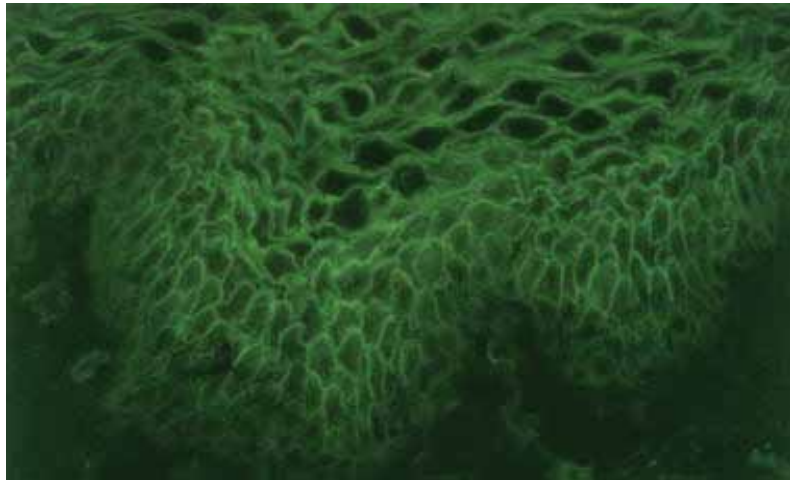


Courtesy B. Zelger

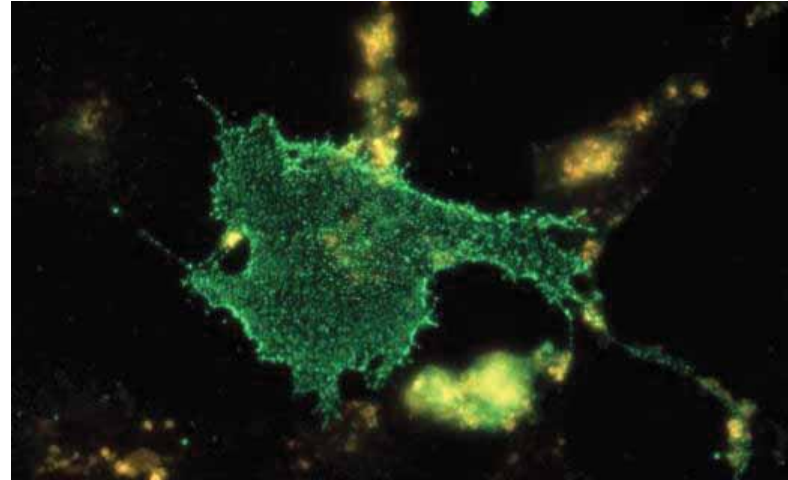
Differential Diagnosis

- Impetigo
- Pemphigus foliaceus
- IgA pemphigus

Immunofluorescence microscopy IgA pemphigus



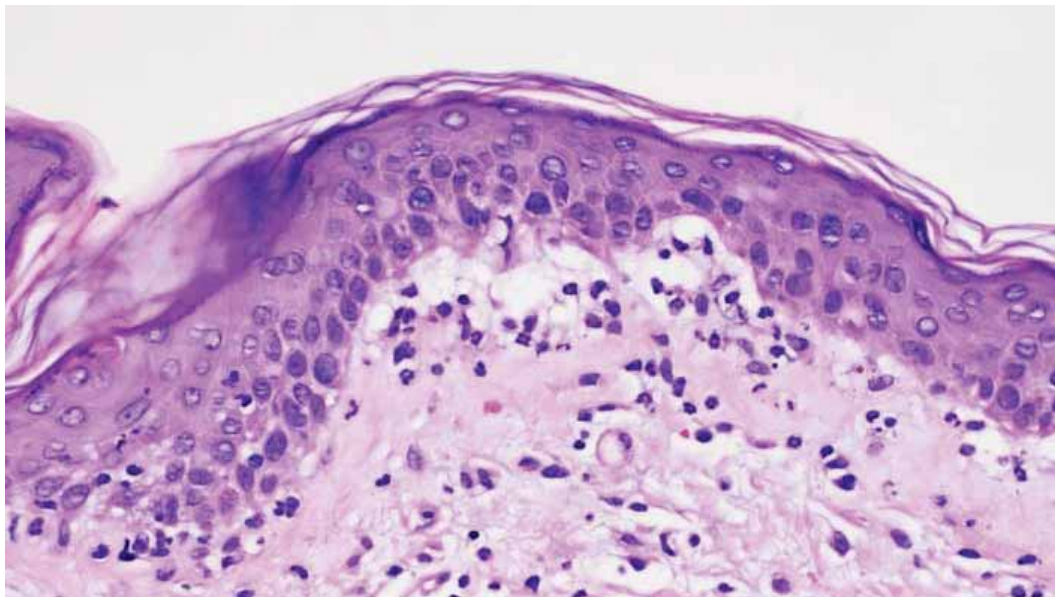
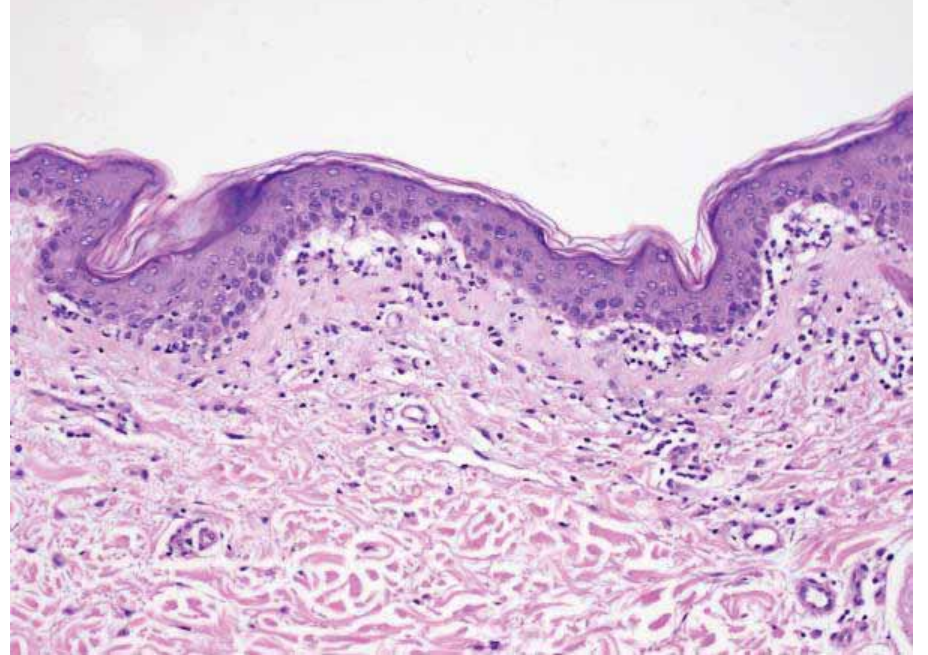
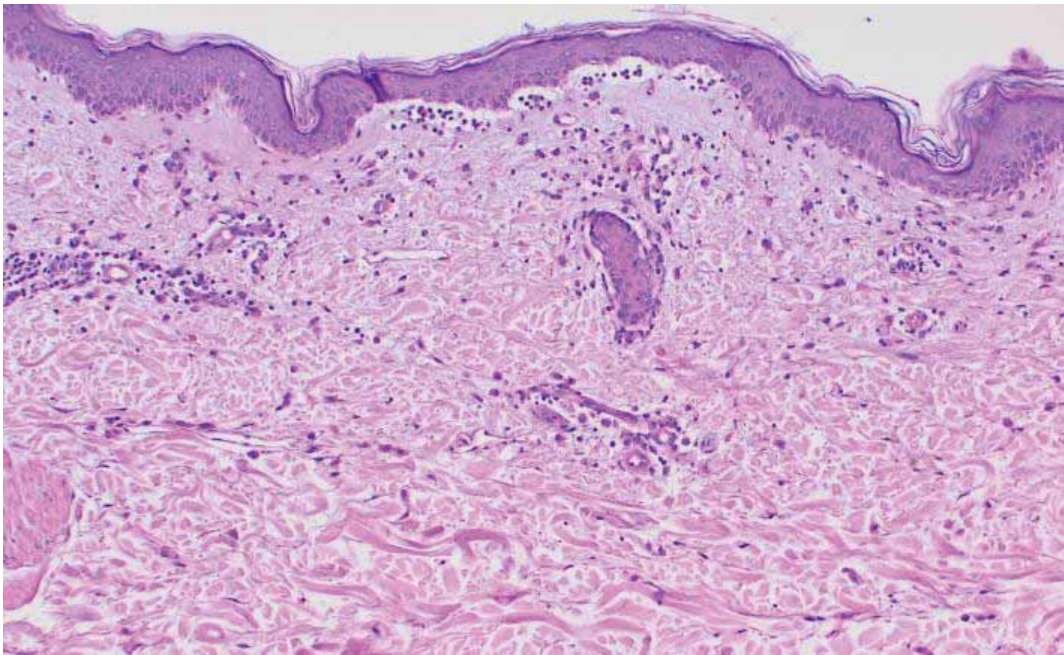
Indirect IF

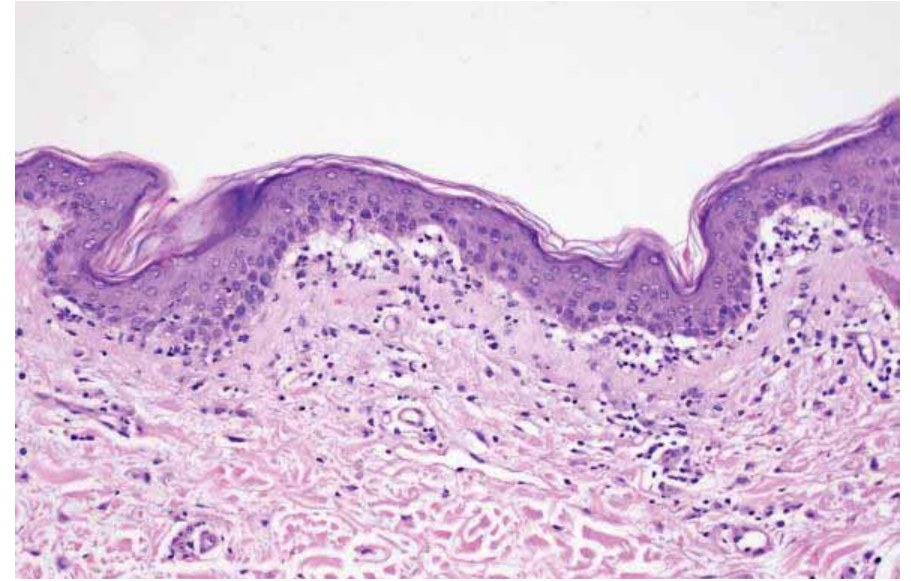
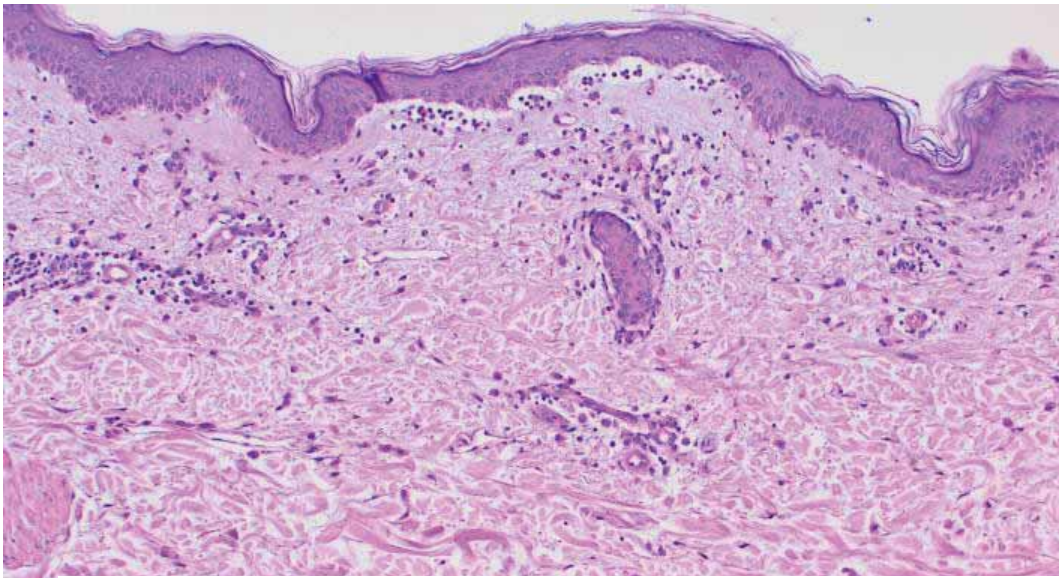


COS7

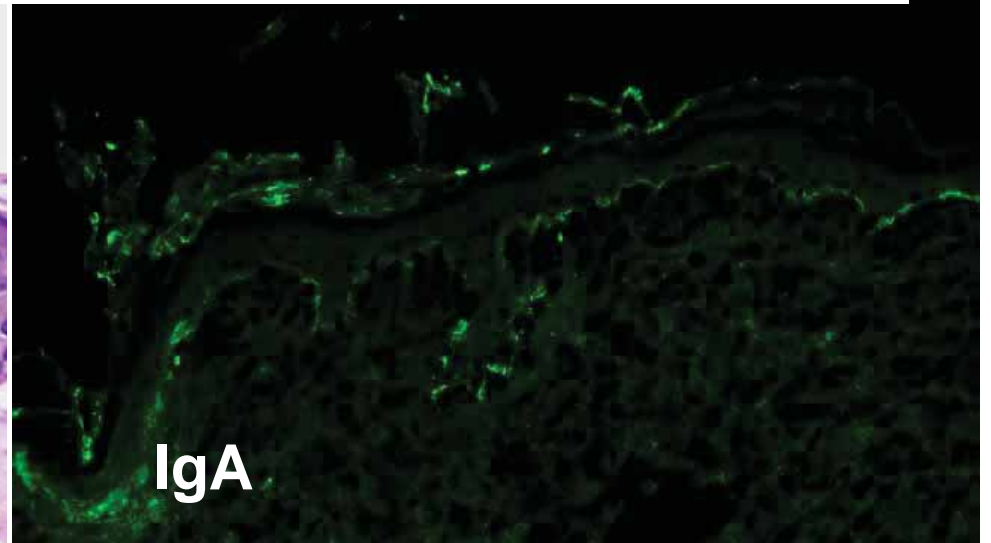
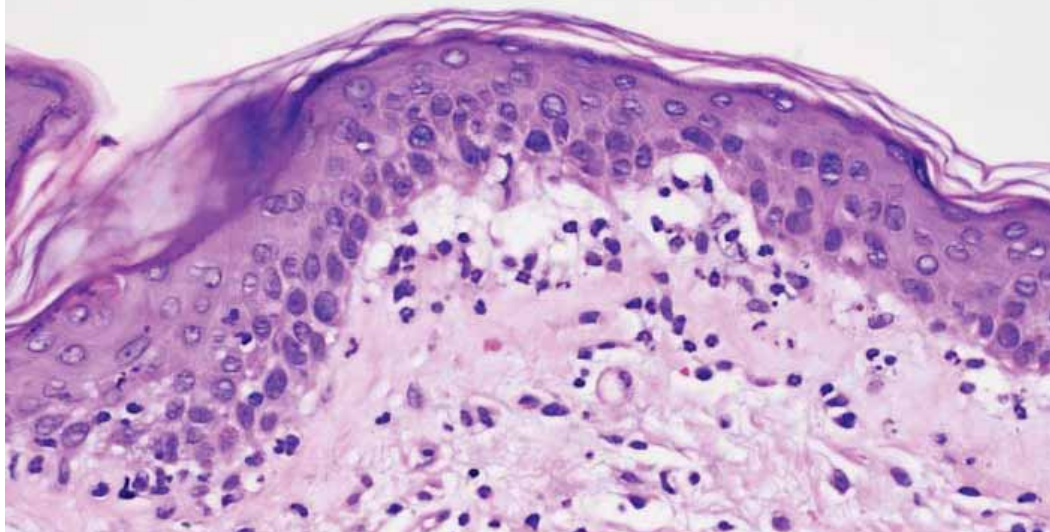


77 y, female
development of
erythema with
blistering after a hip
joint surgery

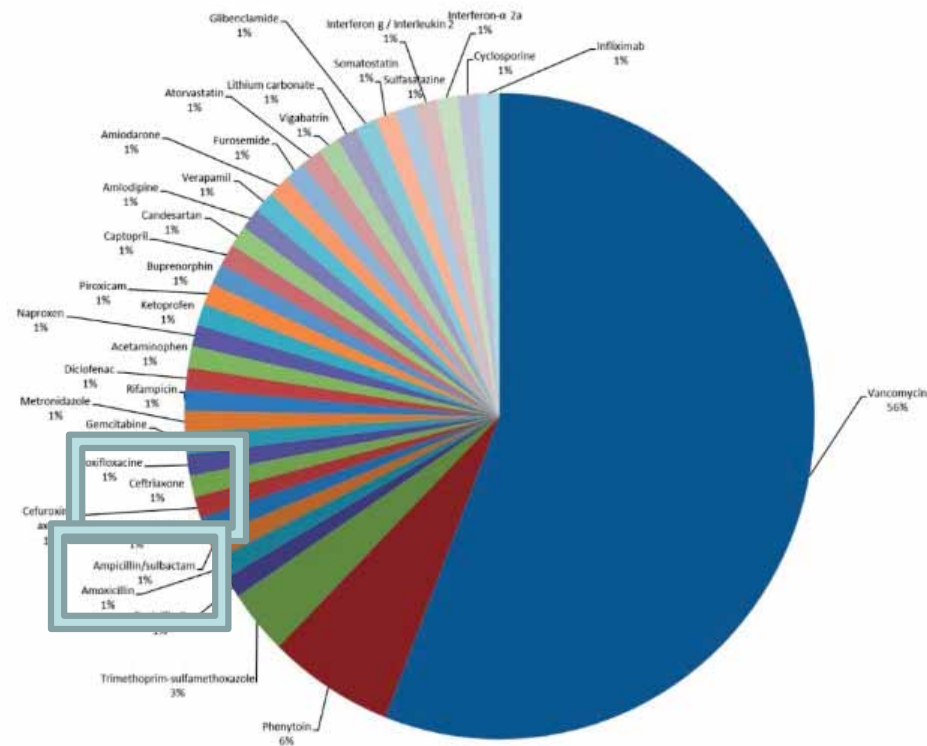




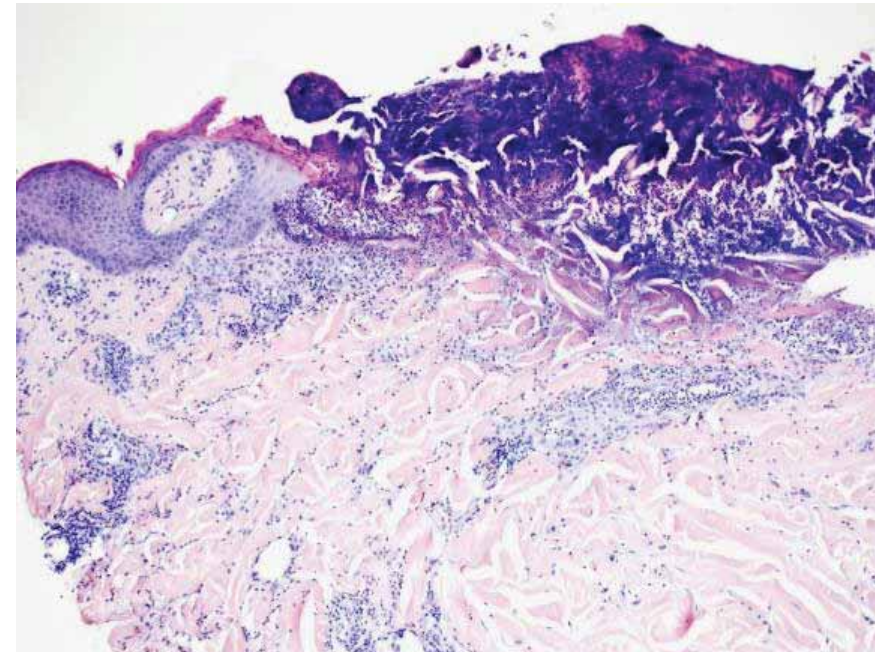
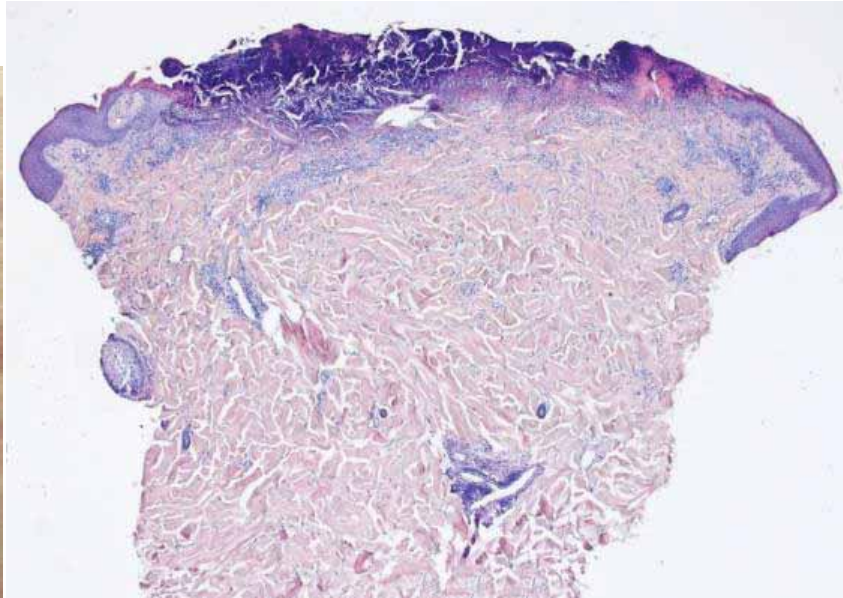
Linear IgA disease induced by ceftriaxone



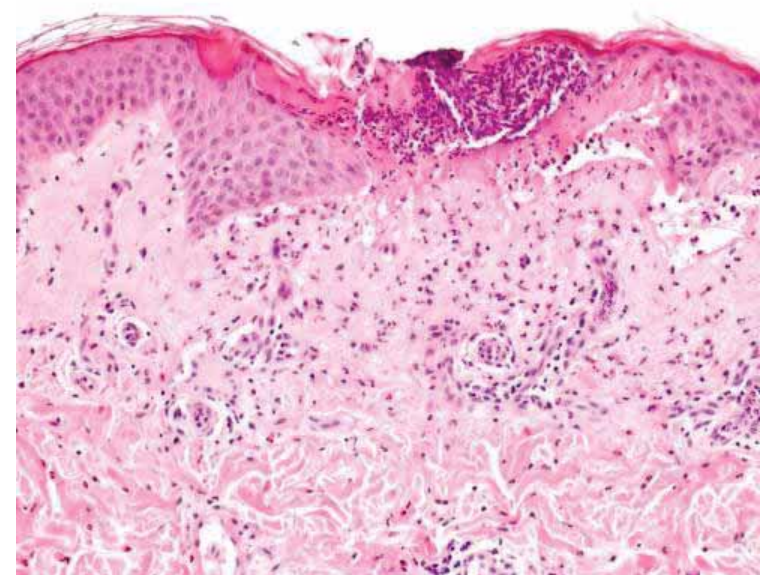
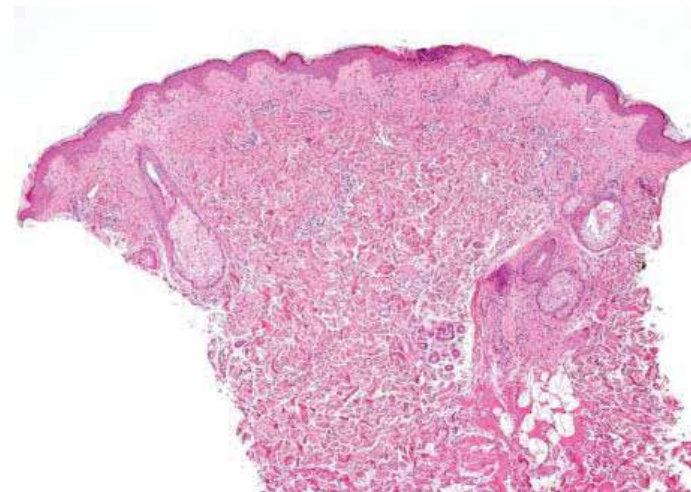
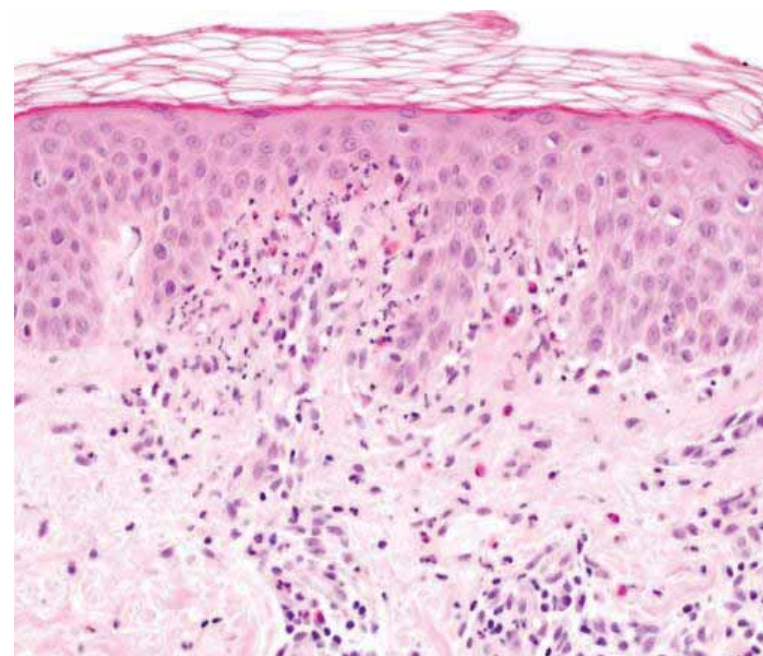
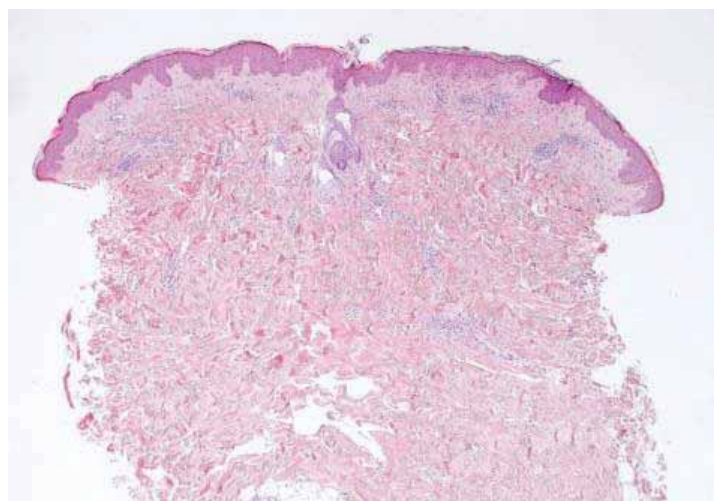
Drug-induced linear IgA bullous dermatosis



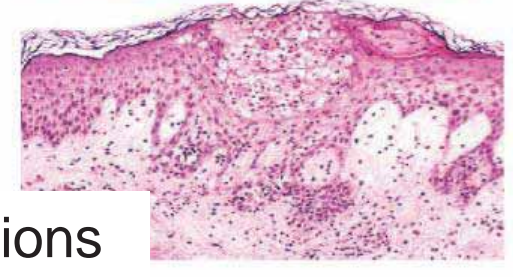
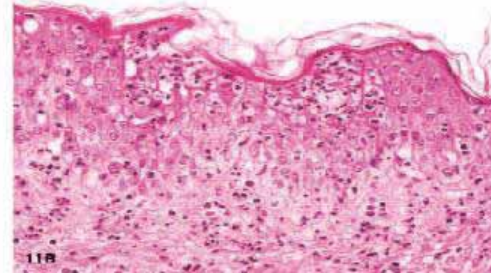
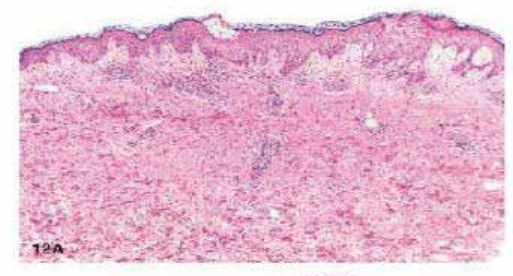
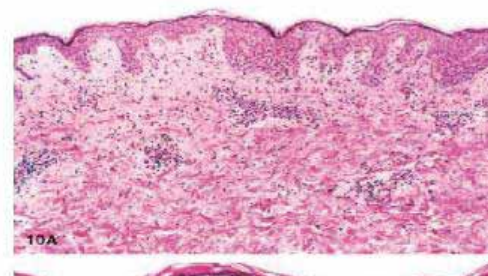
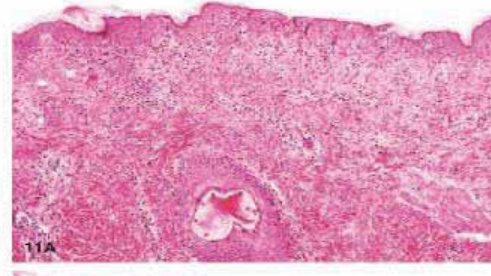
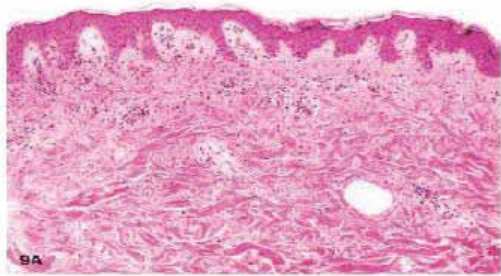
Lammer J, Hein R, Roenneberg S, Biedermann T, Volz T. Drug-induced linear IgA bullous dermatosis: A case report and review of the literature. *Acta Derm Venereol.* 2019; 99: 508



51 y, male
very itchy lesions on the trunk for a few weeks

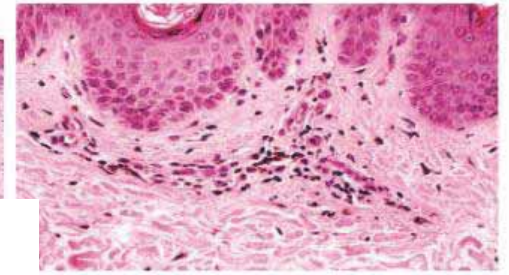
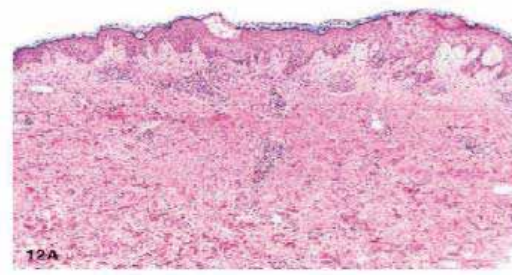
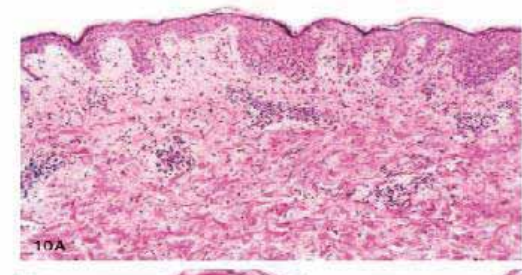


6 months later

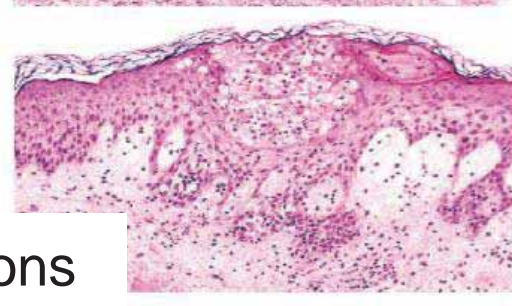
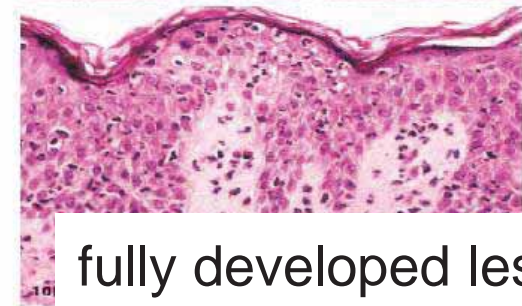


early lesions

fully developed lesions



late lesions

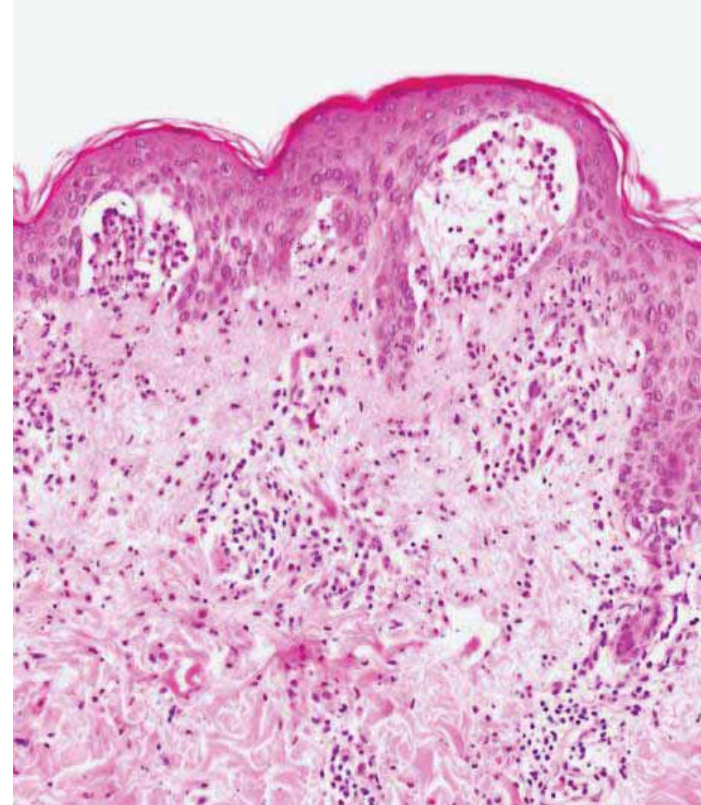
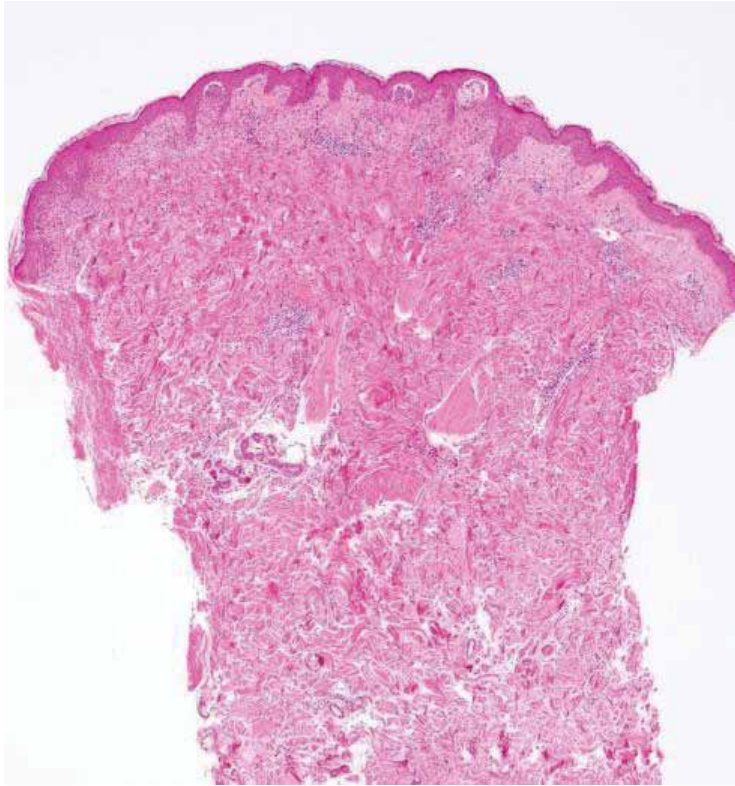


fully developed lesions

Böer-Auer A et al.
Prurigo pigmentosa: a distinctive inflammatory disease of the skin.
Am J Dermatol 2003; 25: 117-29



3 months under minocycline



15 months after first presentation



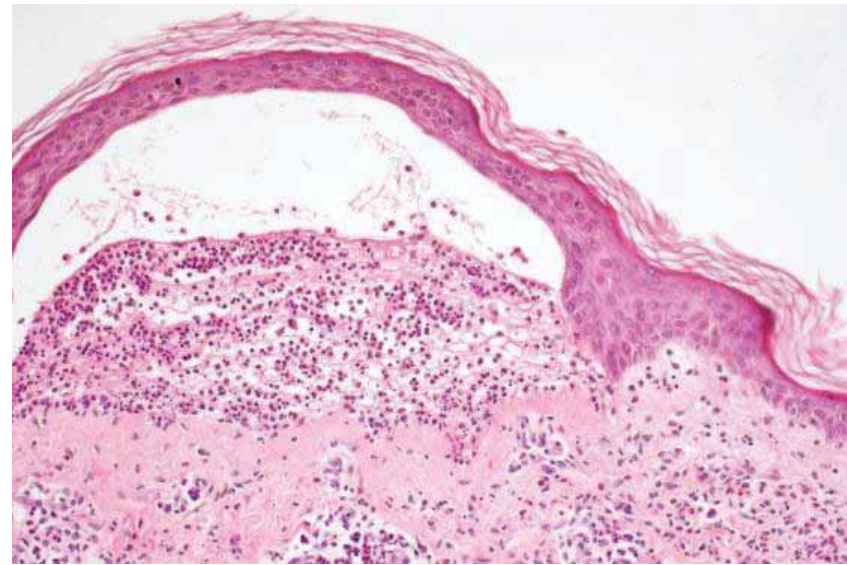
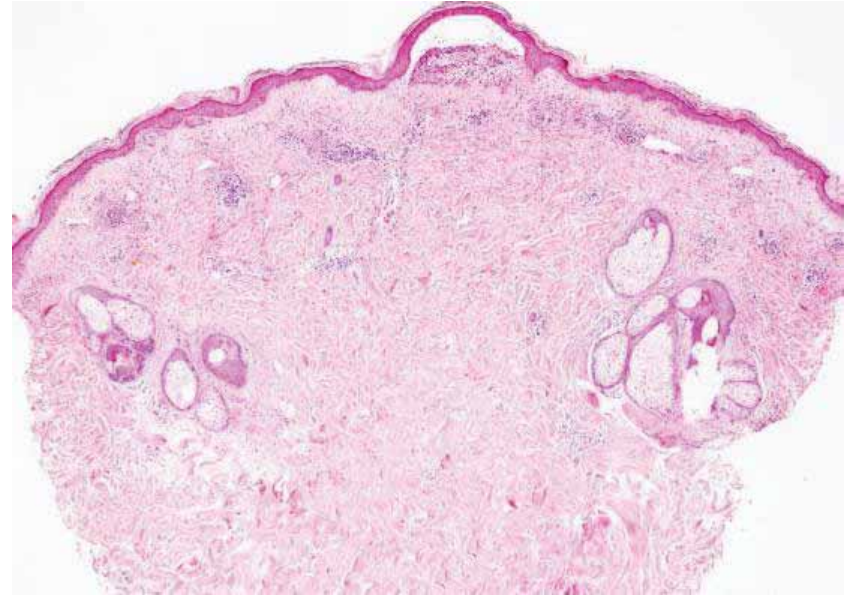
4 weeks under dapson



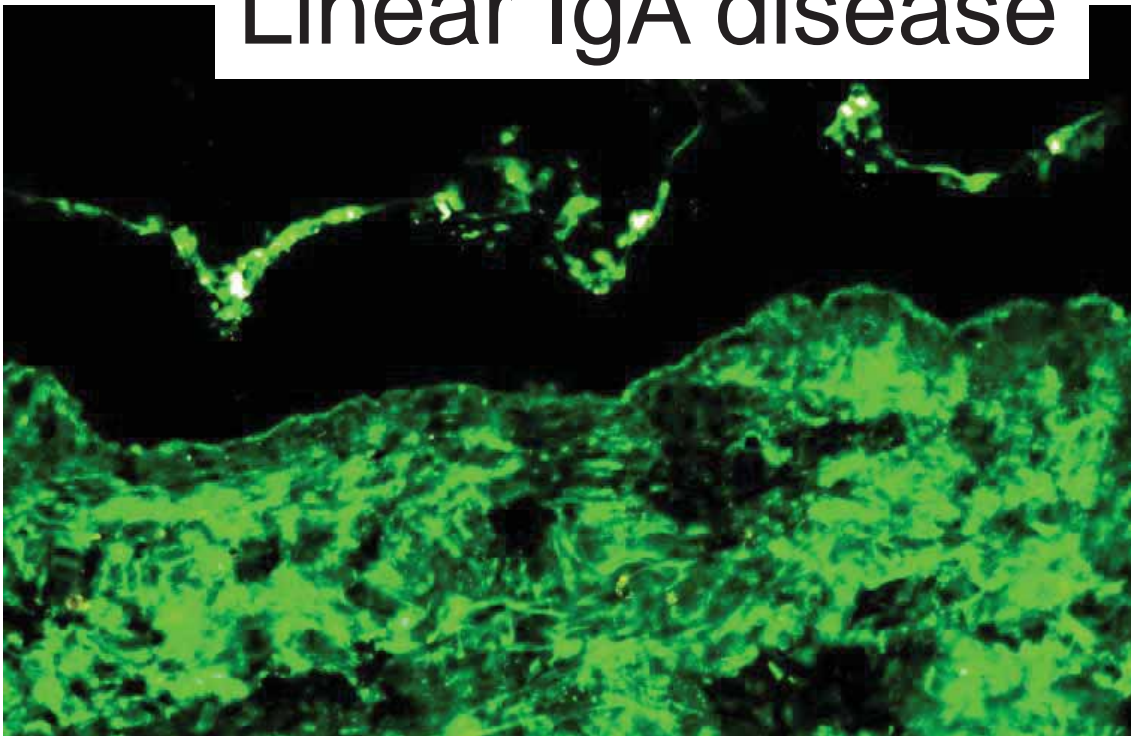
2 years after first presentation



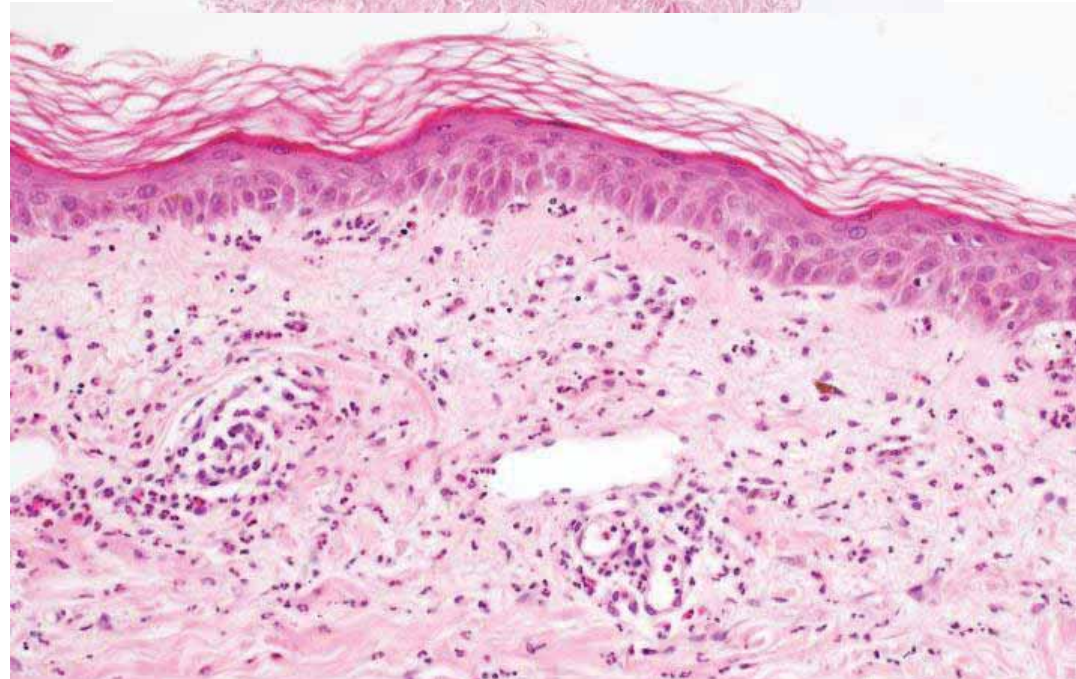
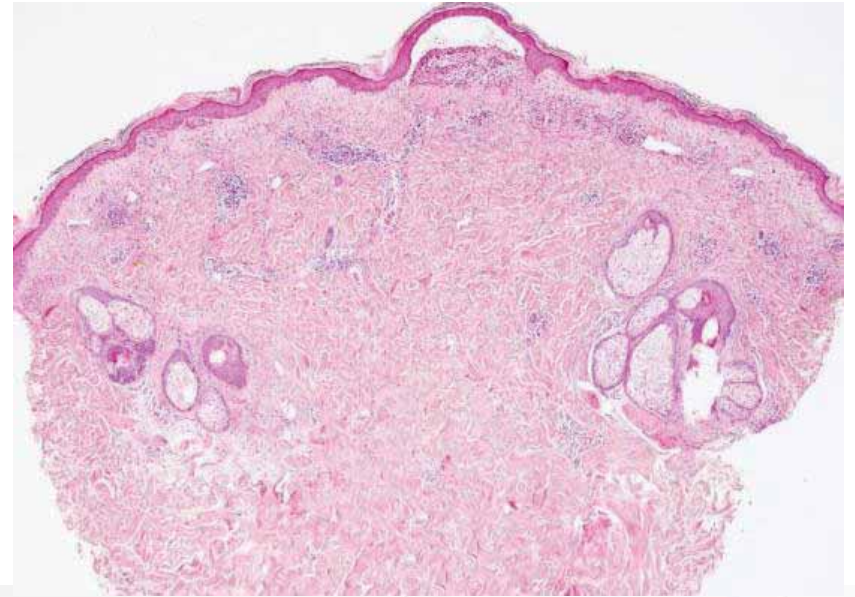
2 years after first presentation



Linear IgA disease



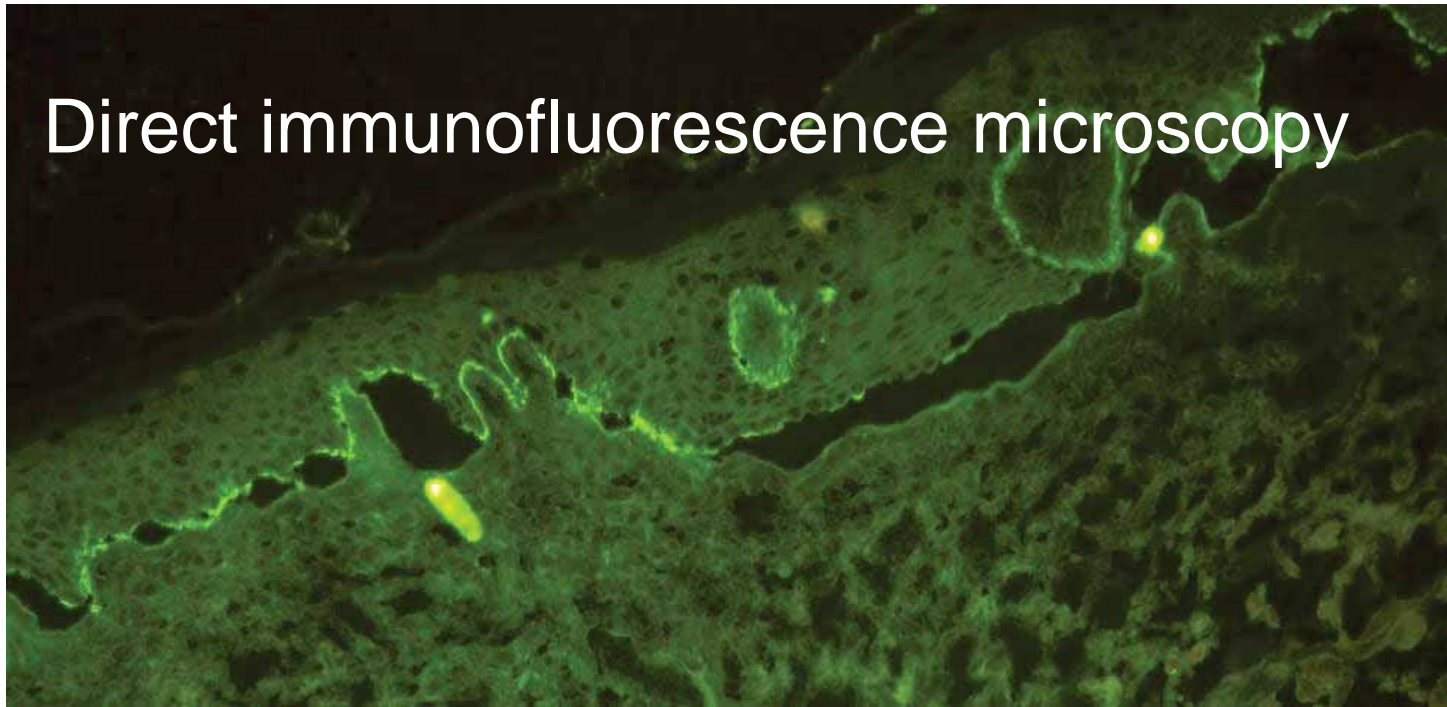
IgA



Blister



Direct immunofluorescence microscopy



Detection of circulating serum autoantibodies


Pemphigus vulgaris	>90%
Pemphigus foliaceus	>90%
IgA pemphigus	50%
Bullous pemphigoid	80-90%
Pemphigoid gestationis	>90%
Linear IgA disease	70%
Mucous membrane pemphigoid	40-50%
Epidermolysis bullosa acquisita	50-60%
Dermatitis herpetiformis	>90%



The American Journal of Dermatopathology

THE JOURNAL OF THE INTERNATIONAL SOCIETY OF DERMATOPATHOLOGY
Editor-in-Chief Philip E. LeBoit, M.D.



 LIPPINCOTT WILLIAMS & WILKINS

www.amjdermatopathology.com


Am J Dermatopathol 2005; 27: 277-8



The American Journal of Dermatopathology

THE JOURNAL OF THE INTERNATIONAL SOCIETY OF DERMATOPATHOLOGY
Editor-in-Chief Philip E. LeBoit, M.D.



 LIPPINCOTT WILLIAMS & WILKINS

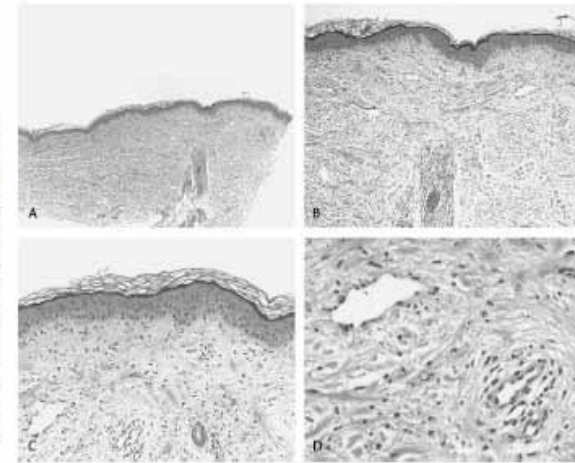
www.amjdermatopathology.com

ON THE COVER

Dust to Dust

Philip E. LeBoit, MD

FIGURE 1. A 59-year-old man had fixed urticarial plaques and underwent biopsy for hematoxylin and eosin and direct immunofluorescent staining. At scanning magnification, there is a vacuolar interface reaction (A). The infiltrates also surround a pilosebaceous unit (B). At higher magnification, the junctional zone shows vacuolar change, with neutrophils and neutrophilic nuclear dust just beneath it (C, and on the cover). There were neutrophils and neutrophilic nuclear dust around superficial vessels as well (D), simulating early leukocytoclastic vasculitis. Examination by direct immunofluorescence showed deposition of IgA in a linear pattern, establishing the diagnosis of linear IgA bullous dermatosis.

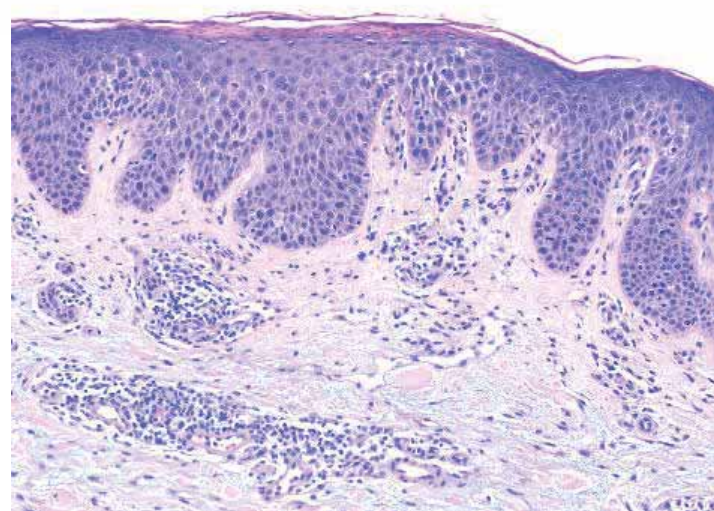
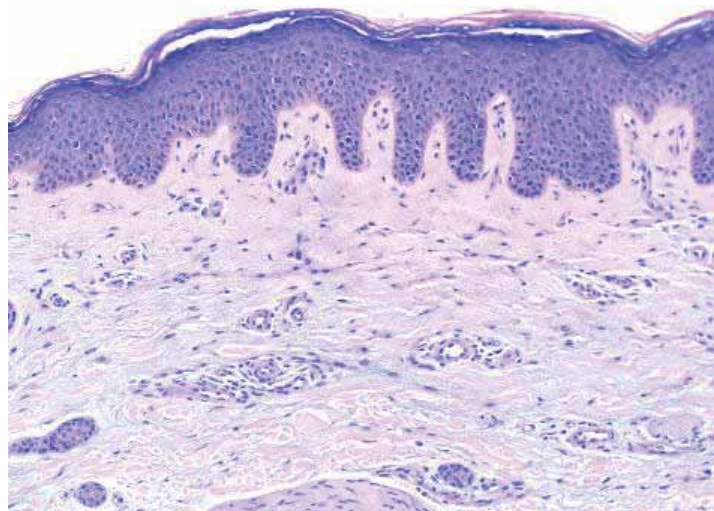
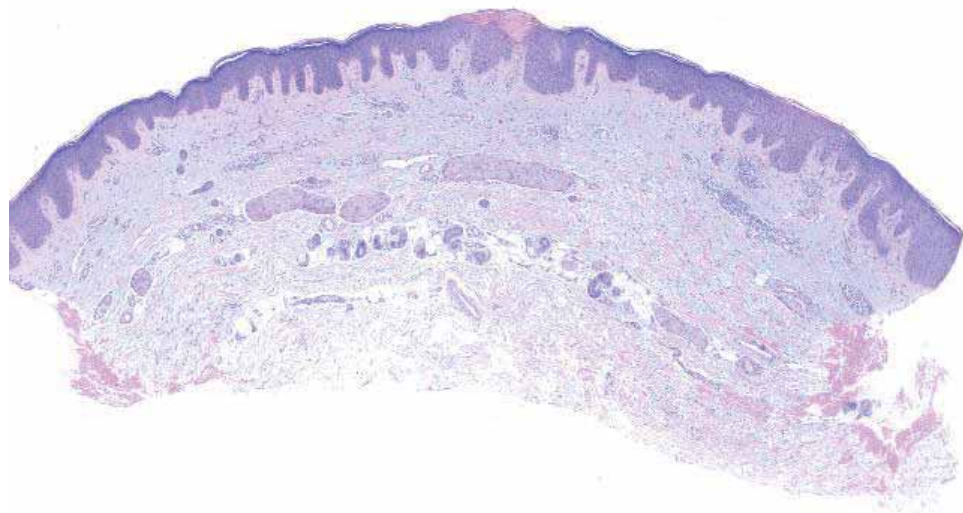


Am J Dermatopathol 2005; 27: 277-8



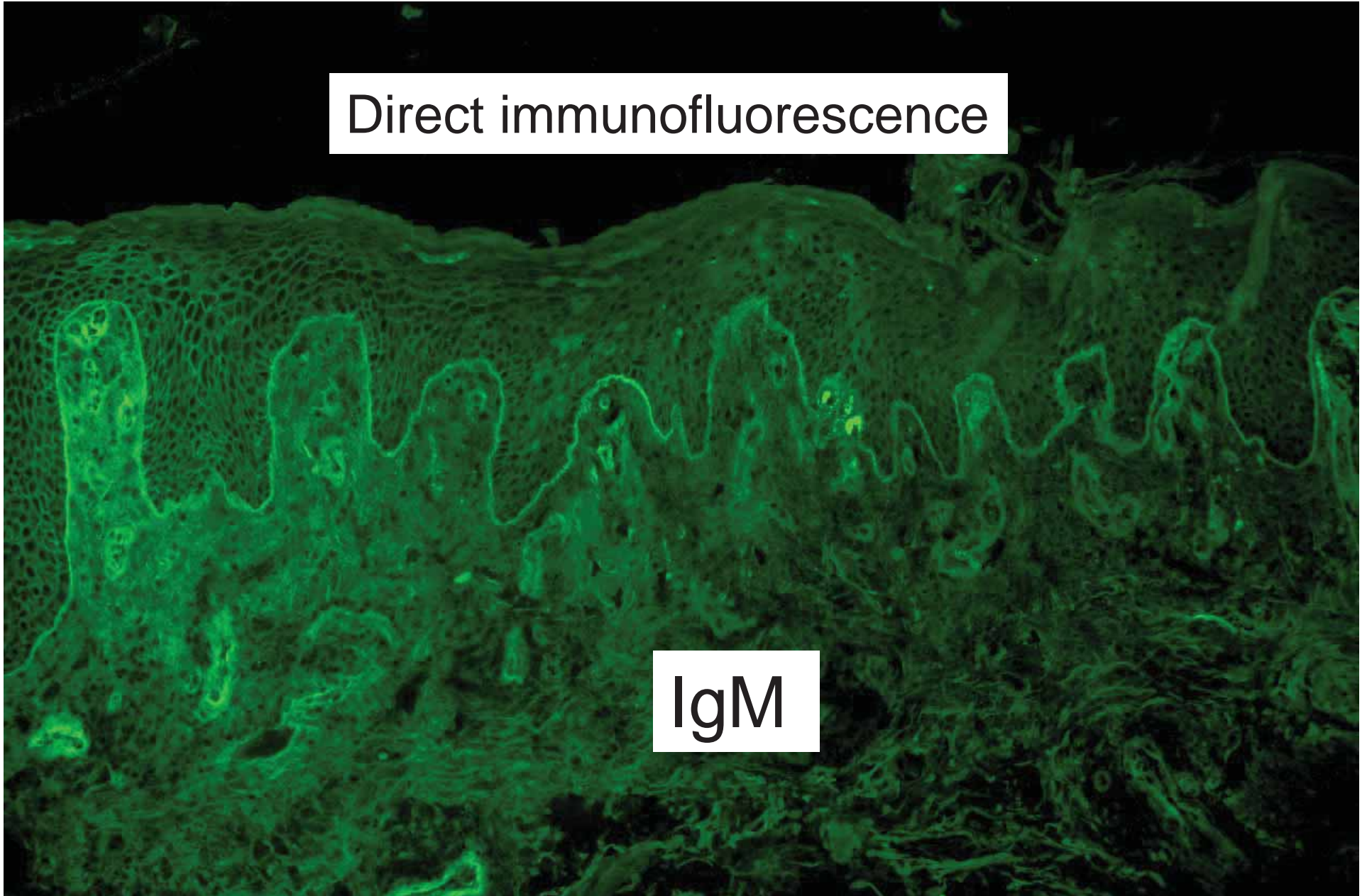
80 y, female

severely itchy skin lesions for one year

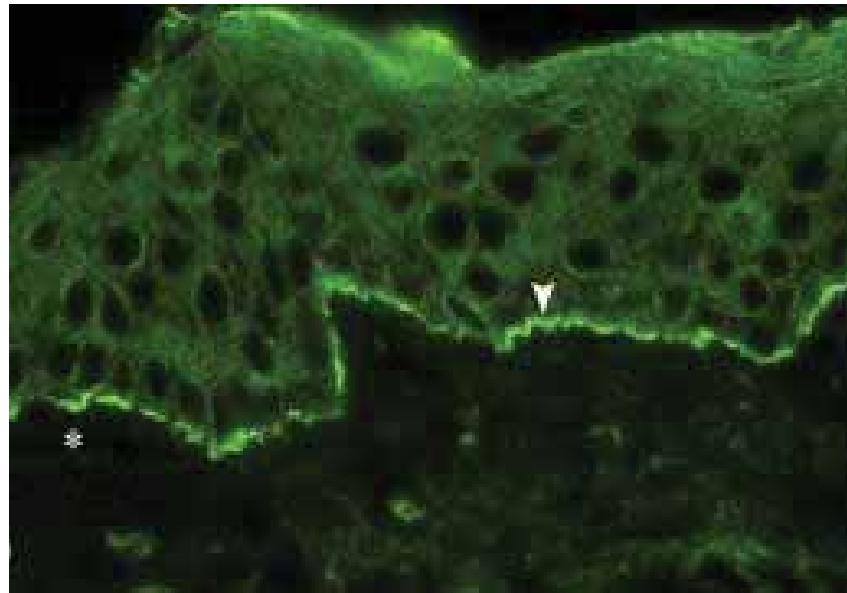


Direct immunofluorescence

IgM



Indirect immunofluorescence on salt-split human skin



IgM-autoantibodies bind to the roof of the blister

Immunoglobulin M pemphigoid

Katharina Boch, MD,^a Christoph M. Hammers, MD, PhD,^{a,b} Stephanie Goletz, PhD,^b
Mayumi Kamaguchi, PhD,^b Ralf J. Ludwig, MD,^b Stefan W. Schneider, MD,^c Detlef Zillikens, MD,^a
Eva Hadaschik, MD,^d and Enno Schmidt, MD, PhD^{a,b}
Lübeck, Hamburg, and Essen, Germany

Background: Pemphigoid diseases are a heterogeneous group of autoimmune blistering disorders characterized by predominant deposition of immunoglobulin G or immunoglobulin A autoantibodies against structural proteins of the dermoepidermal junction (DEJ). Sole linear immunoglobulin M (IgM) deposits at the DEJ in pemphigoid diseases have been observed; however, IgM-specific target antigens have not been identified.

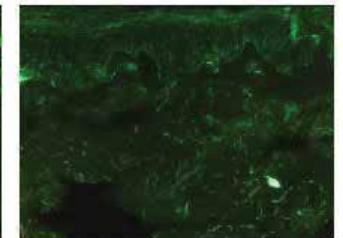
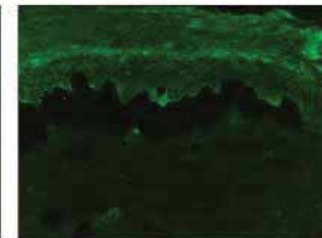
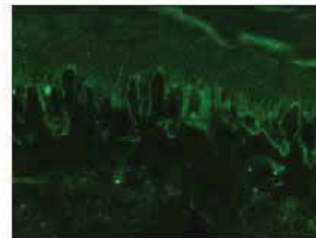
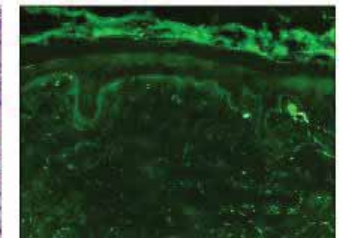
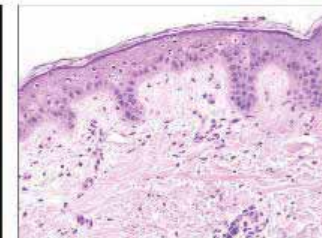
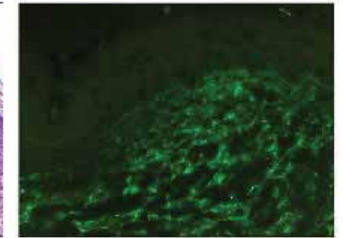
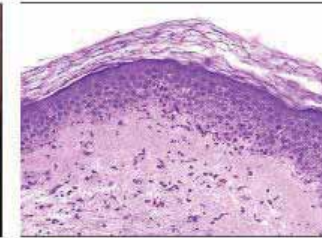
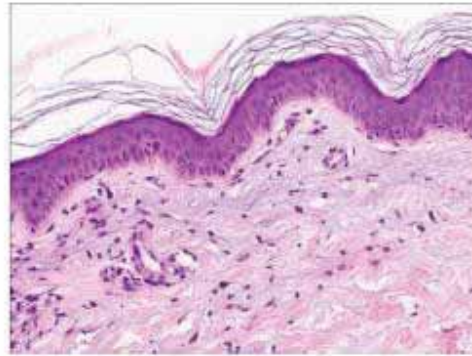
Objective: Characterization of patients with IgM pemphigoid.

Methods: Skin biopsy specimens and sera from IgM-positive patients were assessed using histopathology, direct and indirect immunofluorescence microscopy, enzyme-linked immunosorbent assays, immunoblotting, cryosection assay, complement fixation test, and internalization assays.

Results: Tissue-bound linear IgM deposits along the DEJ and circulating IgM autoantibodies against type XVII collagen (Col17) were detected. These circulating IgM autoantibodies showed no complement activating or blister inducing capacity, but the ability of Col17 internalization *ex vivo*.

Limitations: Limited number of patients.

Conclusion: This study provides further evidence for the role of IgM autoantibodies in pemphigoid disease and highlights Col17 as a target antigen in IgM pemphigoid. (J Am Acad Dermatol <https://doi.org/10.1016/j.jaad.2021.01.017>.)

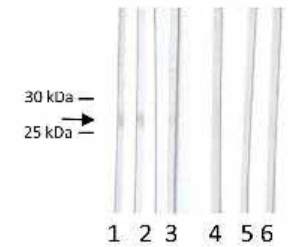
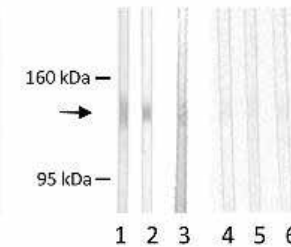
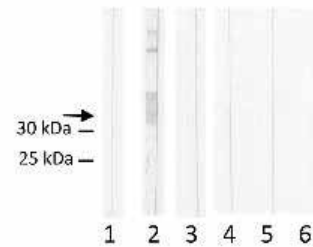


3 patients
52, female
79, male
60, female

NC16A-4x

Col17ec

Col17ec3



J Am Acad Dermatol 2021; 85: 1486-92

Characteristics of IgM-Pemphigoid

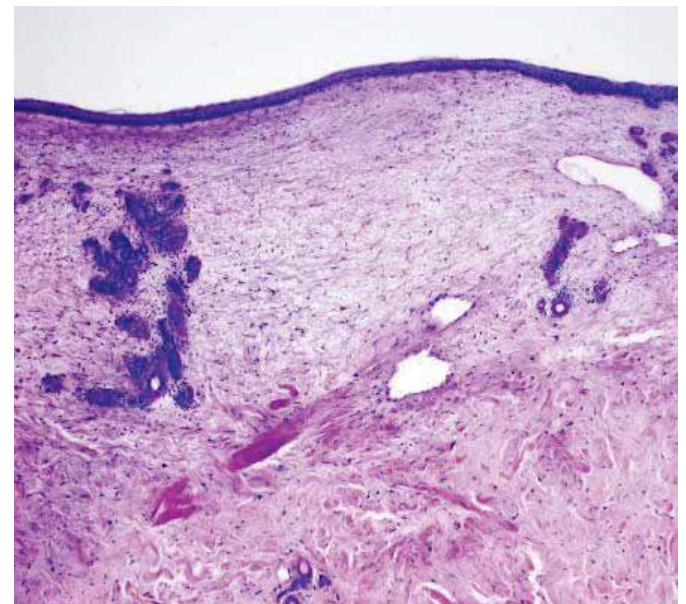
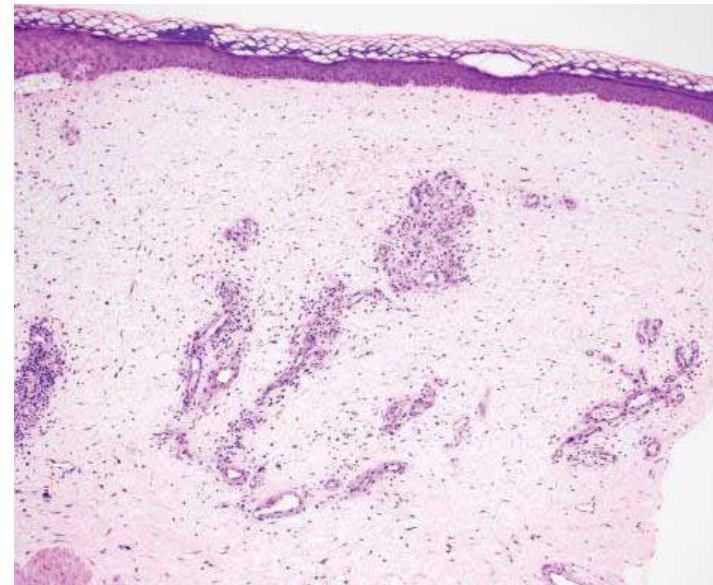
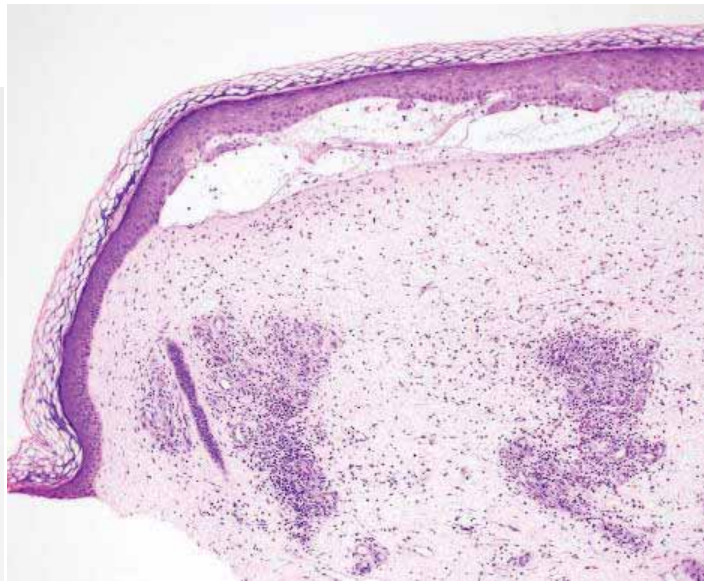
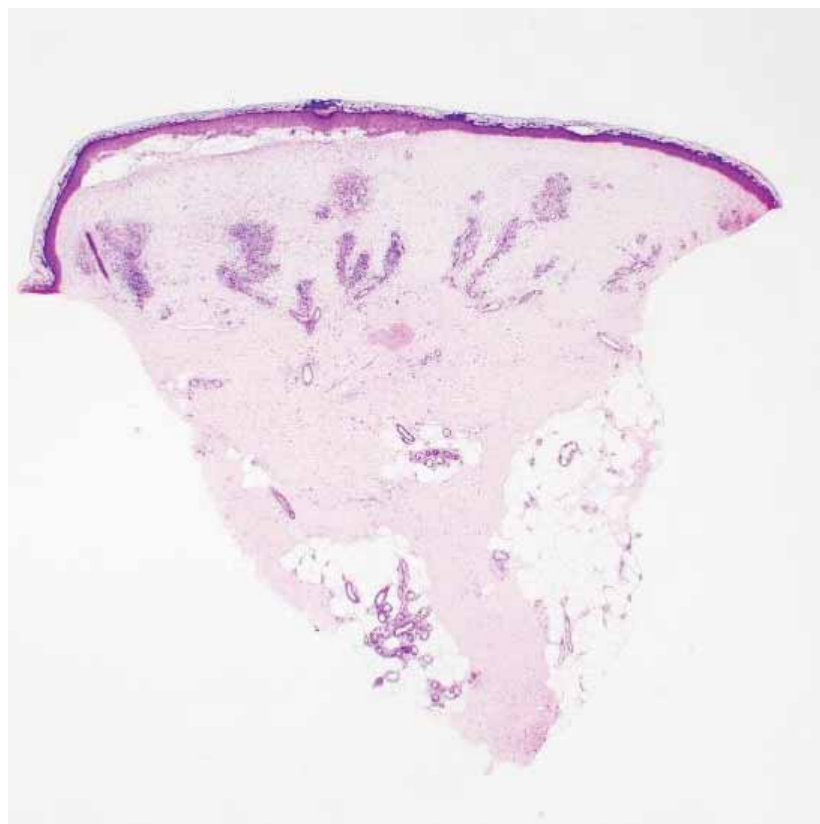
- Very rare in older patients
- Chronic itchy eczematous lesions
- Histology often "unspecific"
- Conventional ELISA negative
- Confirmation by direct immunofluorescence



66 y, female: For 2 years, itchy bullous skin lesions only on both lower legs.



3 years later



Obesity-associated lymphoedematous mucinosis

Background: Mucin deposition on the shins is considered as an indicator of pretibial myxoedema, which is typically seen in patients with Graves' disease.

Objective: The purpose of this study was to report the clinical and histopathological features of a group of patients with pretibial mucinosis in the absence of thyroid disease.

Methods: Five patients are included in this series and studied both clinically and histologically and compared with similar cases in the literature.

Results: All patients were middle aged or elderly. Four patients were women. They were characterized clinically by morbid obesity and bilateral lower extremity pitting oedema sparing the feet.

Semitranslucent papules and/or nodules and sometimes vesicles were

Franco Rongioletti¹, Pietro Donati², Ada Amantea², Gerardo Ferrara³, Martina Montinari¹, Francesca Santoro¹ and Aurora Parodi¹

¹Section of Dermatology, DISEM, University of Genoa, Genoa, Italy,
²San Galiciano Dermatological Institute, IRCCS, Rome, Italy and
³Department of Pathologic Anatomy Unit, Gaetano Rummo General Hospital, Benevento, Italy

J Cutan Pathol 2009, 36: 1089-94



Fig. 3. Patient 5. A) Papulovesicles and nodules merging into plaques on the shin on an erythematous and oedematous background. B) Marked improvement of the lesions after loosing 15 kg.

Obesity-associated lymphoedematous mucinosis

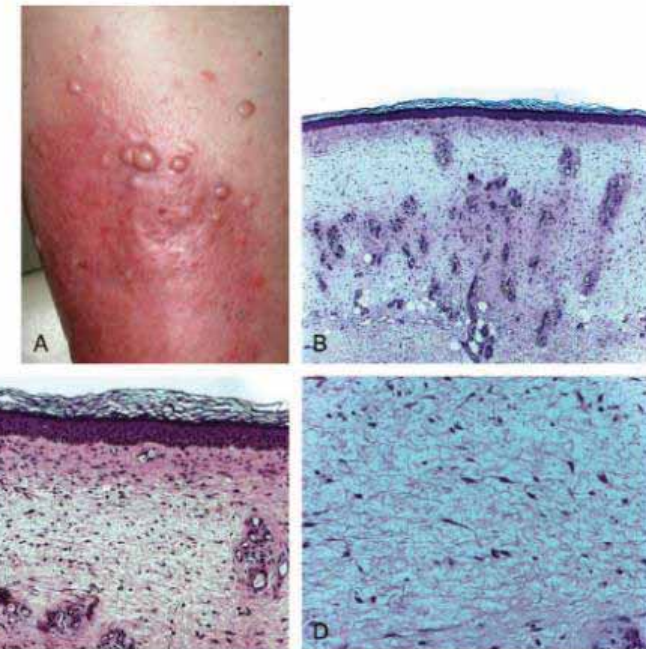


Fig 1. Patient 1. A) Swollen leg with pitting oedema and waxy semitranslucent, skin-coloured papules and nodules on the shin. B) Hyperorthokeratosis, effacement of rete ridge pattern, mucinous oedema of the upper part of dermis with increased fibroblasts and angioplasia with upward-running, increased and thickened capillary vessels (Alcian blue stain $\times 40$). C) The same histological findings at higher power (haematoxylin-eosin $\times 100$). D) Mucinous oedema with fibroblast proliferation (Alcian blue stain $\times 200$).

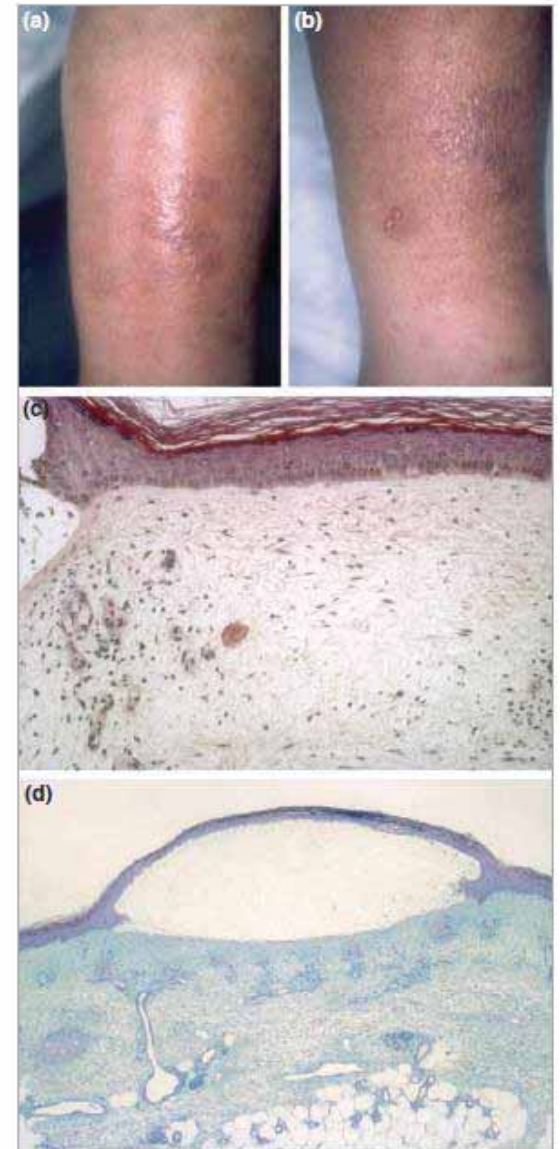
Chronic obesity lymphoedematous mucinosis: three cases of pretibial mucinosis in obese patients with pitting oedema

Y. Tokuda, S. Kawachi,* H. Murata* and T. Saida*

Division of Dermatology, Matsumoto National Hospital, 1209 Yoshikawa Murai-cho, Matsumoto, Nagano 399-8701, Japan

*Department of Dermatology, Shinshu University School of Medicine, Matsumoto, Nagano, Japan

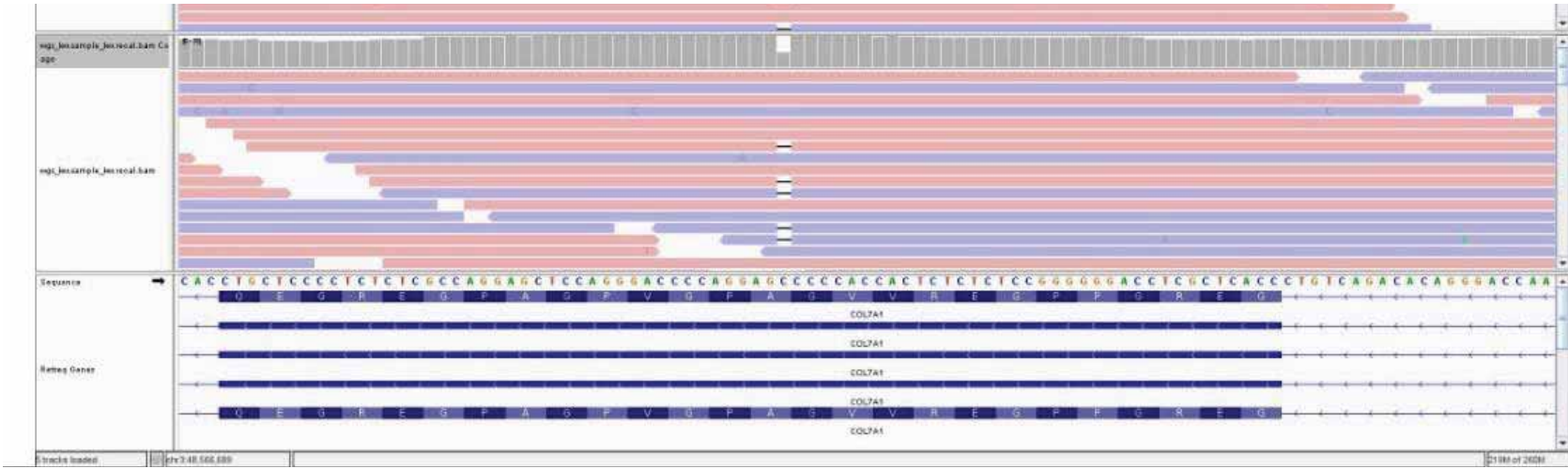
Br J Dermatol 2006, 154: 157-61



Whole-genome and whole-exome sequencing

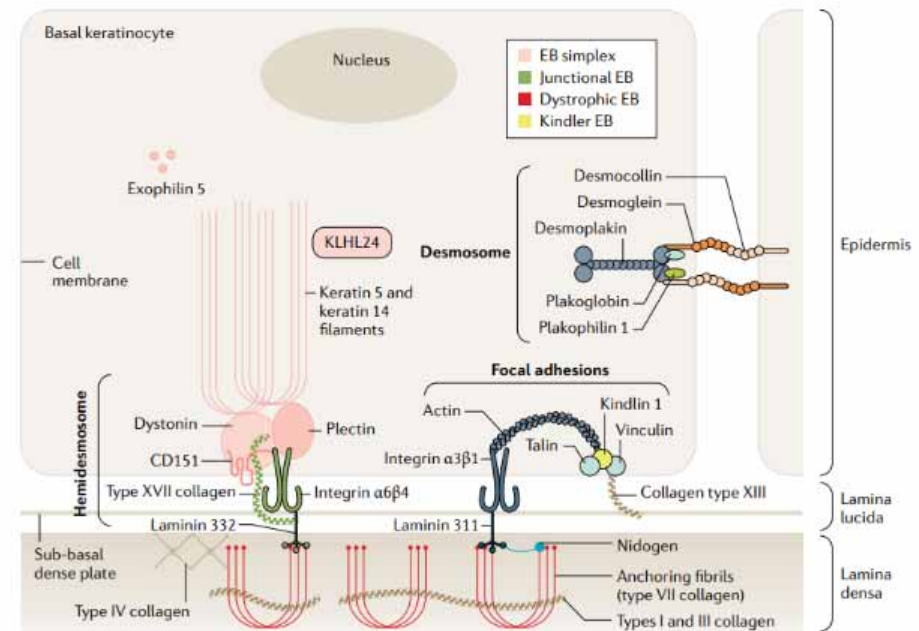


Late-onset pretibial epidermolysis bullosa



Epidermolysis bullosa

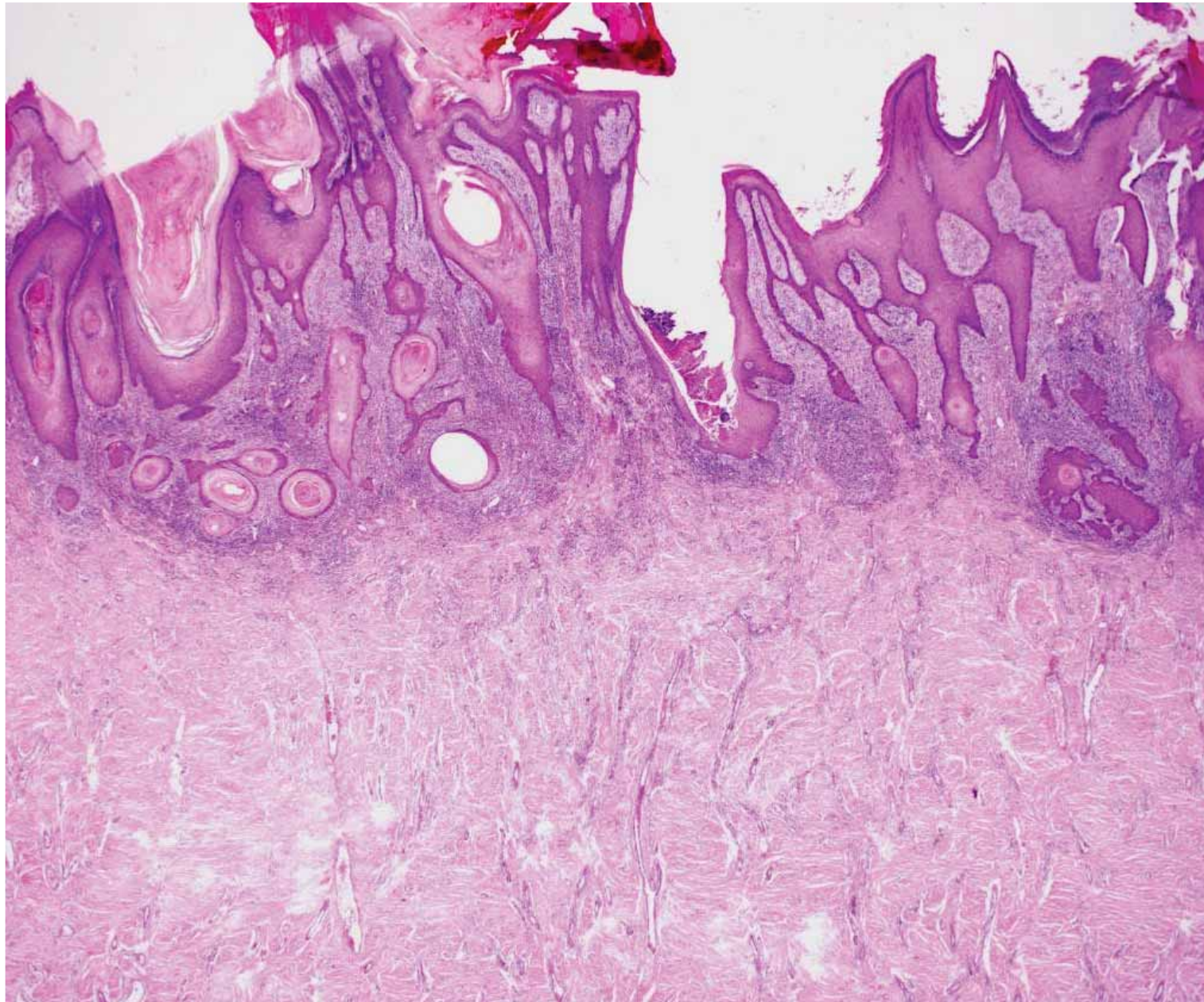
- Epidermolysis bullosa simplex
- Junctional Epidermolysis
- Dystrophic Epidermolysis bullosa
- Kindler Epidermolysis bullosa



Bardham A, et al. Nat Rev Dis Primers 2020; 24: 78

Dystrophic EB — sublamina densa				
Intermediate DDEB ^a	Generalized skin fragility, scarring and milia presenting from birth or early infancy, with prominence over acral sites, elbows and knees; involvement of the mucous membranes may lead to microstomia, ankyloglossia and oesophageal stenosis, although less commonly than in severe RDEB	AD	COL7A1	Reduced or abnormal type VII collagen; DDEB is usually due to missense mutations causing glycine substitution in the hinge region of the type VII collagen triple helix
Localized DDEB ^a	Predominantly acral blistering, scarring and milia seen from birth or early infancy; occasional nails-only presentation, with progressive dystrophy and eventual nail loss; rarely, cutaneous features may predominate over pretibial skin alone (and can present as late-onset disease)	AD	COL7A1	Reduced or abnormal type VII collagen arising from monoallelic deletions, missense mutations or splice site mutations
DDEB, pruriginosa ^a	Profoundly pruritic linear cords of papules associated with fragility, scarring and milia on the shins, and occasionally progressing to arms; may present in childhood or adulthood; nail dystrophy is usual	AD	COL7A1	No specific genotype–phenotype correlation has been elucidated
DDEB, self-improving ^{ab}	Blistering evident at or shortly after birth, usually on extremities where there may be aplasia cutis, whilst scarring and milia may occur; spontaneous resolution of cutaneous fragility within the first 2 years of life	AD	COL7A1	During the active phase, EM reveals cytoplasmic stellate bodies within dilated rough ER composed of unsecreted procollagen VII; immunohistochemistry shows retention of type VII collagen within basal keratinocytes; gradual improvement in type VII collagen formation, and resolution of anchoring fibril formation for reasons unknown
Intermediate RDEB ^b	Phenotype similar to that of intermediate DDEB, although greater severity with flexion contractures, limited digital fusion and occasional striate keratoderma	AR	COL7A1	Biallelic mutations in COL7A1, including missense, nonsense, insertion, deletion and splice site mutations results in reduced or abnormal type VII collagen
Severe RDEB ^b	Widespread blistering from birth, with extensive scarring and development of microstomia, ankyloglossia, oesophageal stenosis, flexion contractures of limbs and pseudosyndactyly; nails are often lost early in disease course; high risk of cutaneous SCC arising in EB wounds.	AR	COL7A1	Biallelic mutations in COL7A1, usually null mutations result in markedly reduced or absent type VII collagen and, therefore, a lack of functional anchoring fibrils
RDEB, inversa ^c	Generalized blistering from birth, of intermediate severity; subsequently, fragility tends to be displayed on flexural sites	AR	COL7A1	Attributed to compound heterozygosity for missense mutation and concurrent loss-of-function mutation with specific arginine and glycine substitution in triple helix of type VII collagen
RDEB, localized ^d	Skin fragility and blistering typically at birth or neonatal period, limited to acral sites such as hands and feet, or occasionally only to pretibial skin, where it may manifest as late-onset disease during adulthood; nail dystrophy and loss usual	AR	COL7A1	Reduced or abnormal type VII collagen
RDEB, pruriginosa ^e	As for DDEB, pruriginosa	AR	COL7A1	As for DDEB pruriginosa
RDEB, self-improving ^f	As for DDEB, self-improving	AR	COL7A1	As for DDEB, self-improving
RDEB, severe ^d	Clinically indistinguishable from severe RDEB, with severe mucocutaneous fragility from birth	Dominant and recessive compound heterozygosity	COL7A1	Compound heterozygosity for dominant COL7A1 glycine substitution mutation and recessive mutation on second allele affecting type VII collagen

Bardham A, et al.
 Nat Rev Dis Primers 2020; 24: 78

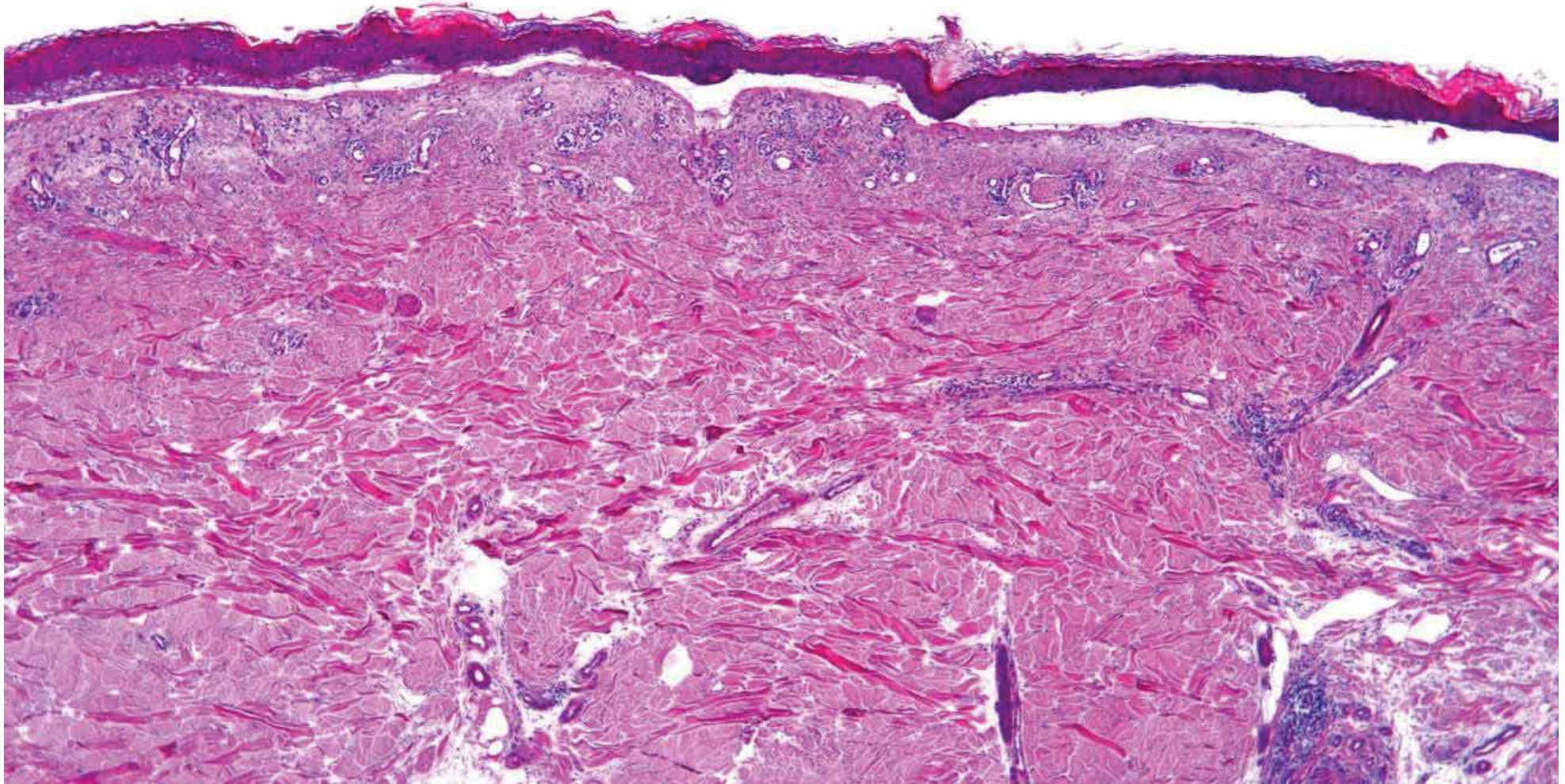


17 y, male



Epidermolysis bullosa acquisita





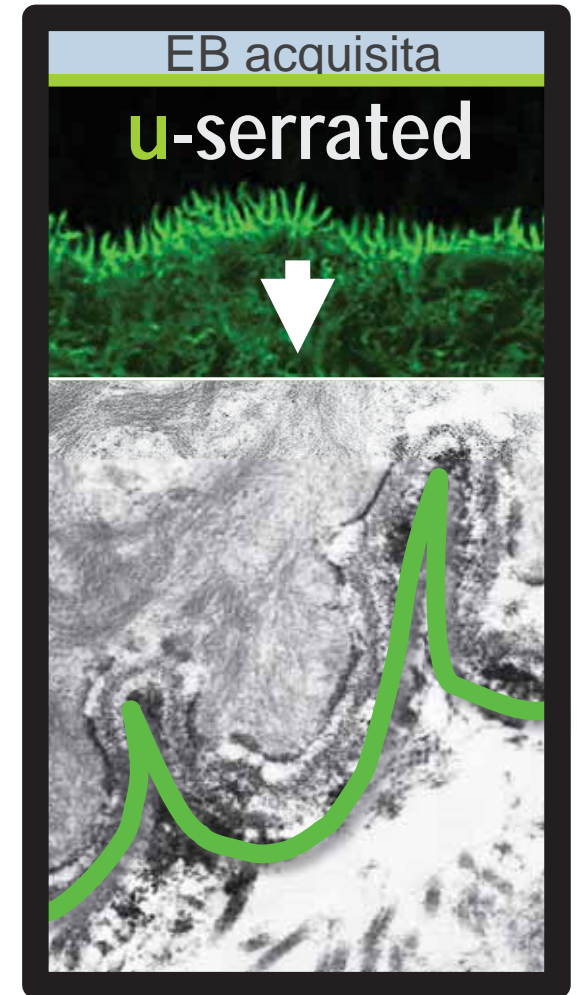
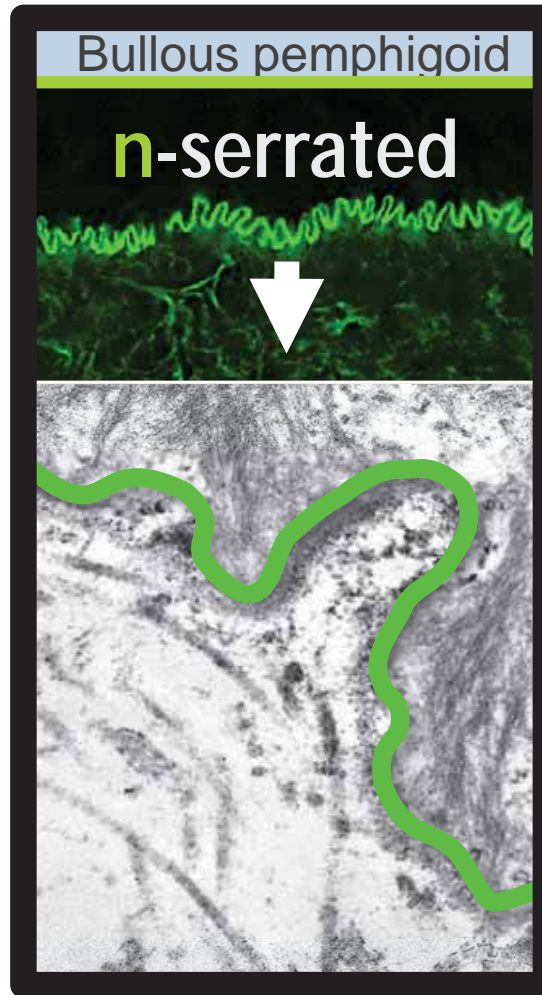
Detection of circulating serum autoantibodies

Pemphigus vulgaris	>90%
Pemphigus foliaceus	>90%
IgA pemphigus	50%
Bullous pemphigoid	80-90%
Pemphigoid gestationis	>90%
Linear IgA disease	70%
Mucous membrane pemphigoid	40-50%
Epidermolysis bullosa acquisita	50-60%
Dermatitis herpetiformis	>90%

Direct immunofluorescence – serration pattern



Marcel Jonkman
(1957-2019)

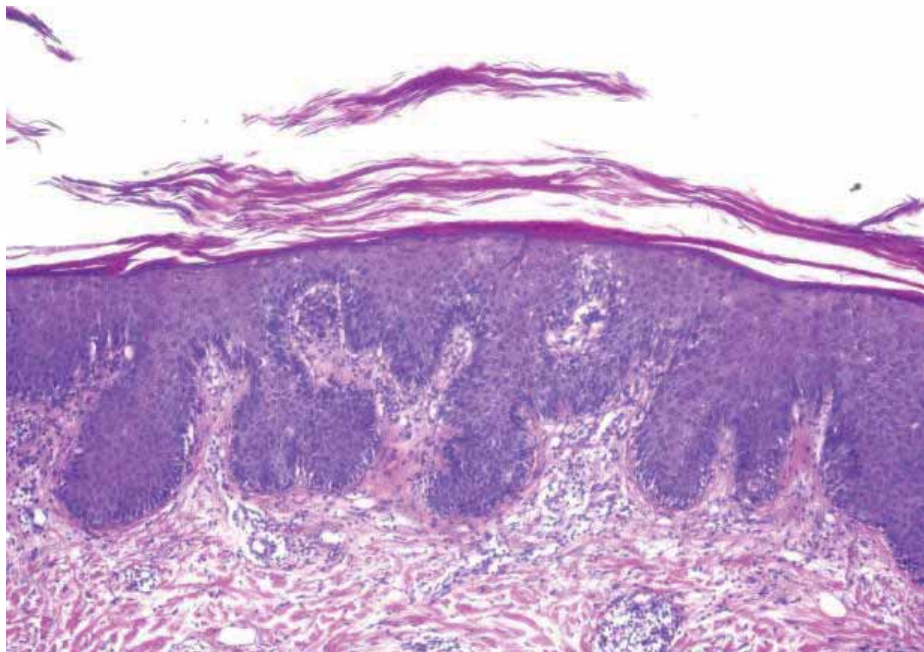
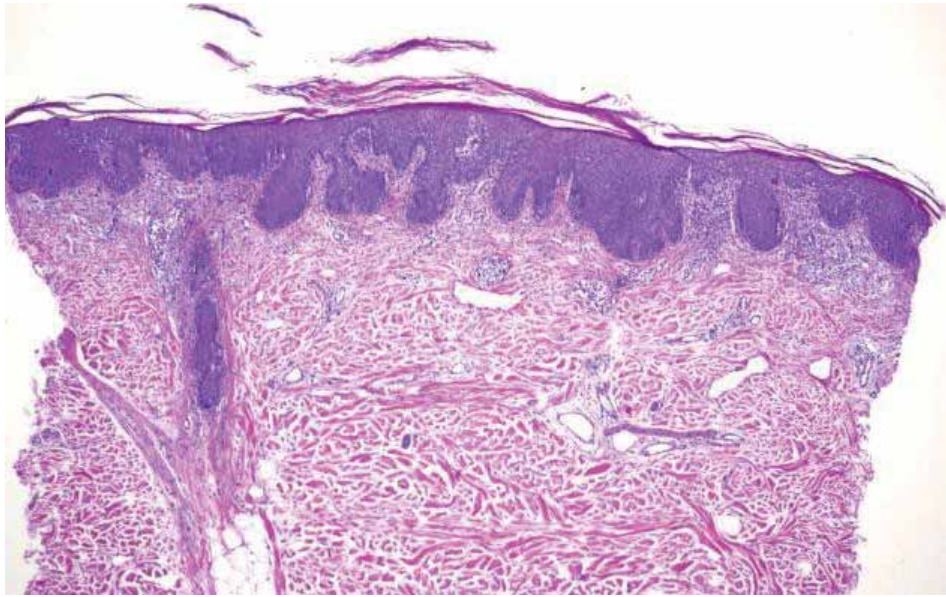


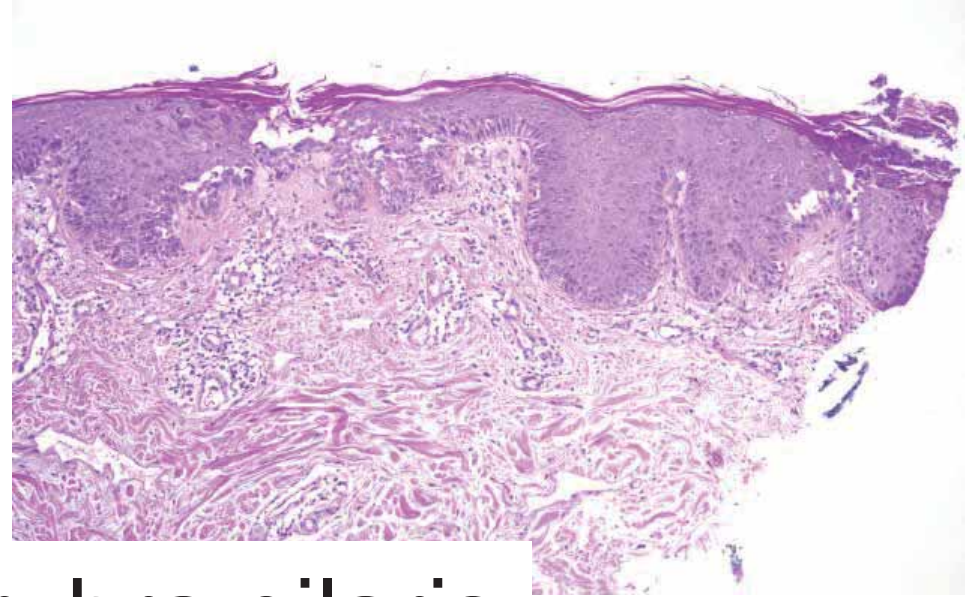
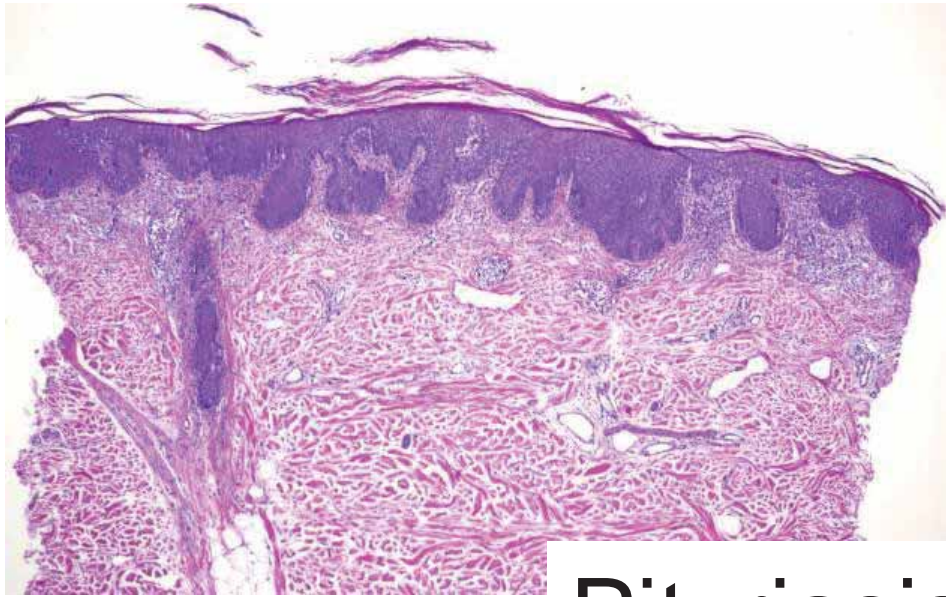


78 y,
male

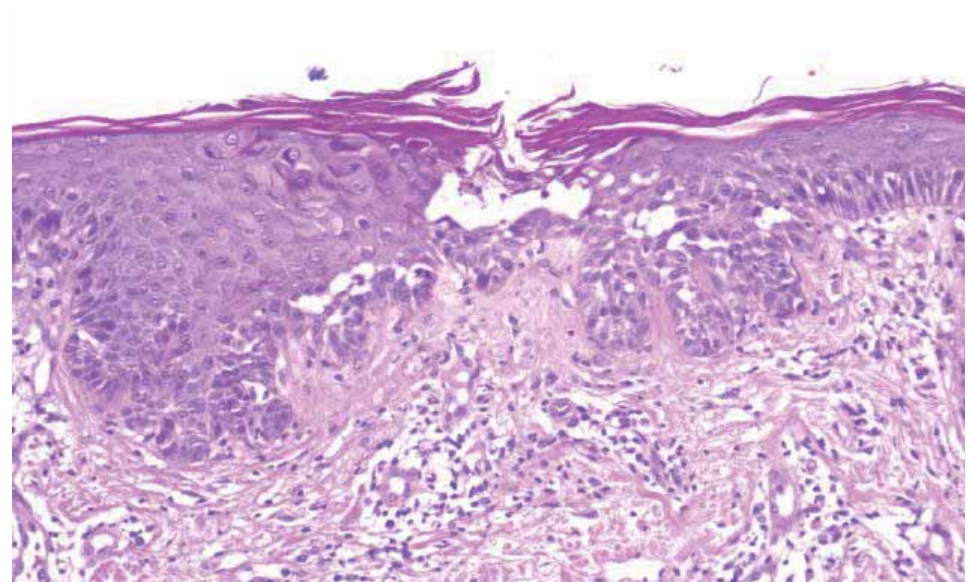
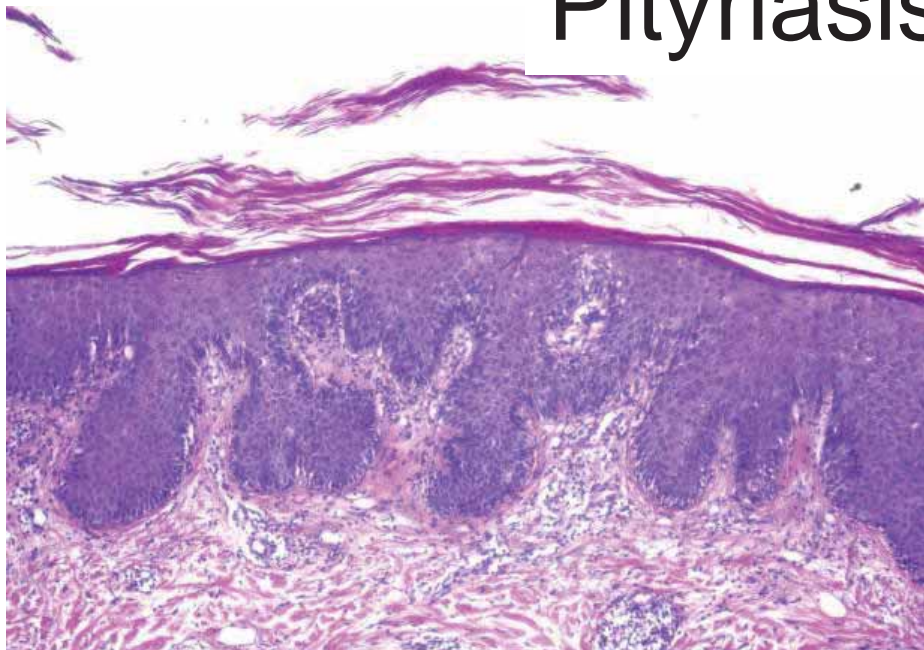


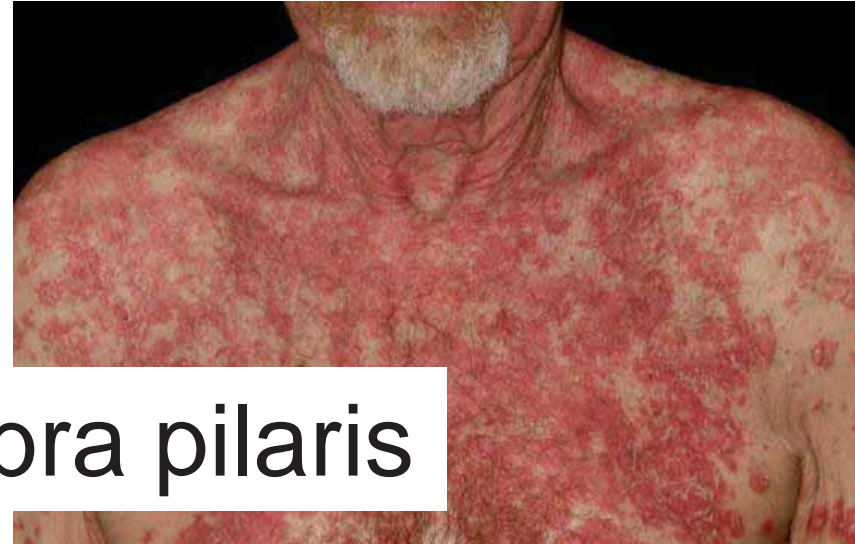
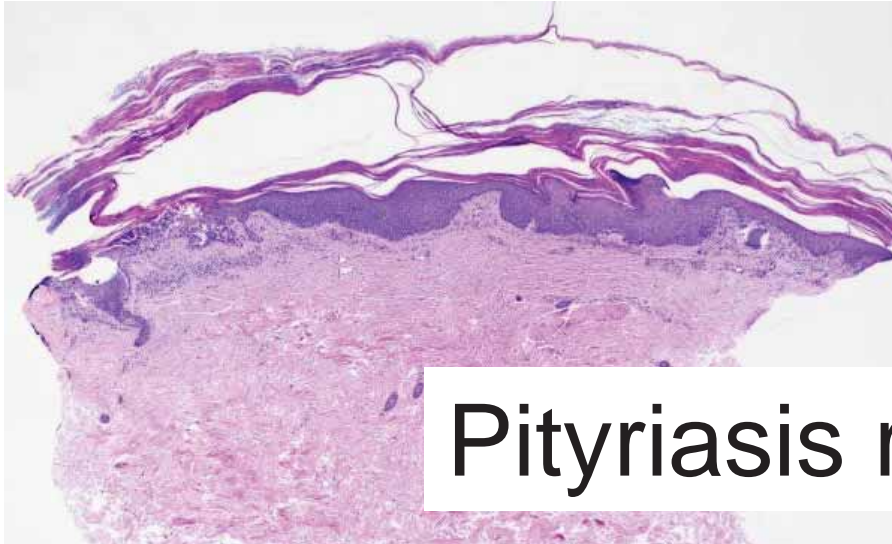
61 y,
female





Pityriasis rubra pilaris





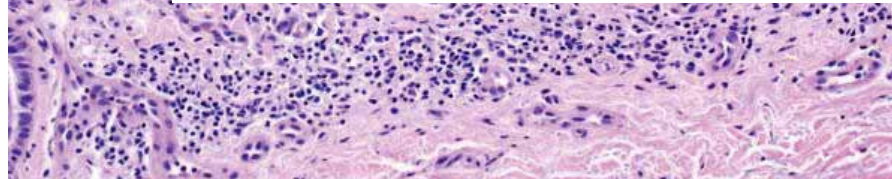
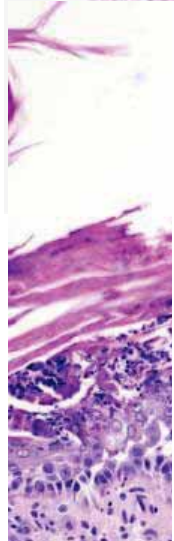
Pityriasis rubra pilaris

International Journal of
Dermatology

Report

Pityriasis rubra pilaris: the clinical context of acantholysis and other histologic features

Christine J. Ko, MD, Leonard M. Milstone, MD, Jaehyuk Choi, MD, PhD, and Jennifer M. McNiff, MD





- Often but not always a simple blood test can render a correct diagnosis of an autoimmune bullous disease
- If histology looks suspicious for an autoimmune bullous dermatosis but direct immunofluorescence is negative, it should be repeated.
- If an autoimmune bullous disease is excluded, an exact clinicopathological correlation is necessary to come to a correct diagnosis.

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