Dermatopatohologic clues for the diagnosis of AIDs in children

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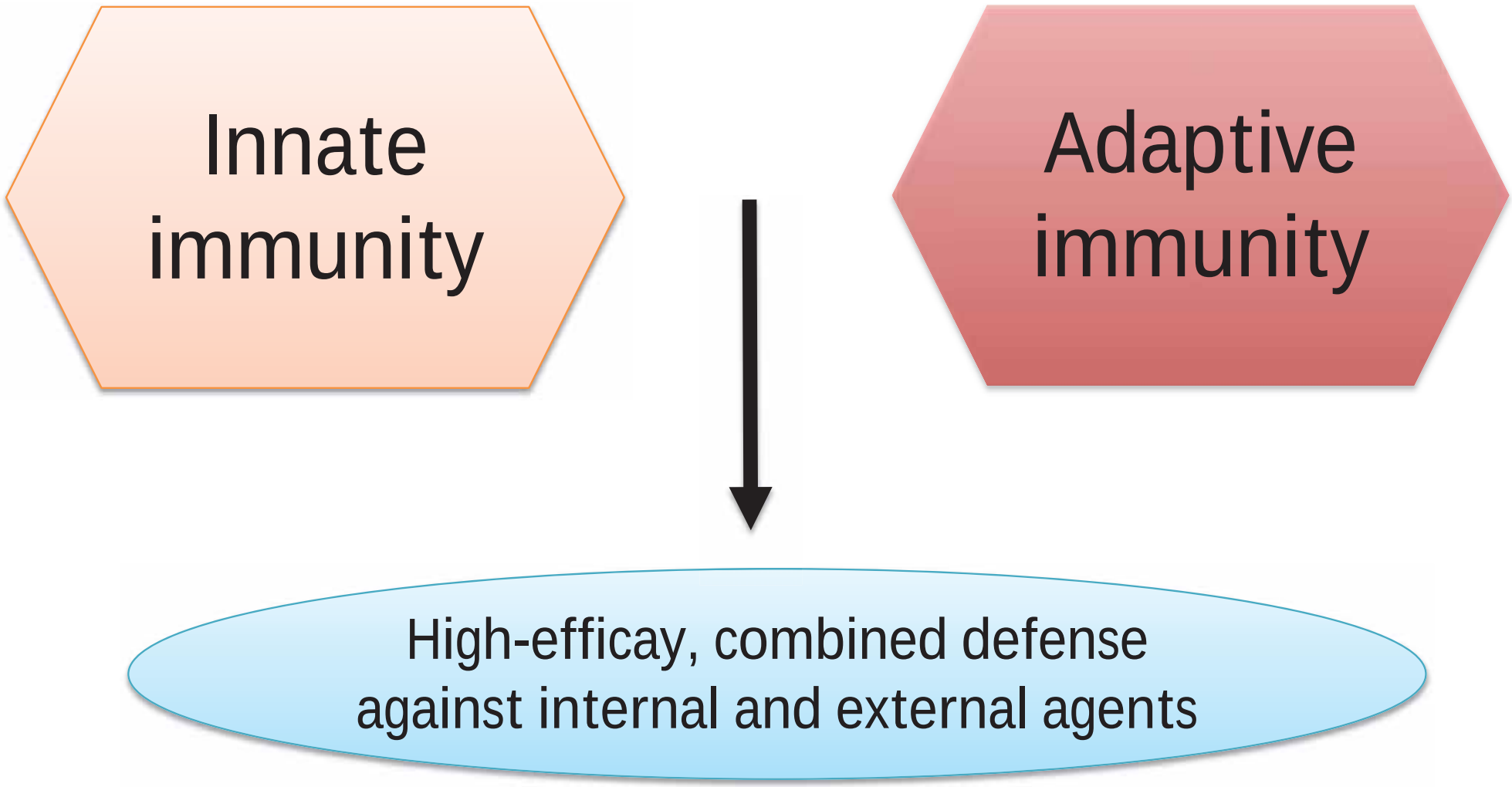
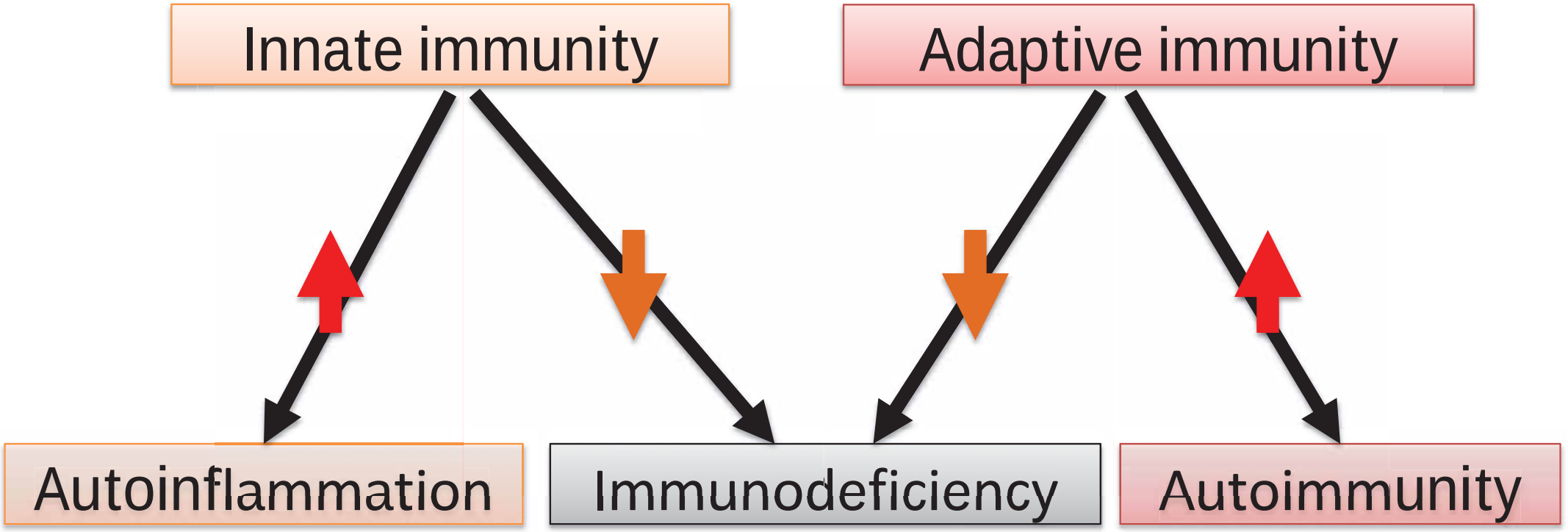
Madrid, Spain

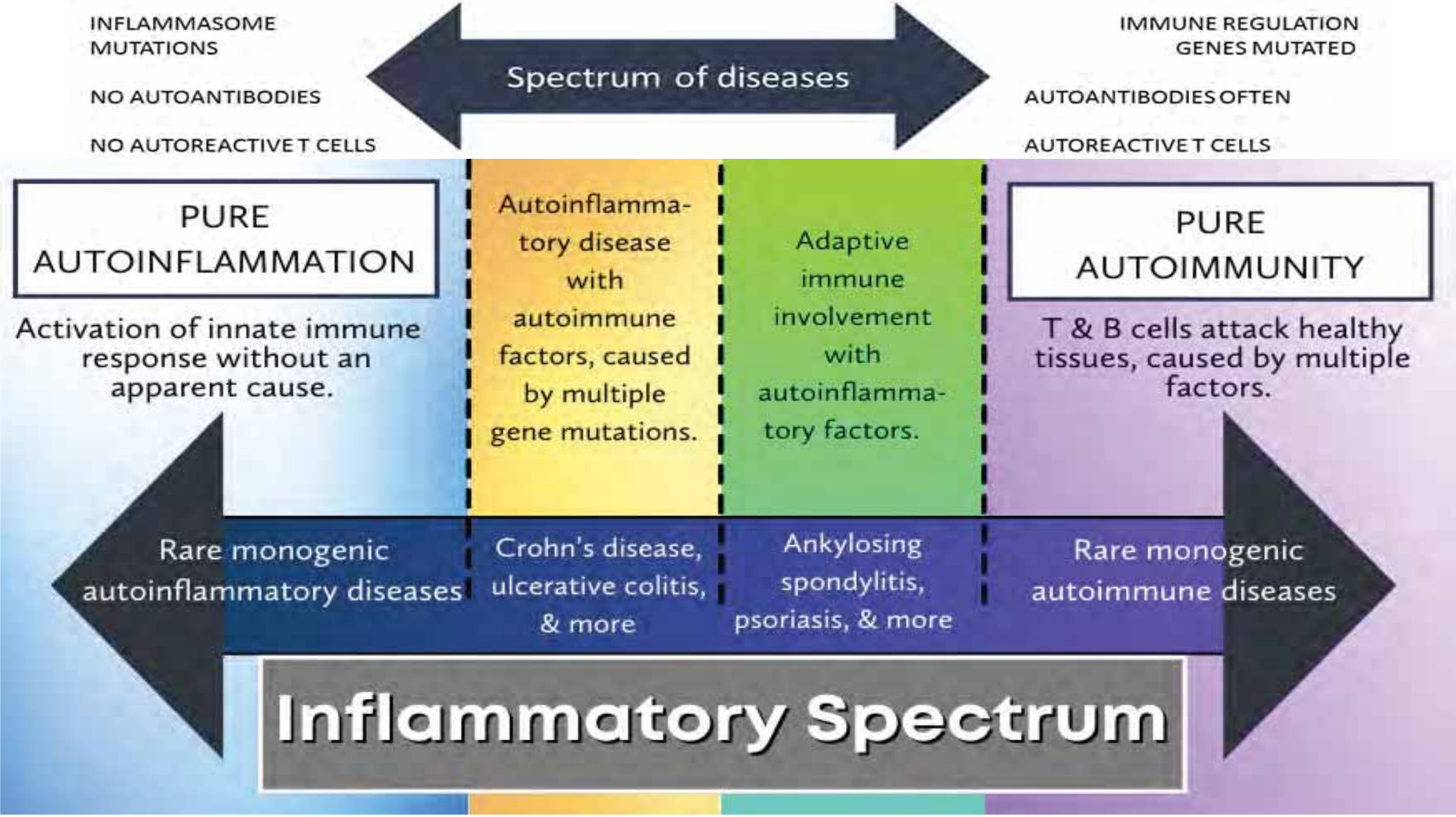
The immune system in health



The immune system in disease




INFLAMMASOME
MUTATIONS
NO AUTOANTIBODIES
NO AUTOREACTIVE T CELLS
Spectrum of diseases
IMMUNE REGULATION
GENES MUTATED
AUTOANTIBODIES OFTEN
AUTOREACTIVE T CELLS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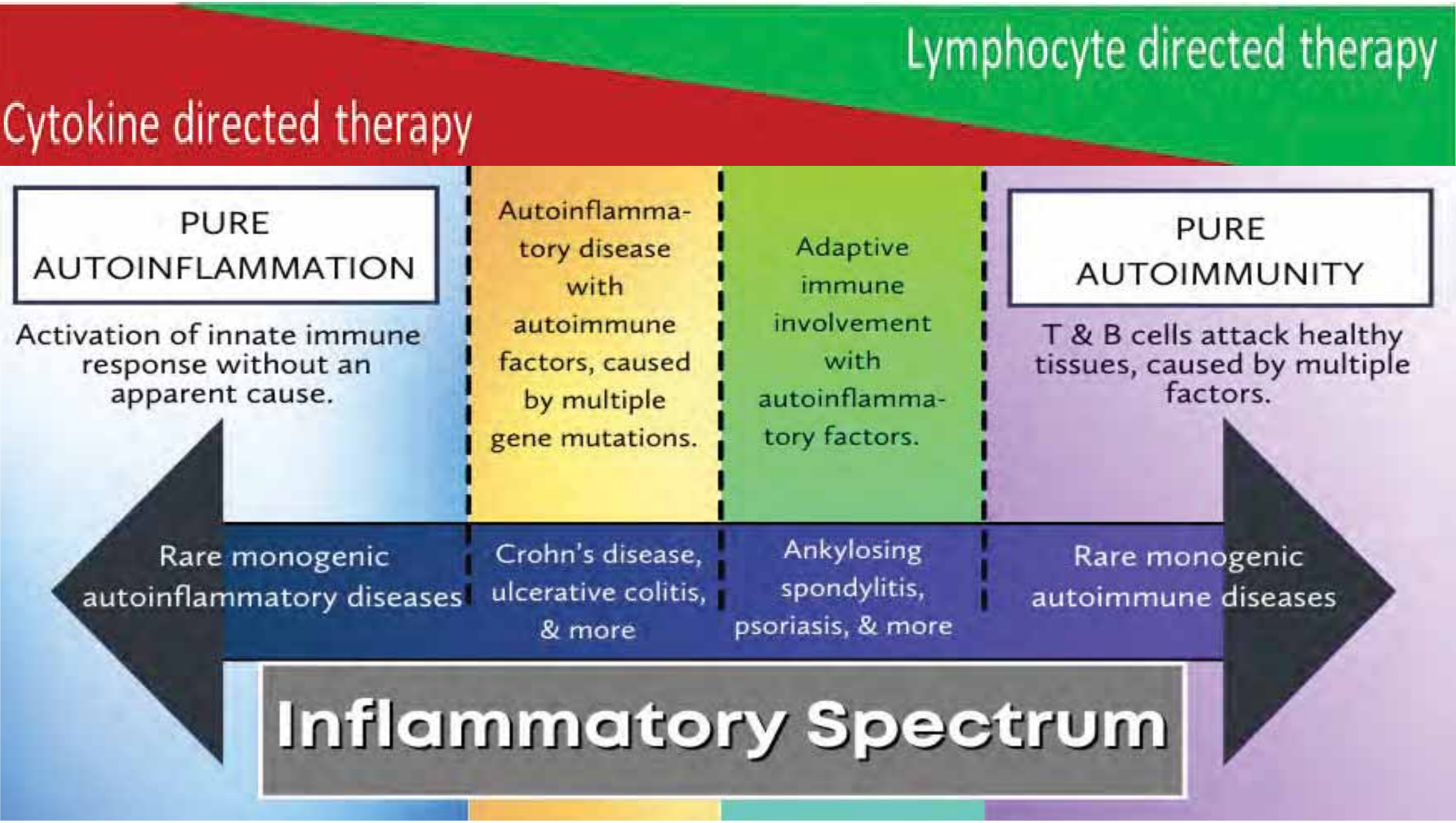
PURE AUTOINFLAMMATION
Activation of innate immune response without an apparent cause.
Autoinflammatory disease with autoimmune factors, caused by multiple gene mutations.
Adaptive immune involvement with autoinflammatory factors.
PURE AUTOIMMUNITY
T & B cells attack healthy tissues, caused by multiple factors.
Rare monogenic autoinflammatory diseases
Crohn's disease, ulcerative colitis, & more
Ankylosing spondylitis, psoriasis, & more
Rare monogenic autoimmune diseases
Inflammatory Spectrum


Lymphocyte directed therapy
Cytokine directed therapy
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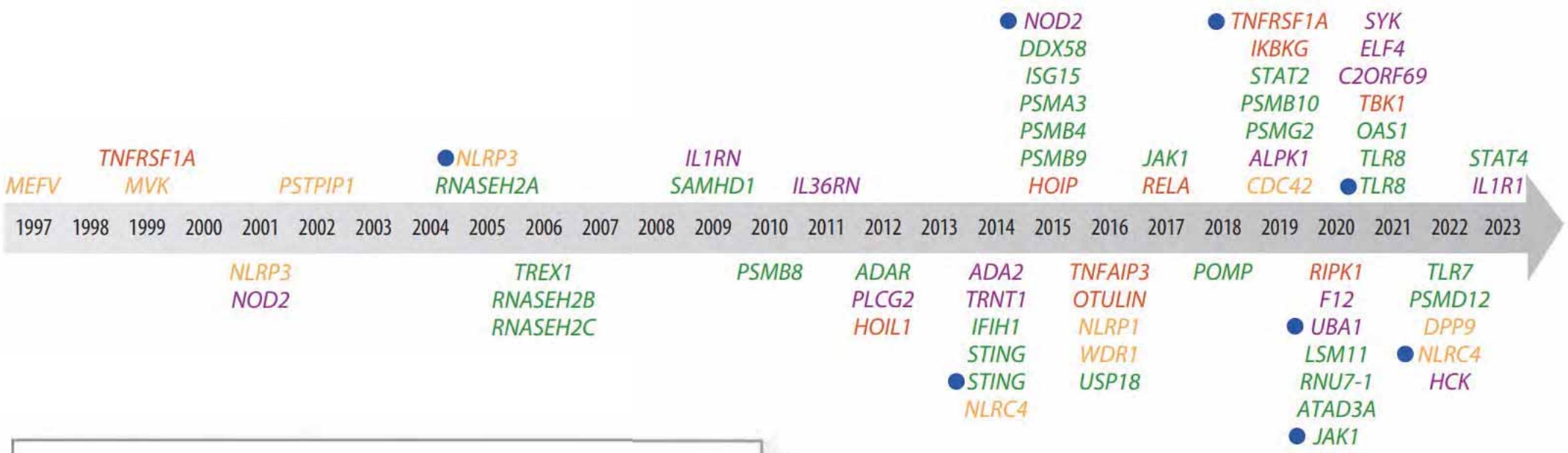
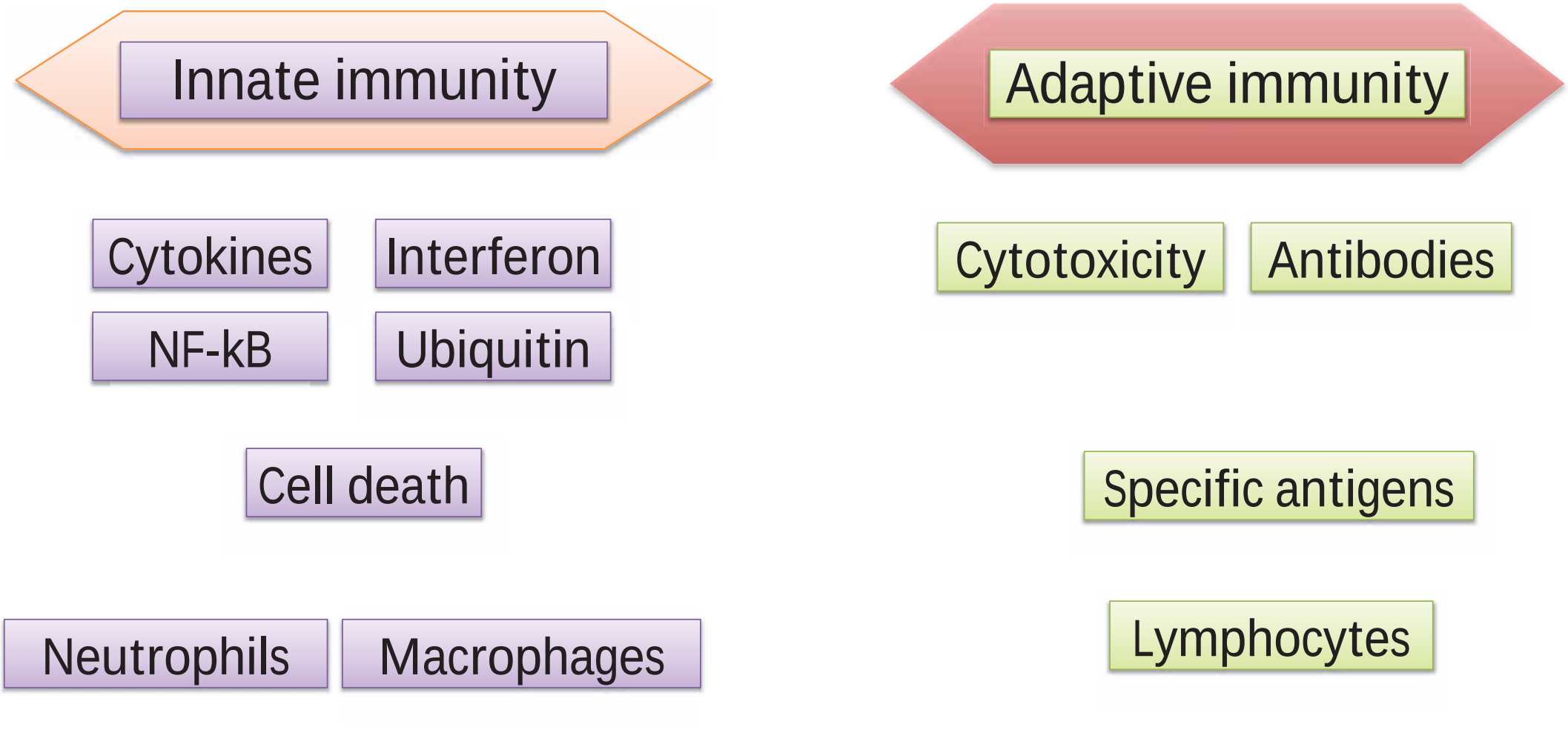

MEFV
TNFRSF1A
MVK
PSTPIP1
NLRP3
RNASEH2A
IL1RN
SAMHD1
IL36RN
NOD2
DDX58
ISG15
PSMA3
PSMB4
PSMB9
HOIP
JAK1
RELA
TNFRSF1A
IKBKG
STAT2
PSMB10
PSMG2
ALPK1
CDC42
SYK
ELF4
C2ORF69
TBK1
OAS1
TLR8
TLR8
STAT4
IL1R1
1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023
NLRP3
NOD2
TREX1
RNASEH2B
RNASEH2C
PSMB8
ADAR
PLCG2
HOIL1
ADA2
TRNT1
IFIH1
STING
STING
NLRC4
TNFAIP3
OTULIN
NLRP1
WDR1
USP18
POMP
RIPK1
F12
UBA1
LSM11
RNU7-1
ATAD3A
JAK1
TLR7
PSMD12
DPP9
NLRC4
HCK
Cell death–driven inflammation
Uncategorized monogenic autoinflammatory disease
Type I interferonopathy
Inflammasomopathy
Somatic mutation


Innate immunity
Adaptive immunity
Cytokines
Interferon
NF-kB
Ubiquitin
Cell death
Neutrophils
Macrophages
Cytotoxicity
Antibodies
Specific antigens
Lymphocytes

Onset in infancy


Onset in infancy
Skin lesions

Classification of AIDs

Inflammasomopathy	Interferonopathy	NF-kBopathy	Others
Fevers Organ involvement • Abdominal pain • Non-vasculitic rashes • Uveitis • Arthritis Elevated WBC/neutrophils Highly elevated inflammatory markers	Fevers Organ involvement • Vasculitic rashes • Interstitial lung disease • Intracranial calcifications Inflammatory markers may not be as elevated Autoantibodies may be present	Fevers Highly variable organ involvement • Oral/GI/GU ulcerations • Granulomas	Fevers Organ involvement • Ulcers • Granulomas • Vasculitis • Panniculitis • Pyoderma gangrenosum • Immunodeficiency
IL-1 blockade	JAK inhibitor	NF-kB blockade	

URTICARIAL RASHES AND SYSTEMIC INFLAMMATION

CAPS, NLRC4-MAS, PLAID

MACULOPAPULAR RASHES WITH RECURRENT FEVER AND ABDOMINAL PAIN

Familial Mediterranean fever, HIDS/MVK, TRAPS, ORAS

PUSTULAR AND NEUTROPHILIC DERMATOSIS-LIKE SKIN RASHES AND EPISODIC FEVERS

DIRA, Majeed syndrome

PAPA, HA20, PAAND

DITRA, CAPE

ERYTHEMATOUS NODULES / PLAQUES AND PANNICULITIS / LIPOATROPHY

CANDLE, NEMO-NDAS

VASCULOPATHY / VASCULITIS WITH LIVEDO RETICULARIS

Without significant CNS disease

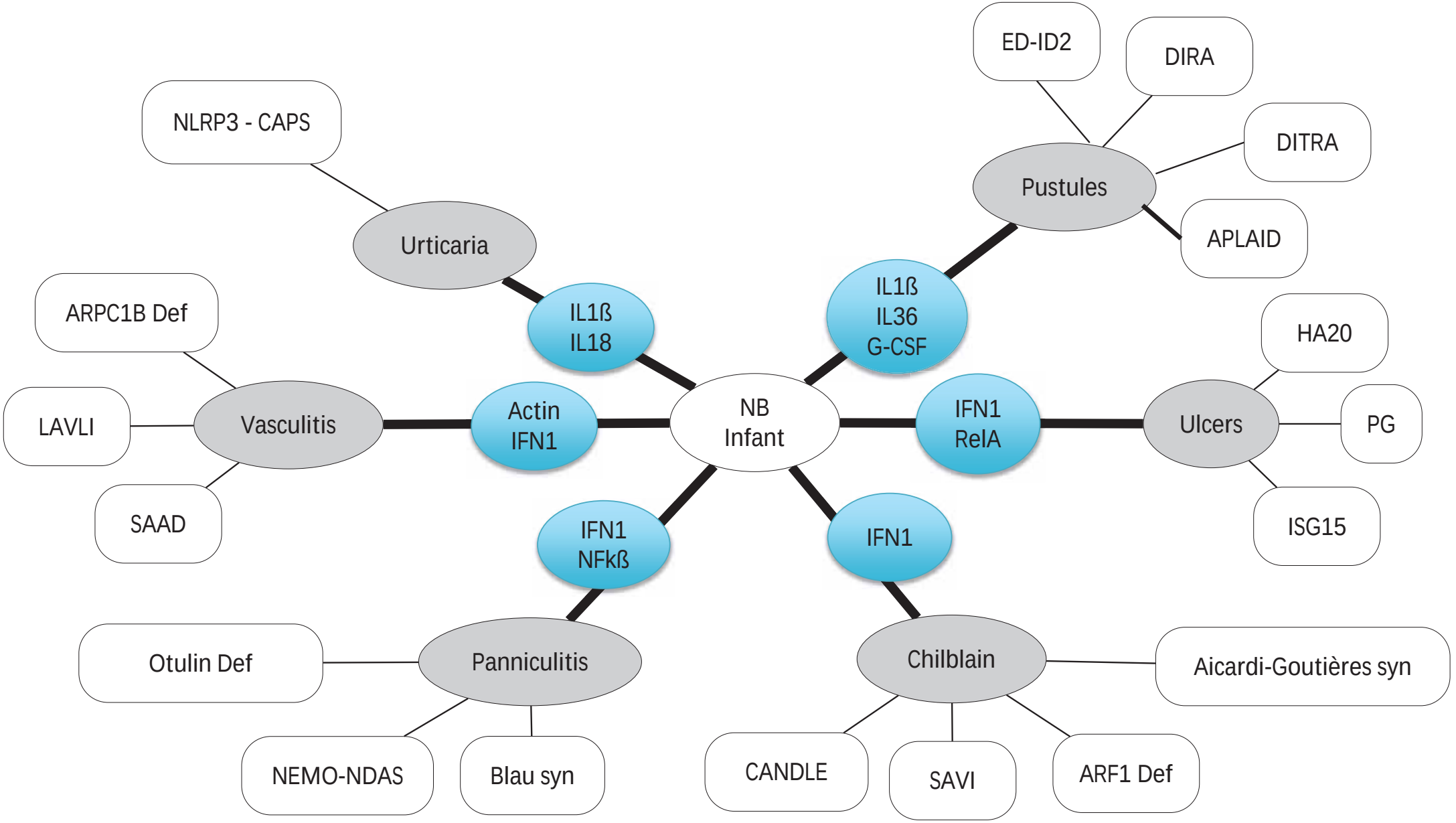
SAVI

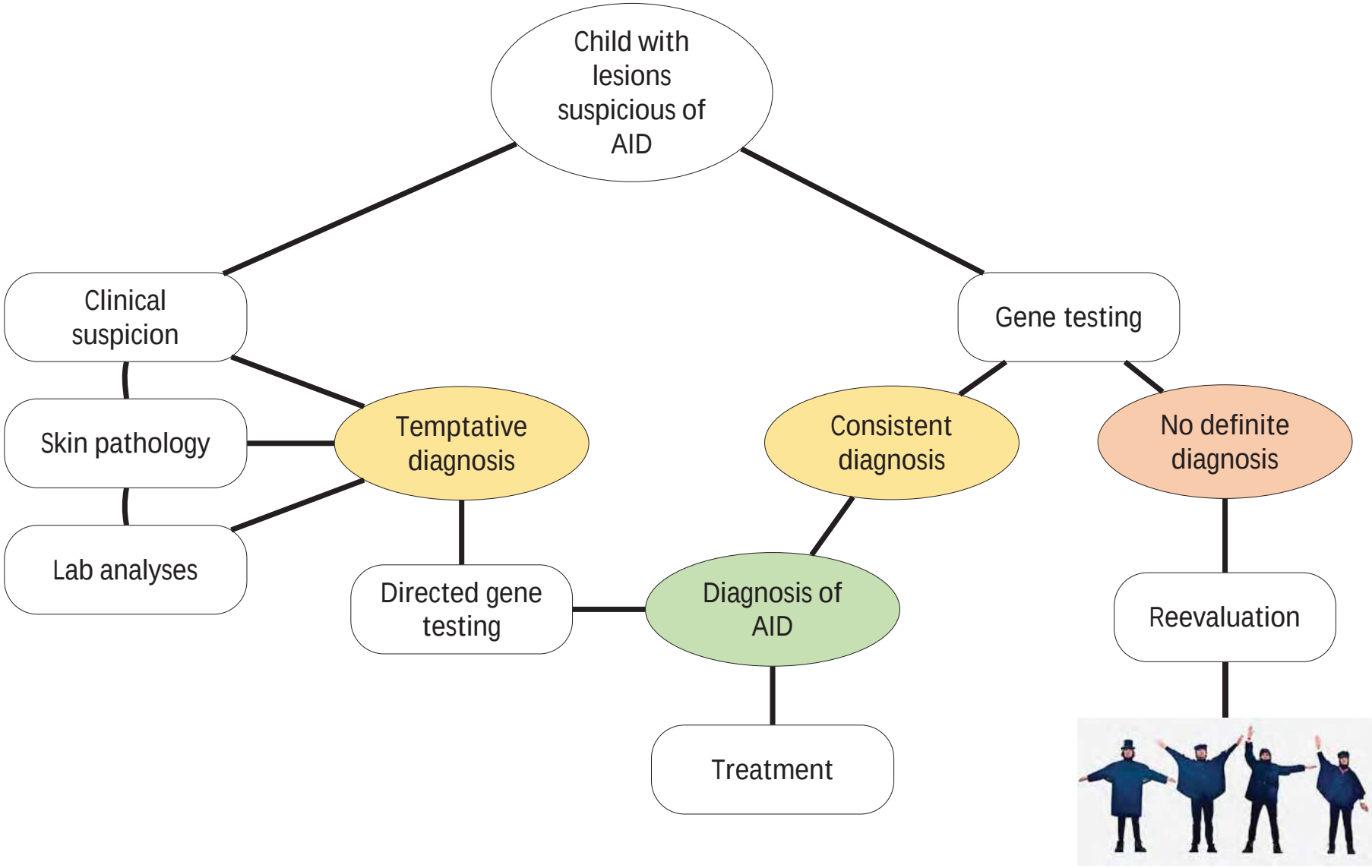
With severe CNS disease

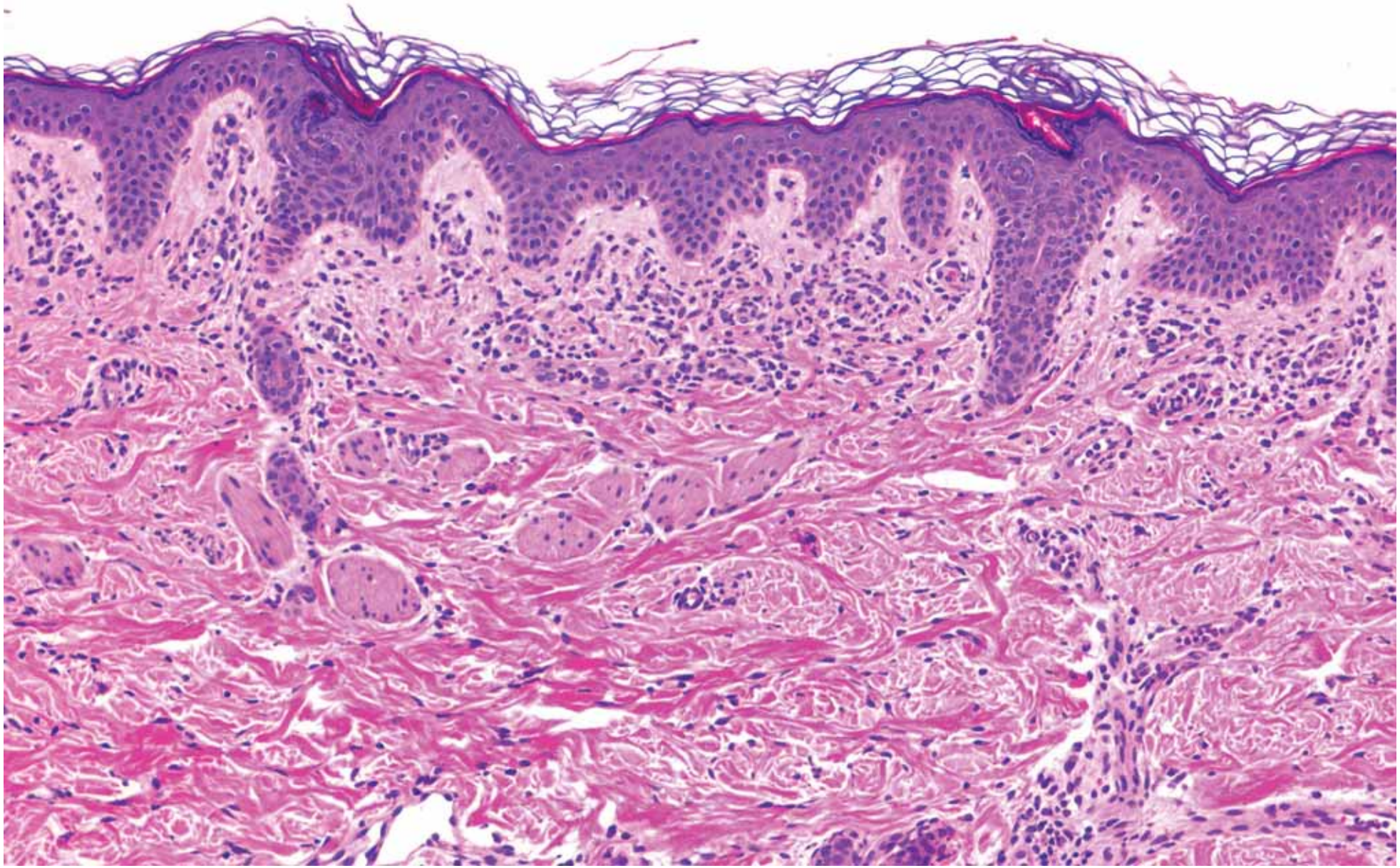
AGS, DADA2, SPENCD

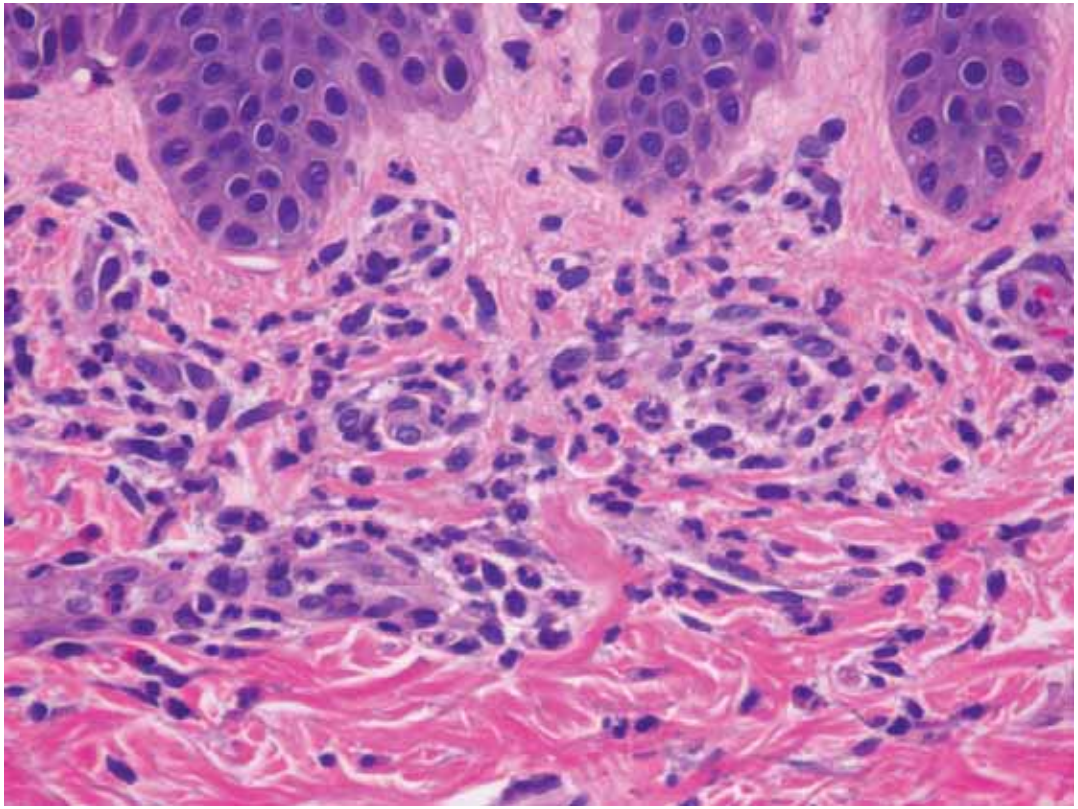
GRANULOMATOUS / HISTIOCYTIC DERMATITIS

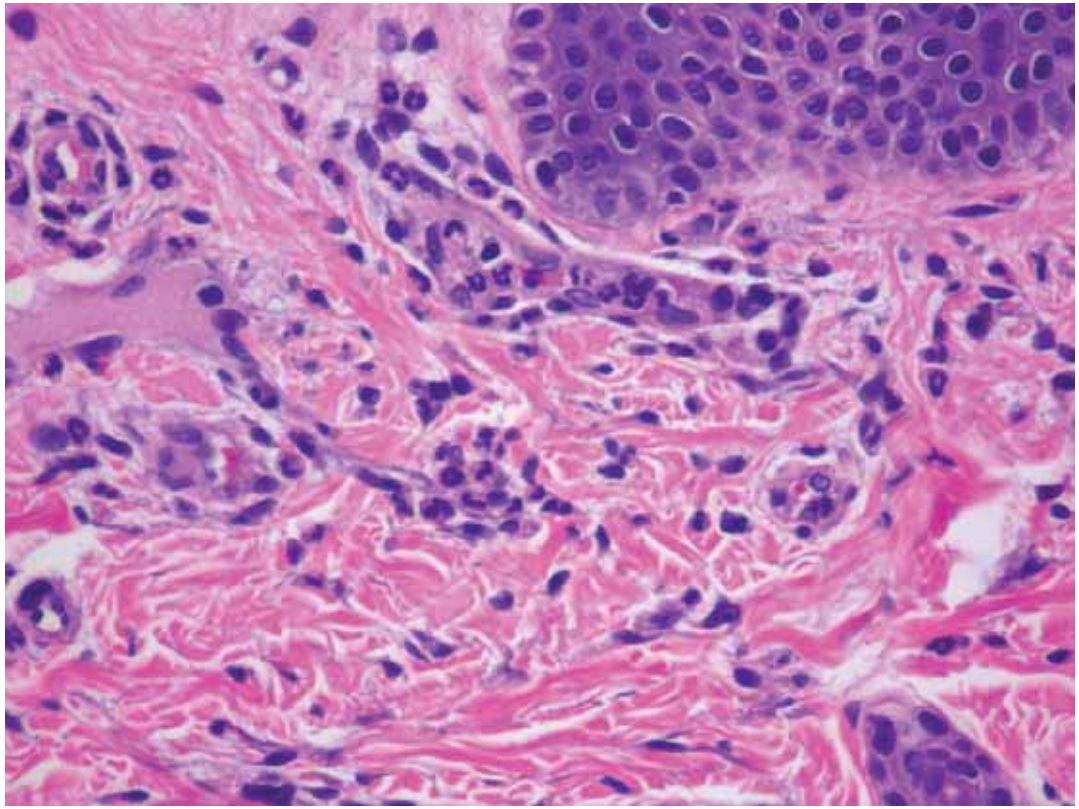
Blau syndrome, H syndrome

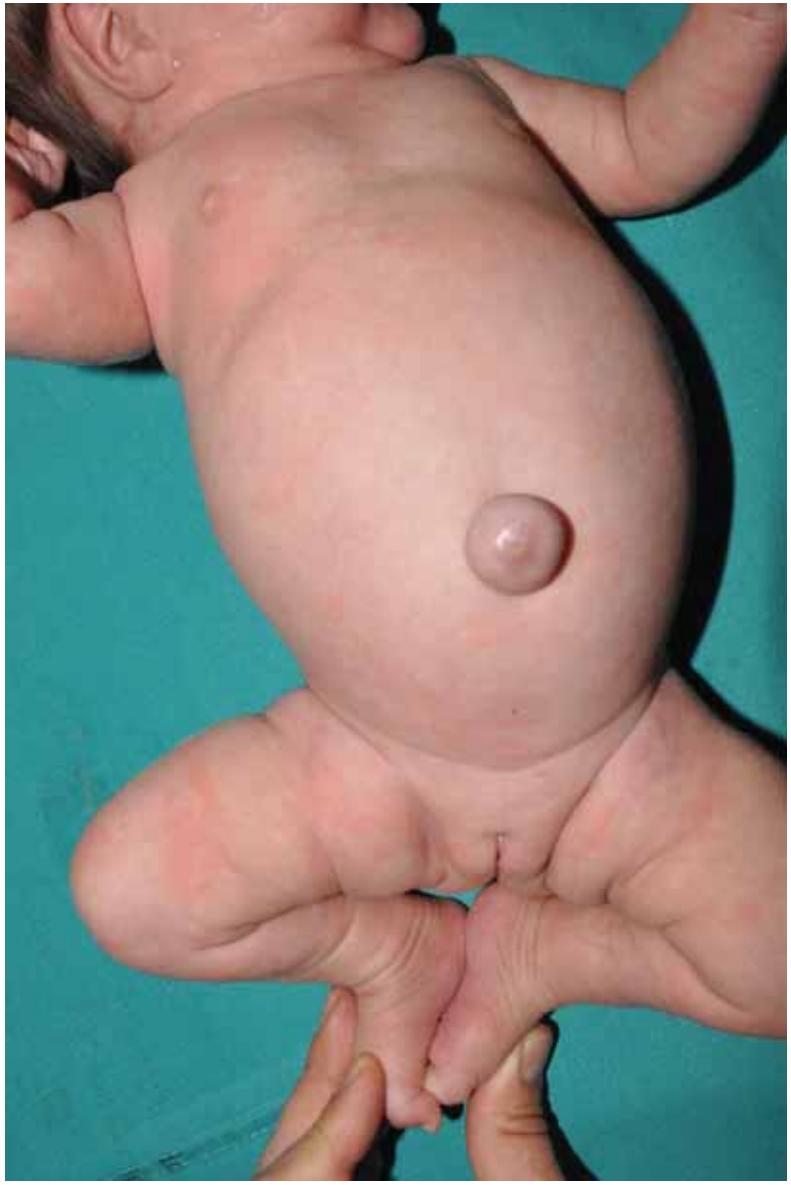

NB
Infant
IL1ß
IL18
IL1ß
IL36
G-CSF
Actin
IFN1
IFN1
RelA
IFN1
NFkß
IFN1
Urticaria
Pustules
Vasculitis
Ulcers
Panniculitis
Chilblain
NLRP3 - CAPS
ED-ID2
DIRA
DITRA
APLAID
ARPC1B Def
LAVLI
SAAD
HA20
PG
ISG15
Otulin Def
NEMO-NDAS
Blau syn
CANDLE
SAVI
ARF1 Def
Aicardi-Goutières syn

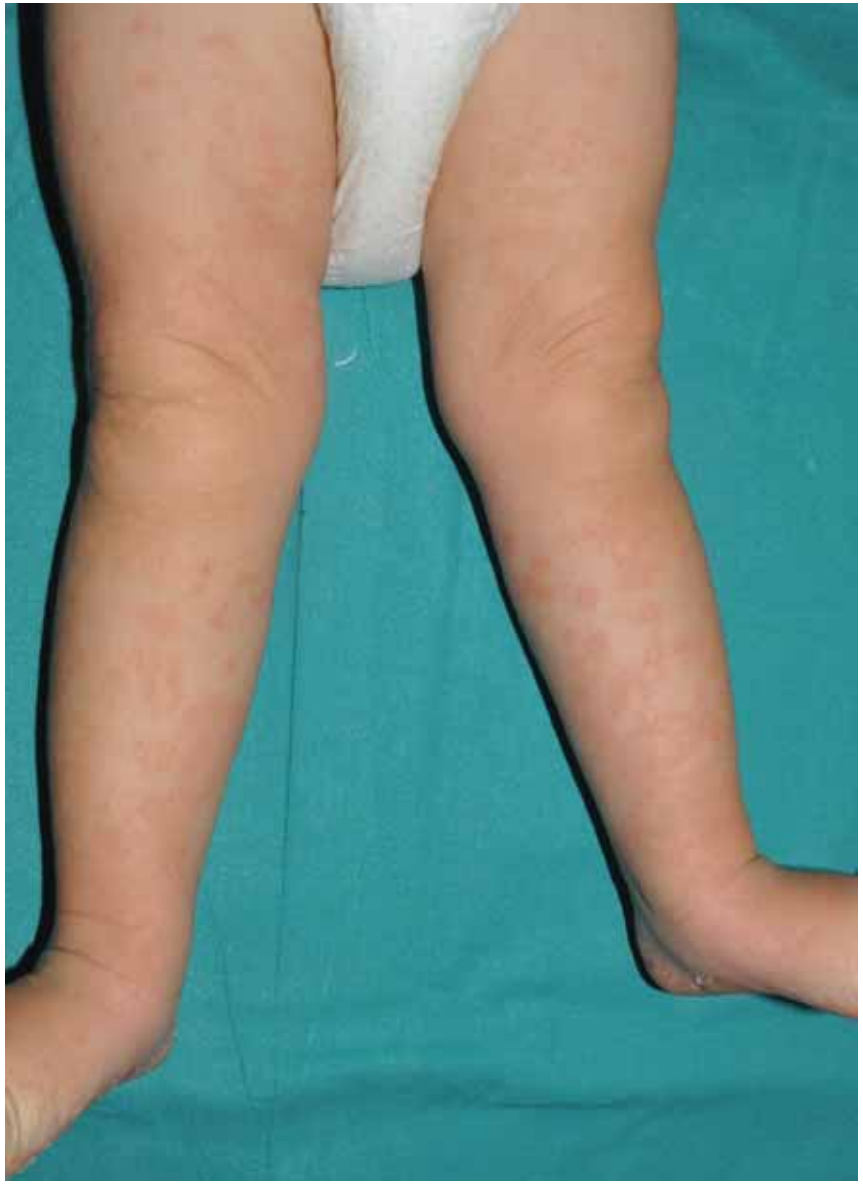

Child with lesions suspicious of AID
Clinical suspicion
Gene testing
Skin pathology
Temptative diagnosis
Consistent diagnosis
No definite diagnosis
Lab analyses
Directed gene testing
Diagnosis of AID
Reevaluation
Treatment











NLRP3 pathogenic change identified c.784C>T; p.Arg262Trp

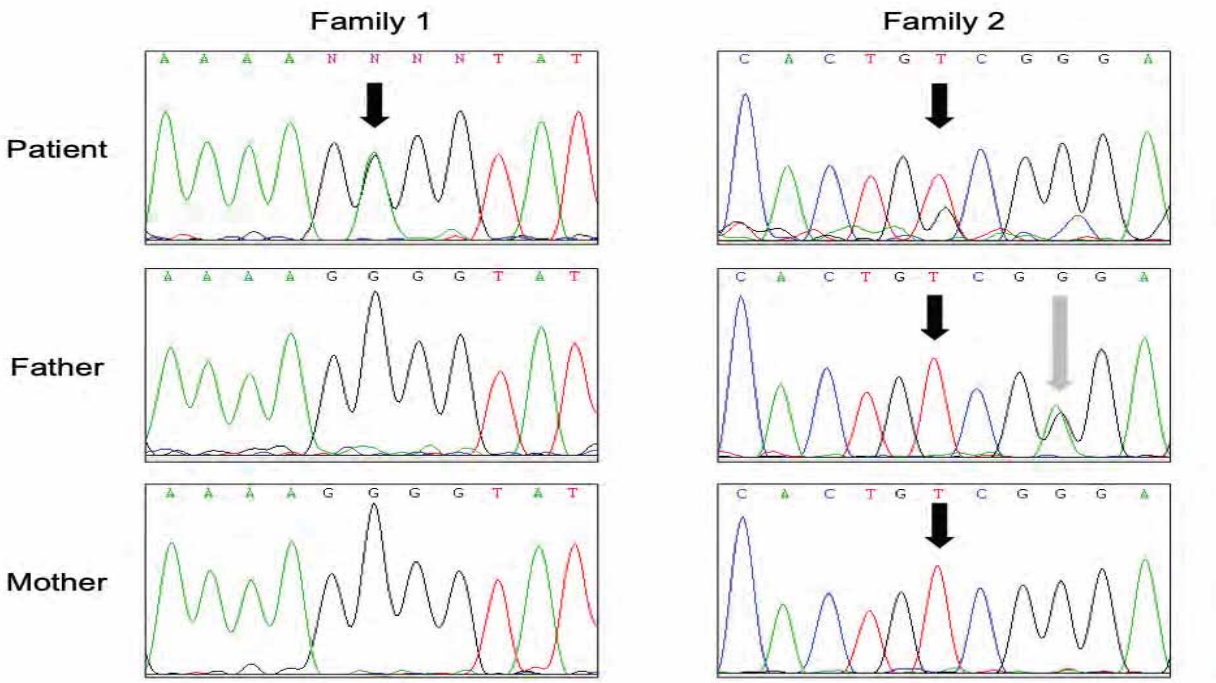
Interpretation (Last evaluated)	Review status (Assertion criteria)	Condition (Inheritance)	Submitter	Supporting information (See all)
Pathogenic (Jun 27, 2018)	criteria provided, single submitter (GeneDx Variant Classification (06012015)) Method: clinical testing	Not Provided Allele origin: germline	GeneDx Accession: SCV000278937.9 Submitted: (Jan 29, 2019)	Evidence details Comment: The R262W missense variant in the NLRP3 gene has been reported previously in association withboth Muckle-Wells and Familial Cold Autoinflammatory syndromes (Dode et al., 2002; Leslie et al.,2006; Lepore et al., 2010; Parker et al., 2016). Carriers of the R262W variant, reported as R260W,have also presented with the additional symptoms of sensorineural hearing loss and vision impairment(Alejandre et al., 2014). R262W was observed in approximately 6,500 individuals of European andAfrican American ancestry in the NHLBI Exome Sequencing Project, indicating it is not a commonbenign variant in these populations. It is a non-conservative amino acid substitution, which is likely toimpact secondary protein structure as these residues differ in polarity, charge, size and/or otherproperties. This substitution occurs at a position that is conserved across species and in silico analysispredicts this variant is probably damaging to the protein structure/function. In addition, missensevariants at the same (R262P) and in nearby residues (C261W, V264A, V264G, L266F/V, L266R/H)have been reported in the Human Gene Mutation Database in association with NLRP3-relateddisorders (Stenson et al., 2014), supporting the functional importance of this region of the protein. (less)

Neonatal urticria

Triggered by cold

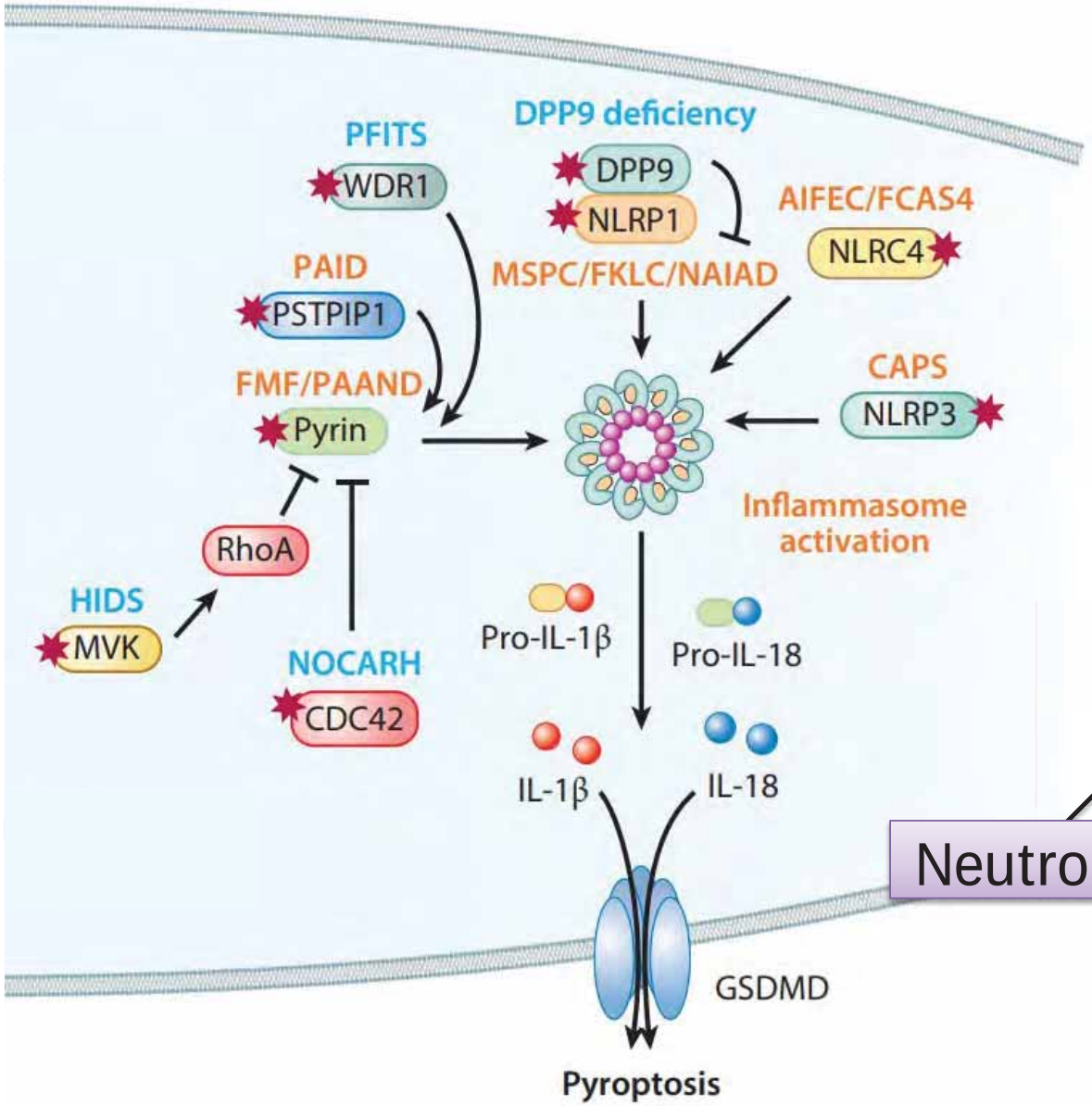
Neutrophilic infiltrate

CAPS - NLRP3



Inflammasomopathies

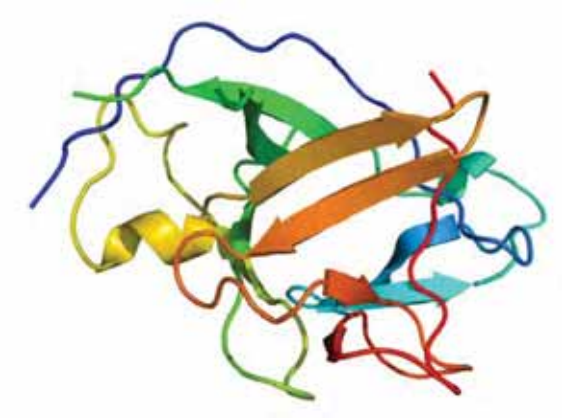
Constitutional inflammasome activation leading to chronic cytokine release

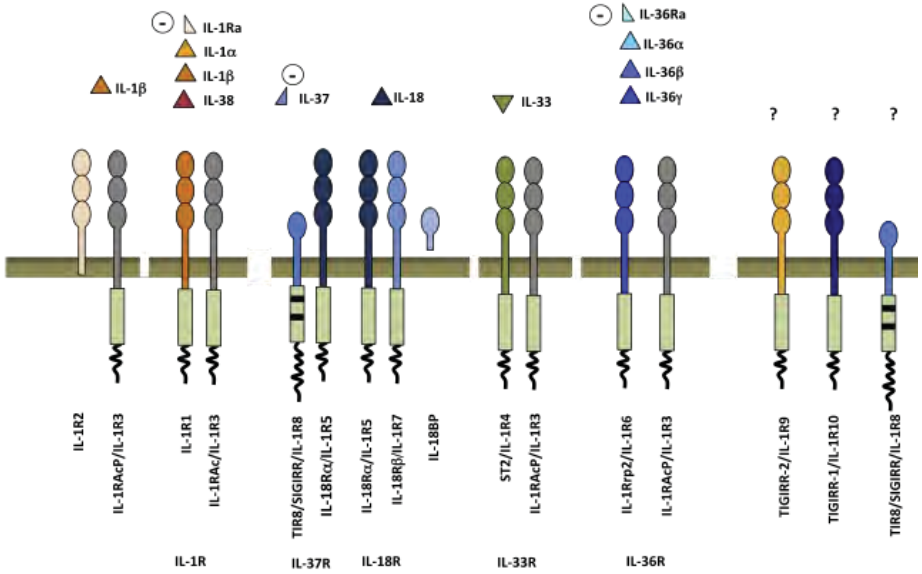


Neutrophils

- Neutrophilic urticaria
- Pustular eruptions
- Neutrophilic panniculitis

IL-1: the first interleukin identified





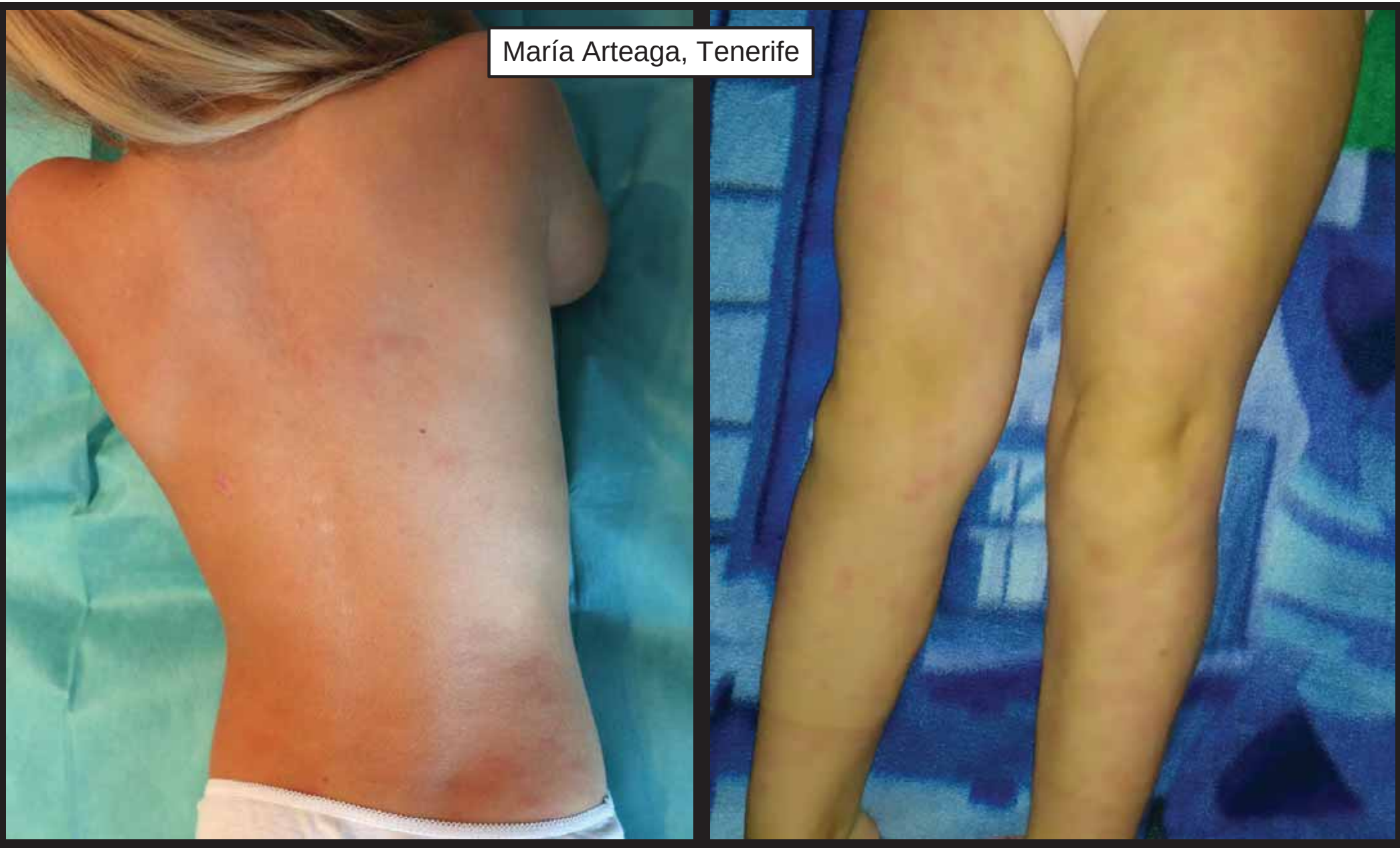
IL-1 family of cytokines

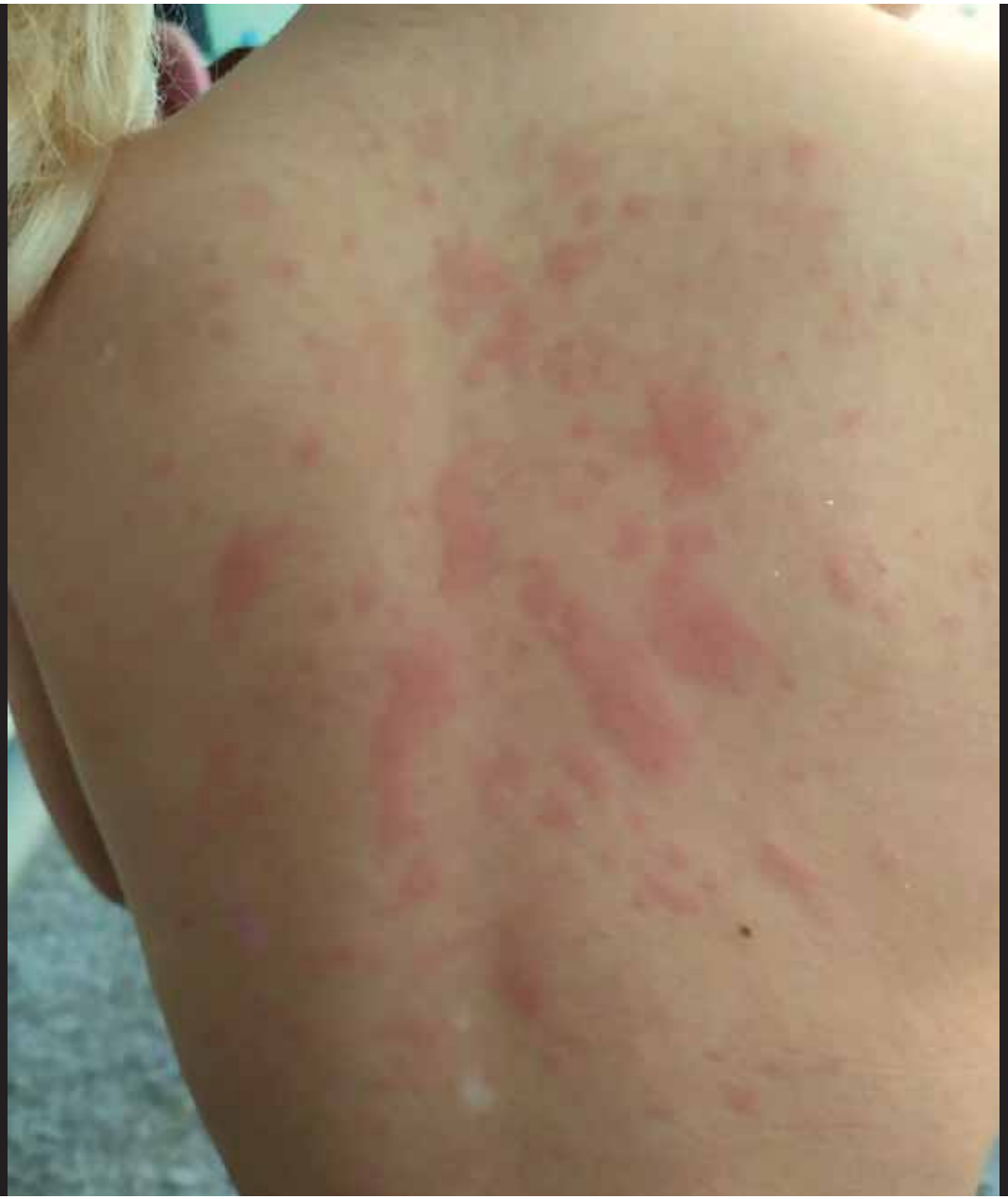
Table 1 The IL-1 family members

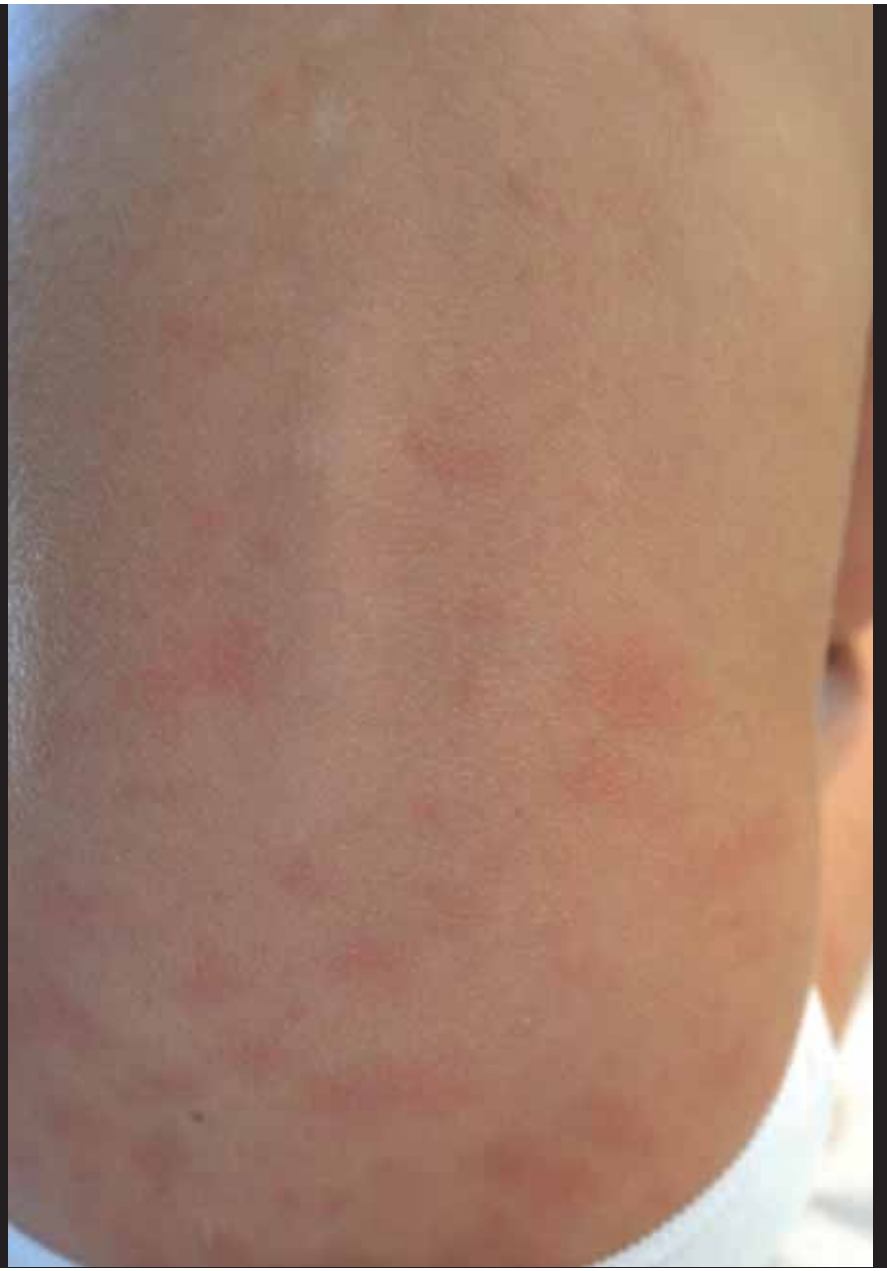
IL-1 family members	Receptor	Property
IL-1α	IL-1RI	Inflammatory
IL-1β	IL-1RI	Inflammatory
IL-1Ra	IL-1RI	IL-1RI antagonist
IL-18	IL-18Rα	Inflammatory
IL-33	ST2	Th2 inflammation
IL-36Ra	IL-1Rrp2	IL-1Rrp2 antagonist
IL-36α	IL-1Rrp2	Inflammatory
IL-36β	IL-1Rrp2	Inflammatory
IL-36γ	IL-1Rrp2	Inflammatory
IL-37	IL-18Rα	Anti-inflammatory
IL-38	IL-1Rrp2	IL-1Rrp2 antagonist

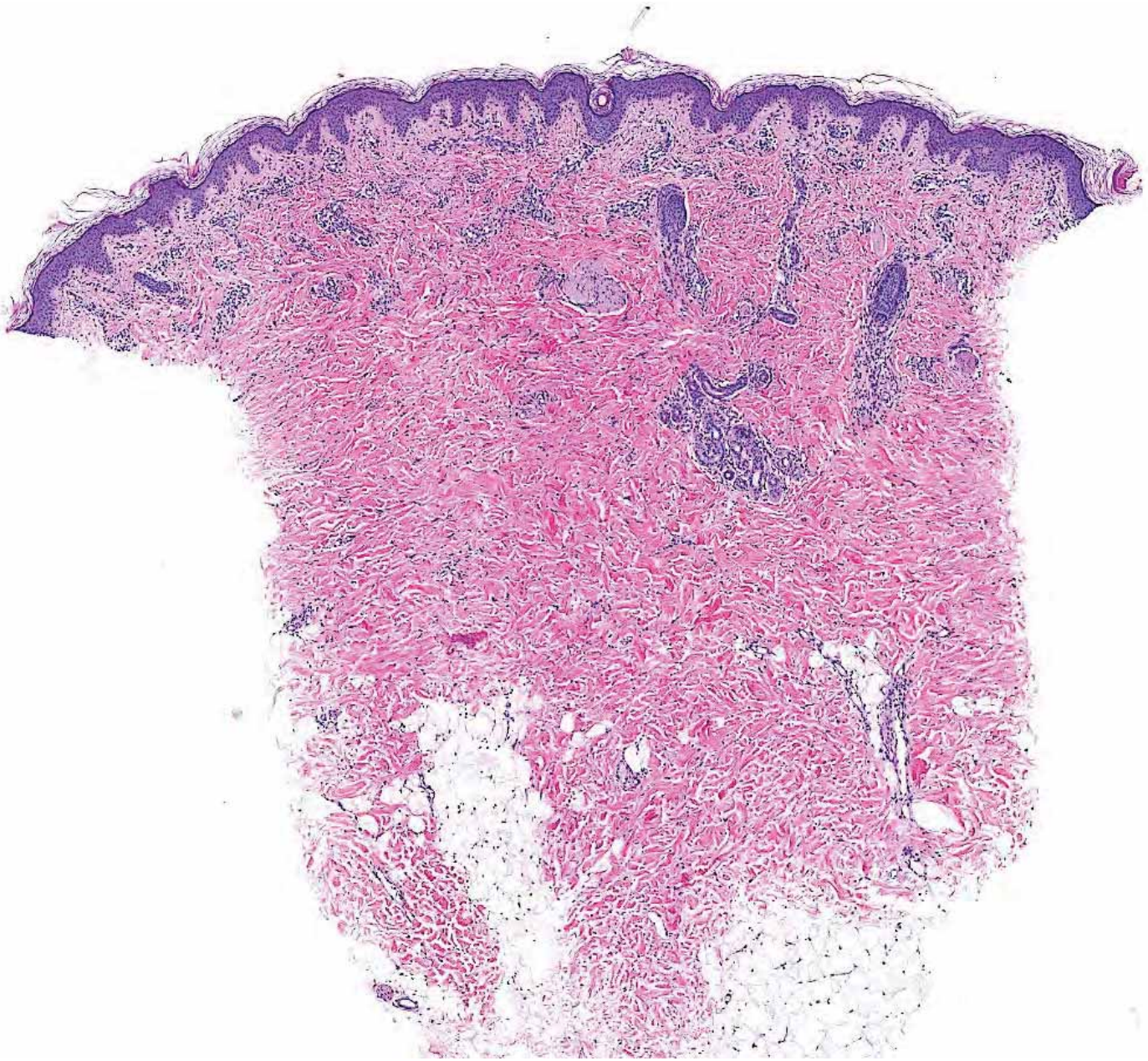
Case for consultation (Dr. María Arteaga)

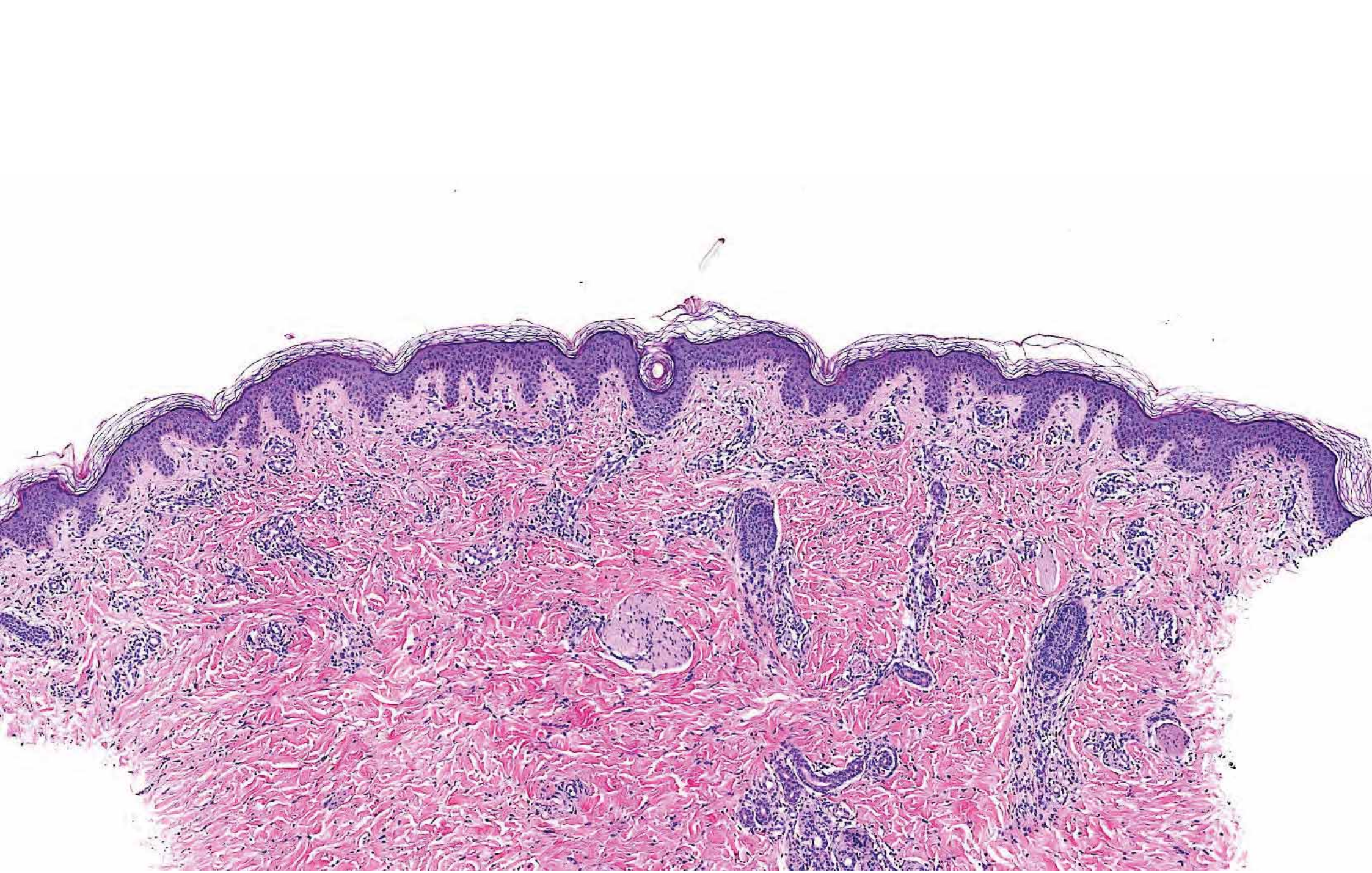
- A 7-year-old girl
- Started at 1 year of age
- Repeated attacks of fever, arthralgia, conjunctivitis and skin lesions
- Lasting for a few days
- Good response to corticosteroids

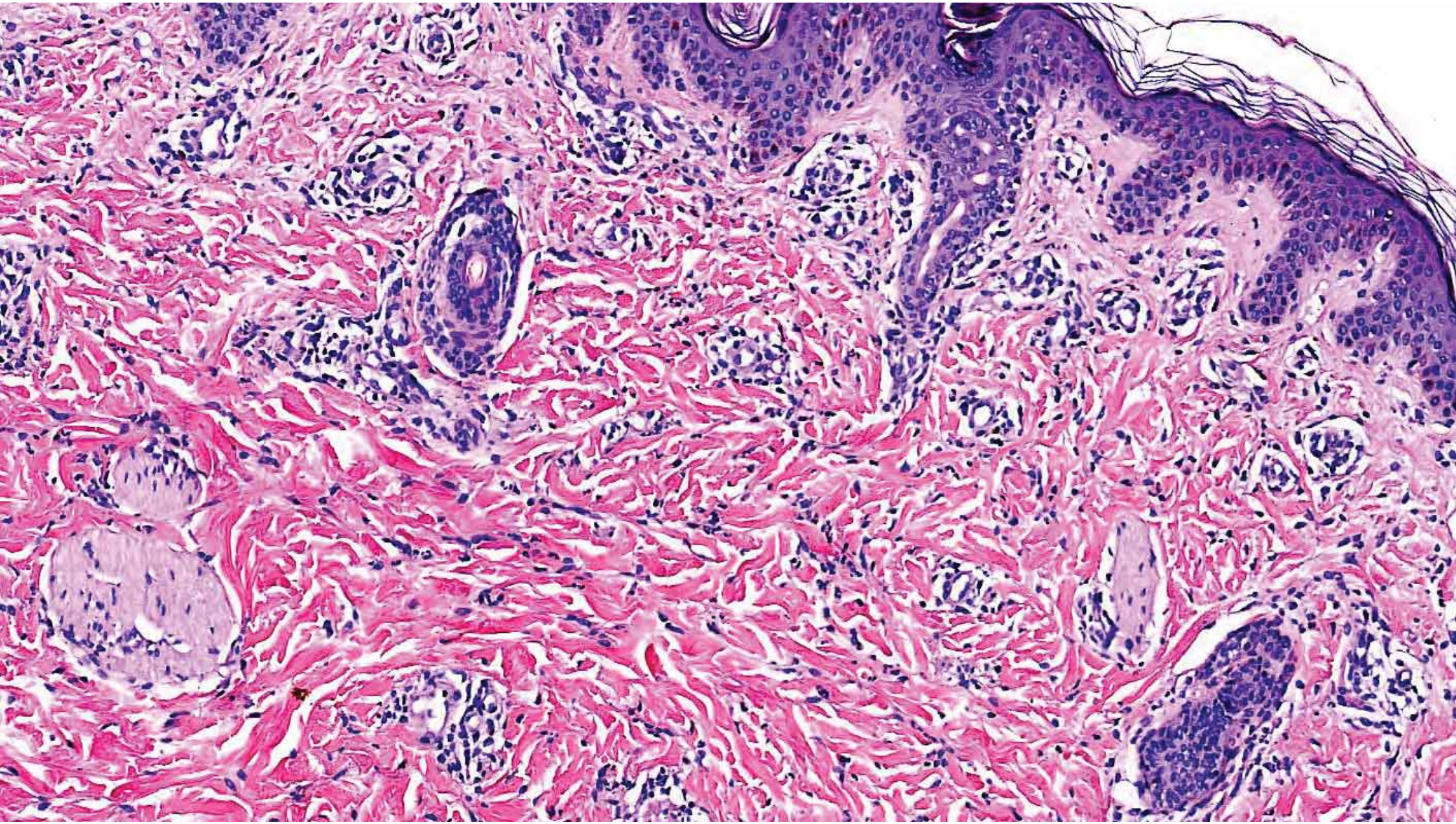

María Arteaga, Tenerife



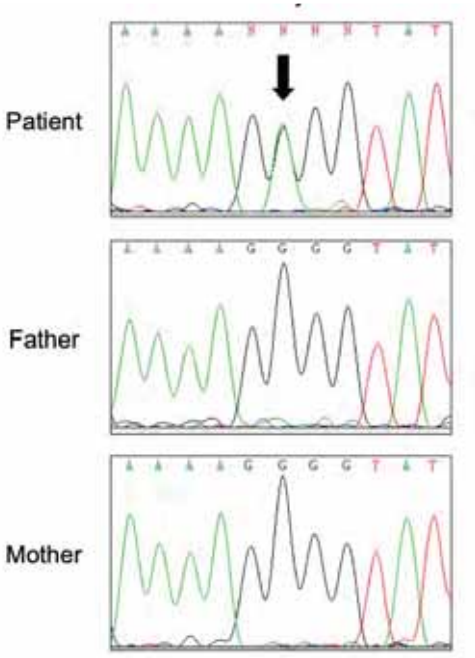


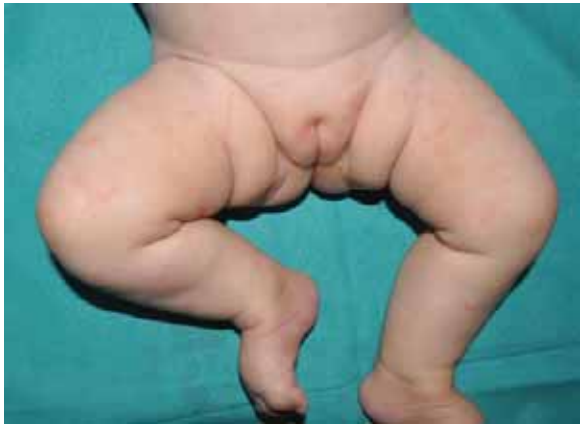




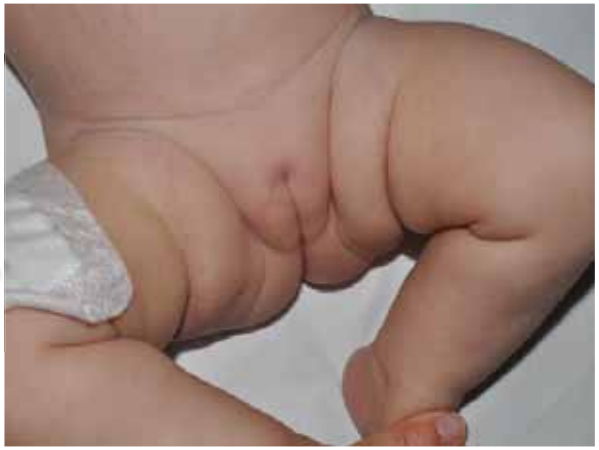


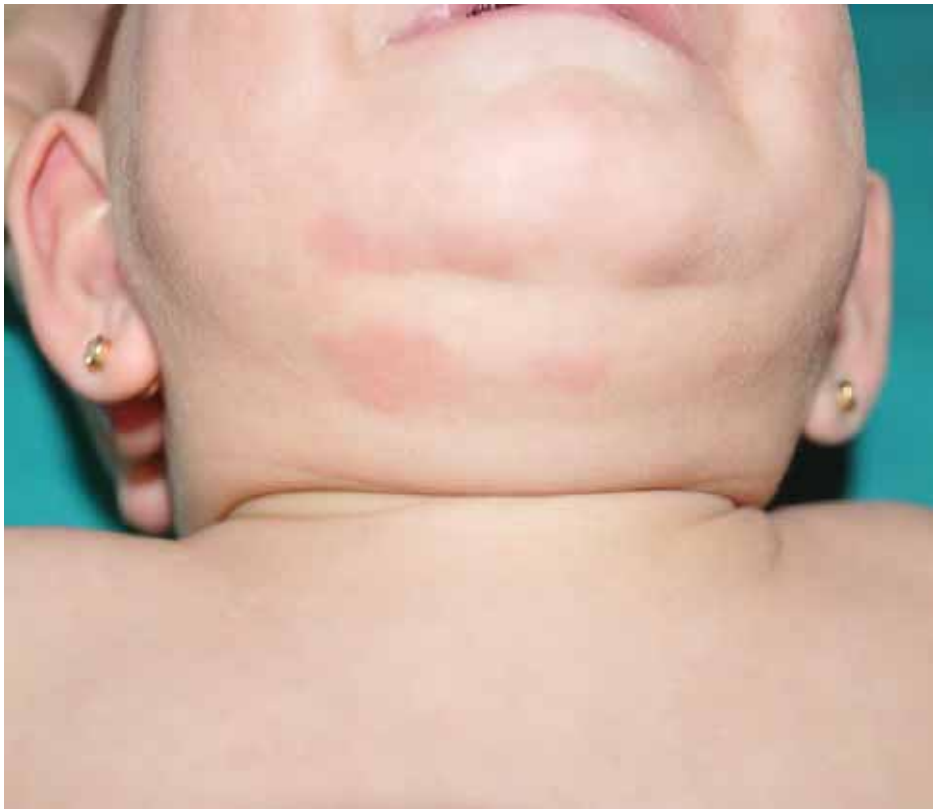
Neonatal urticria | Triggered by cold | Neutrophilic infiltrate | NLRP3

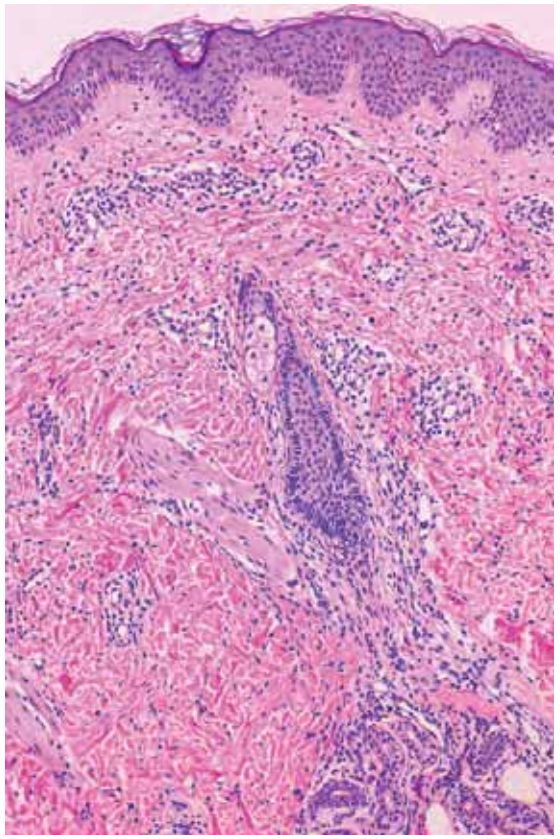


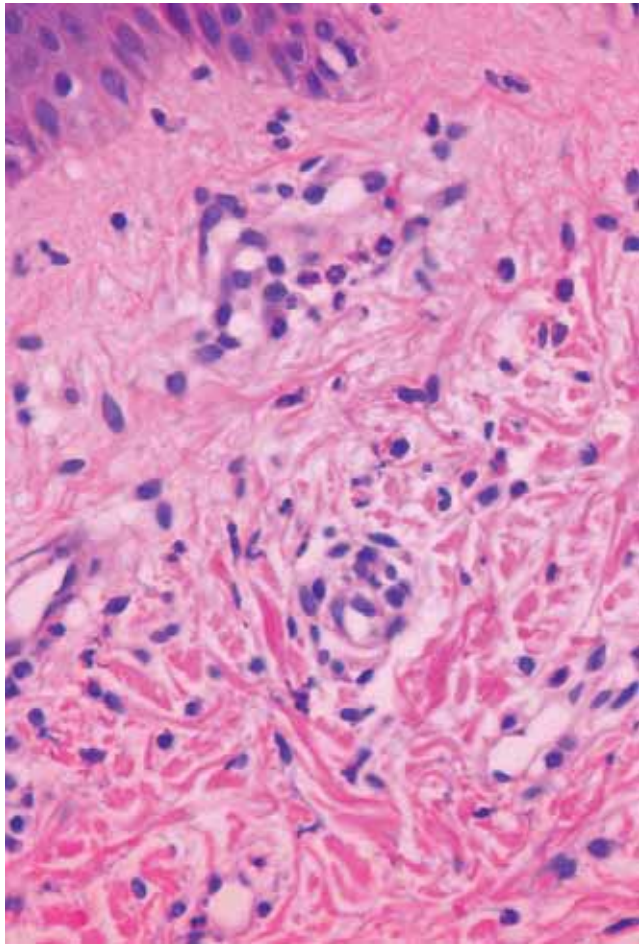


Anakinra – 24 h later







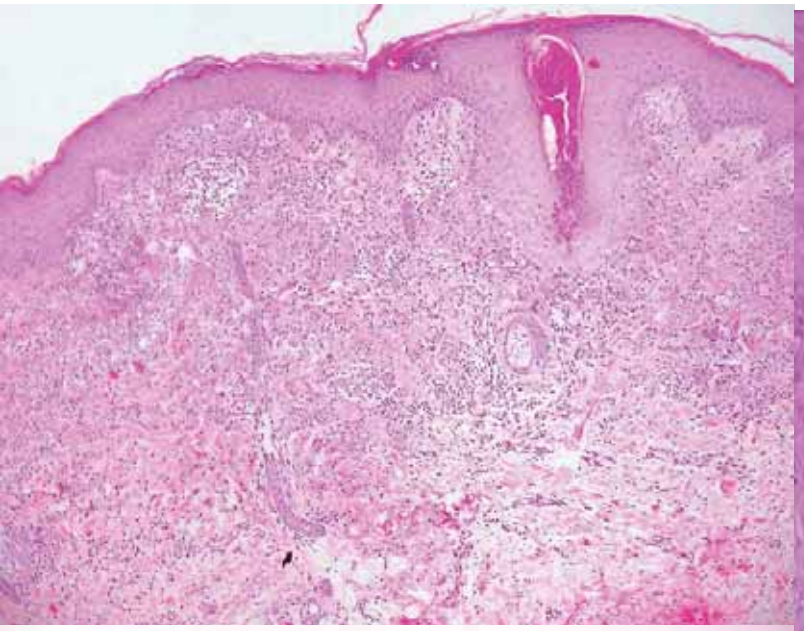


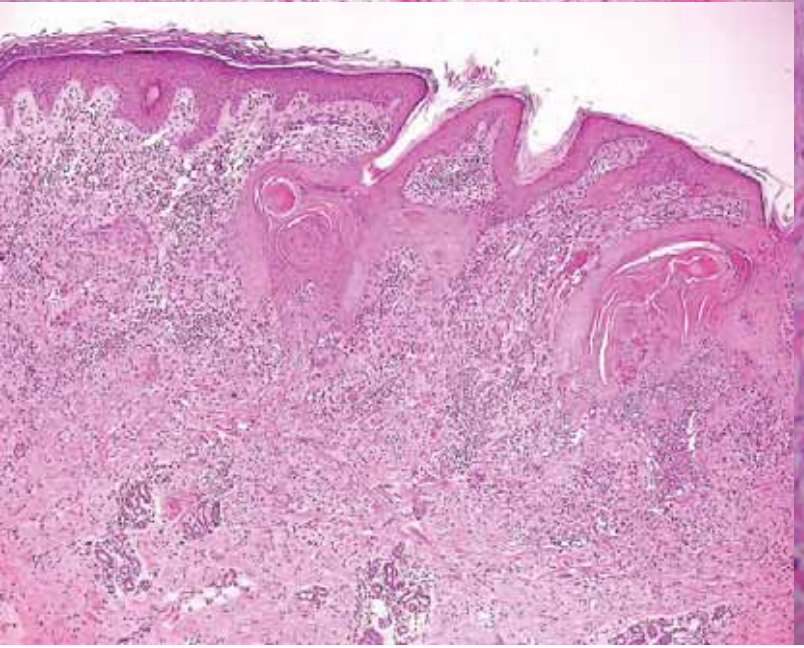
Currently 9 years old
Canakinumab
No further skin lesions

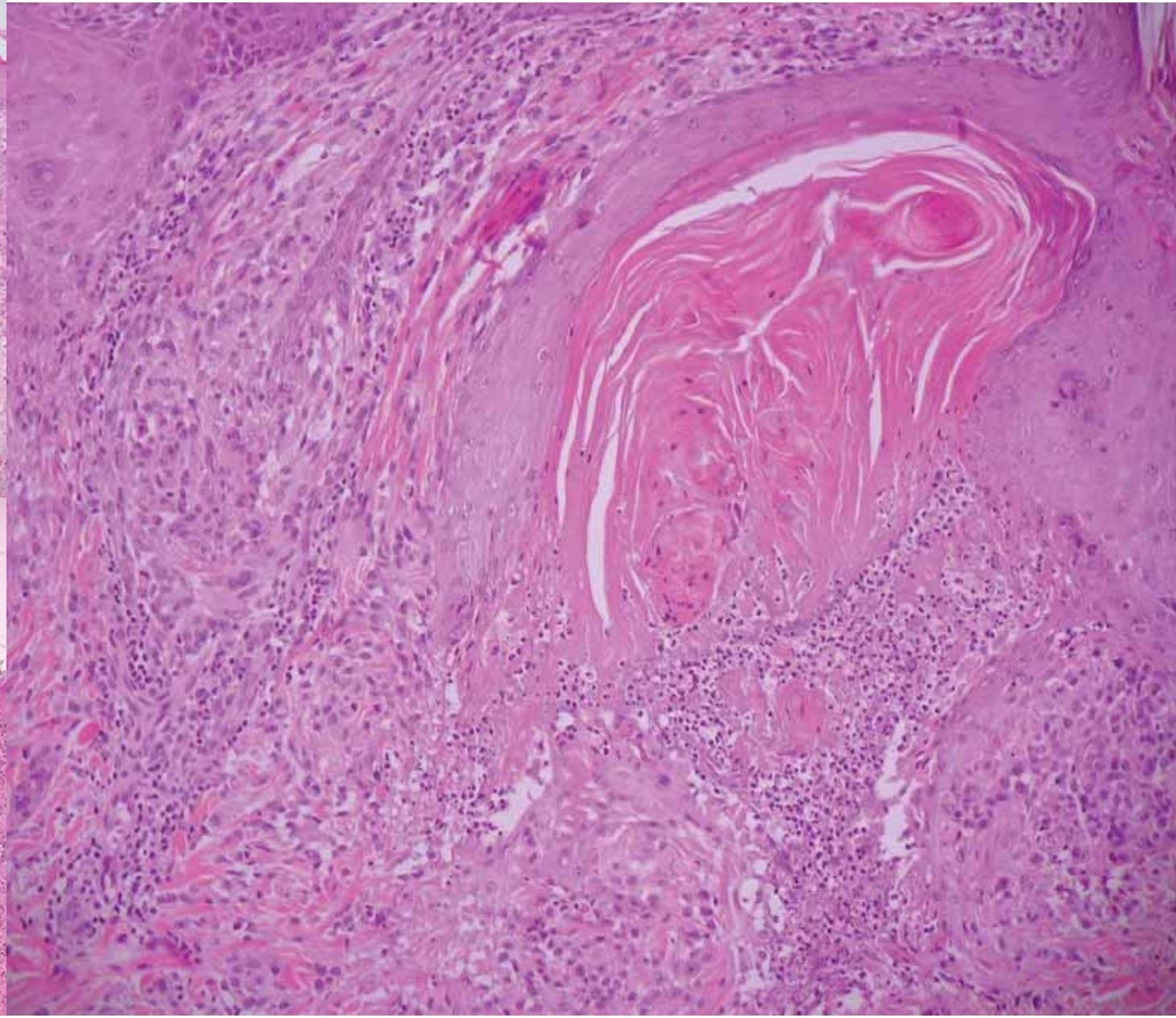
Dermatopathologic clue #1

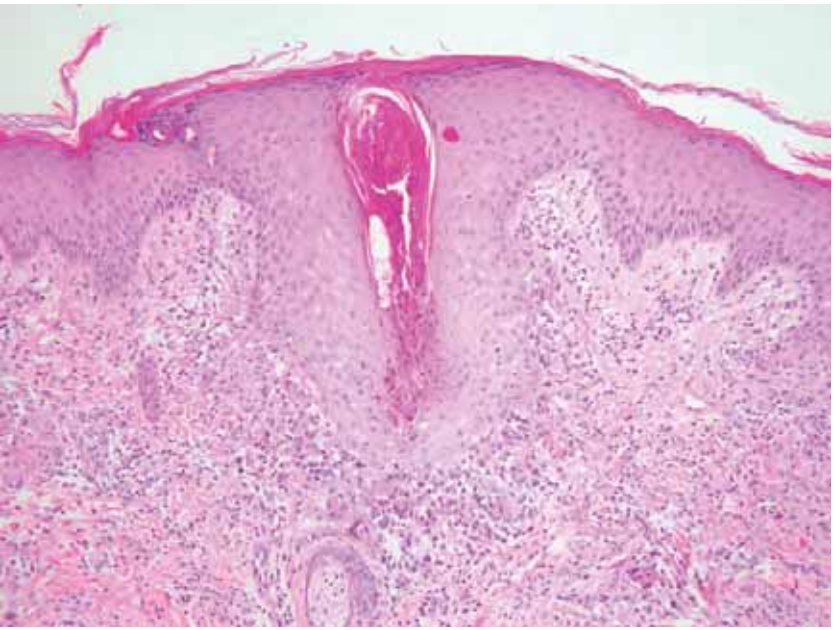
Urticarial dermatitis with neutrophils

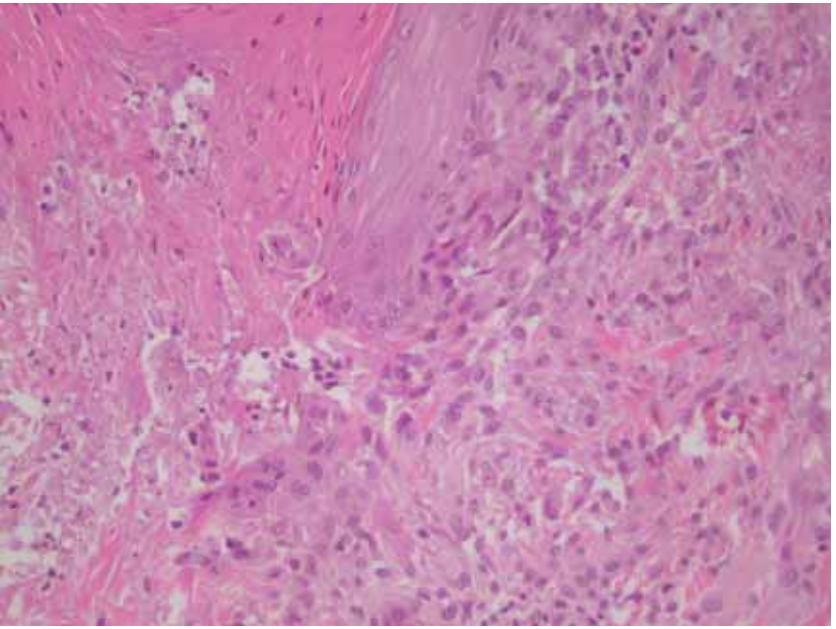
Cryopyrin-associated periodic syndrome (NLRP3)

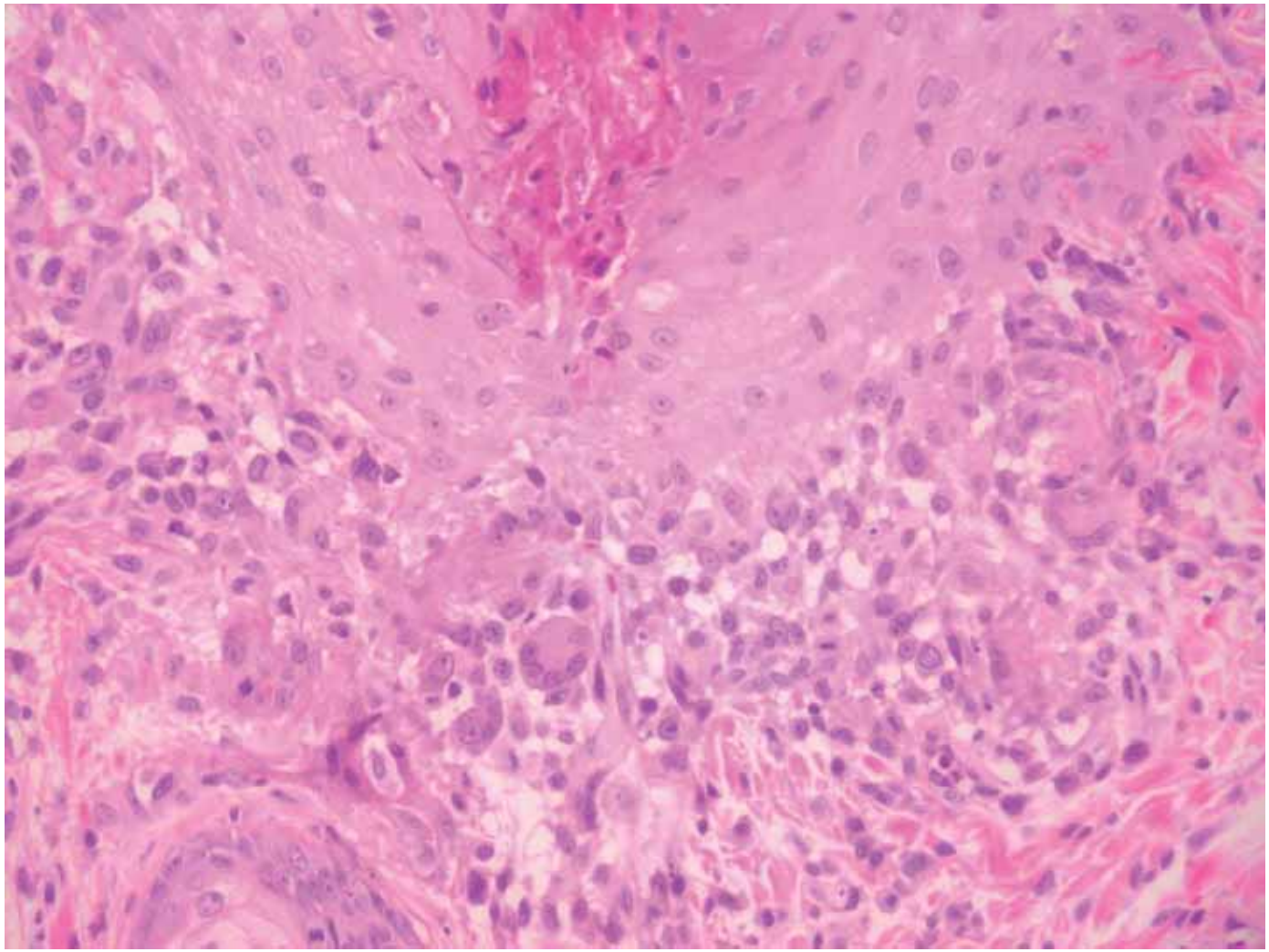


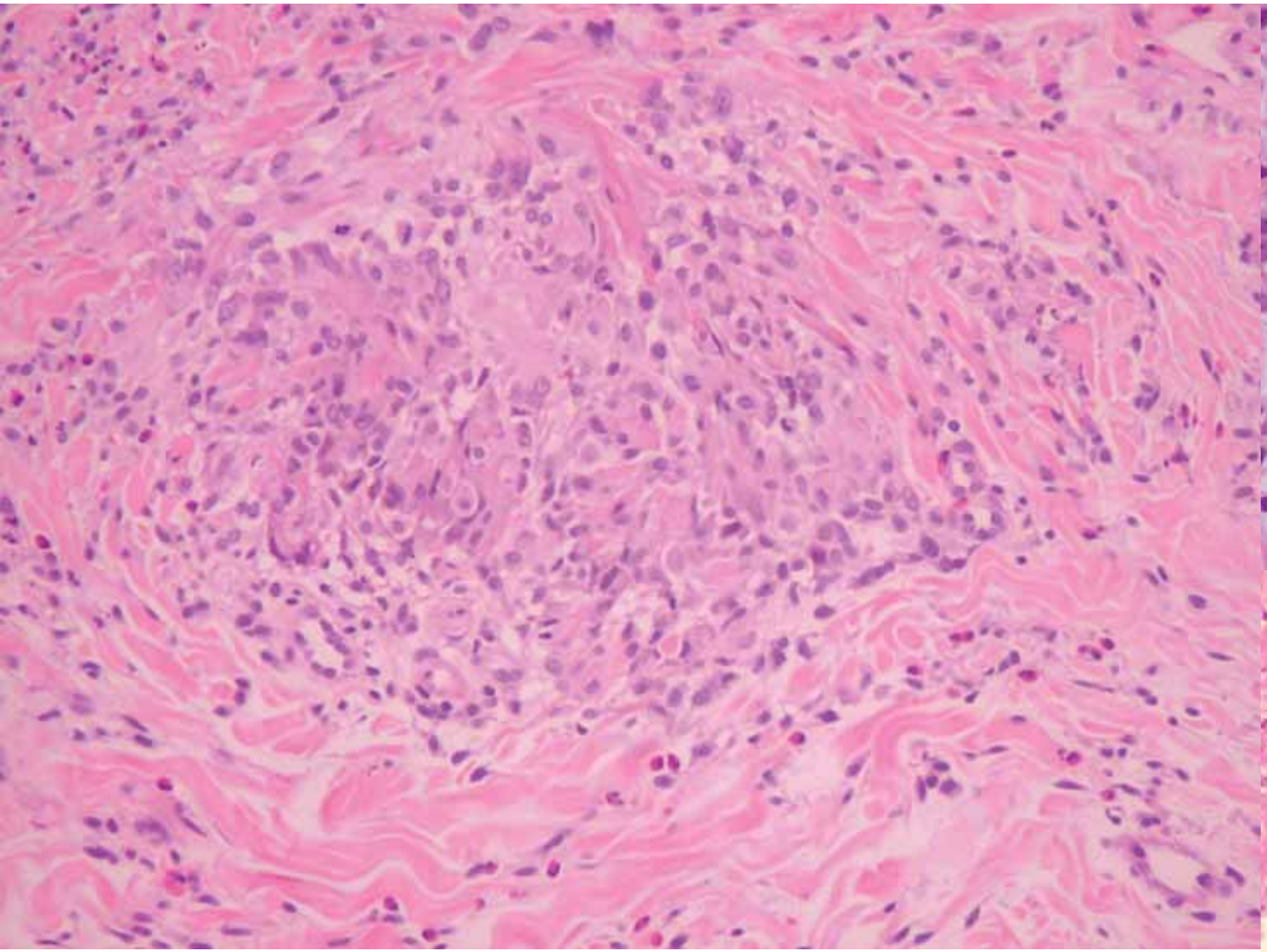


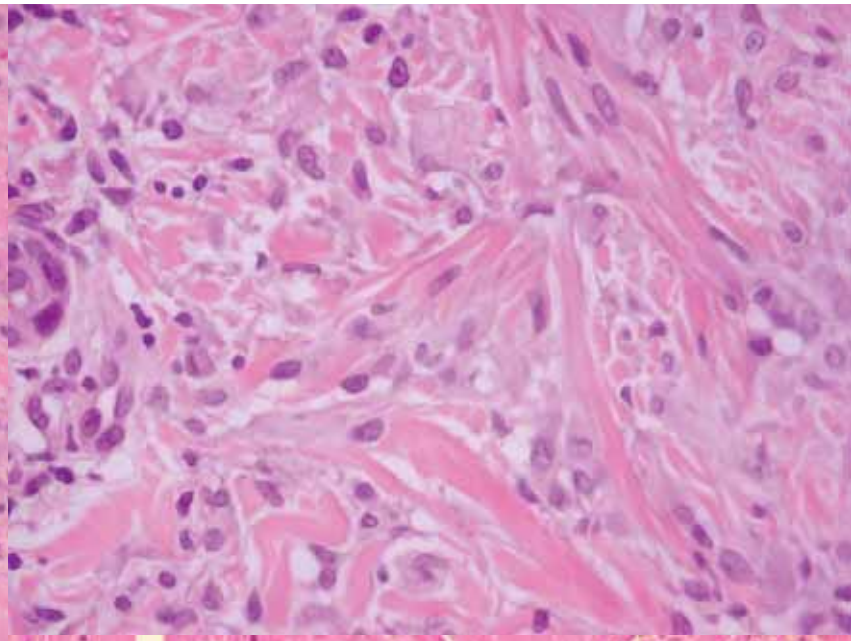


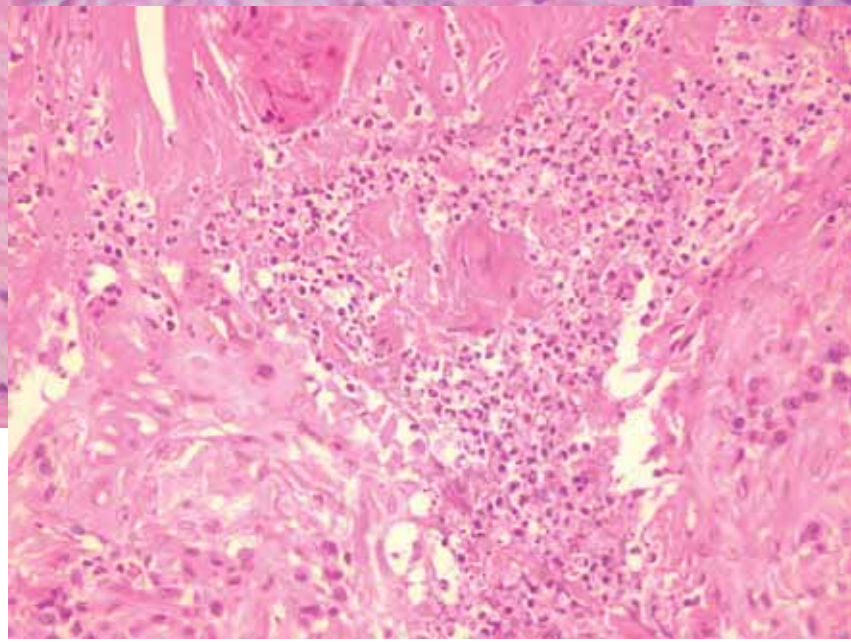


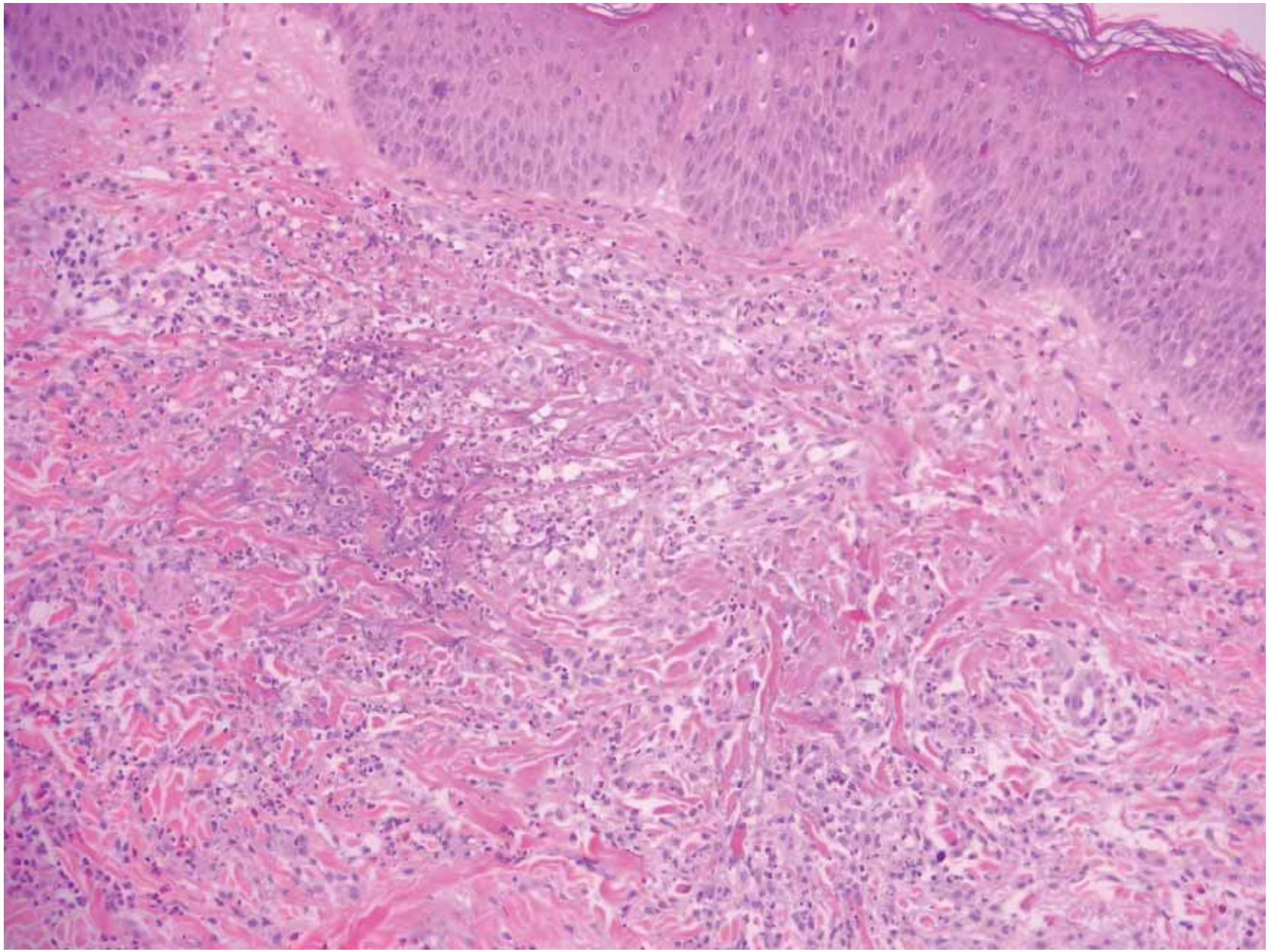


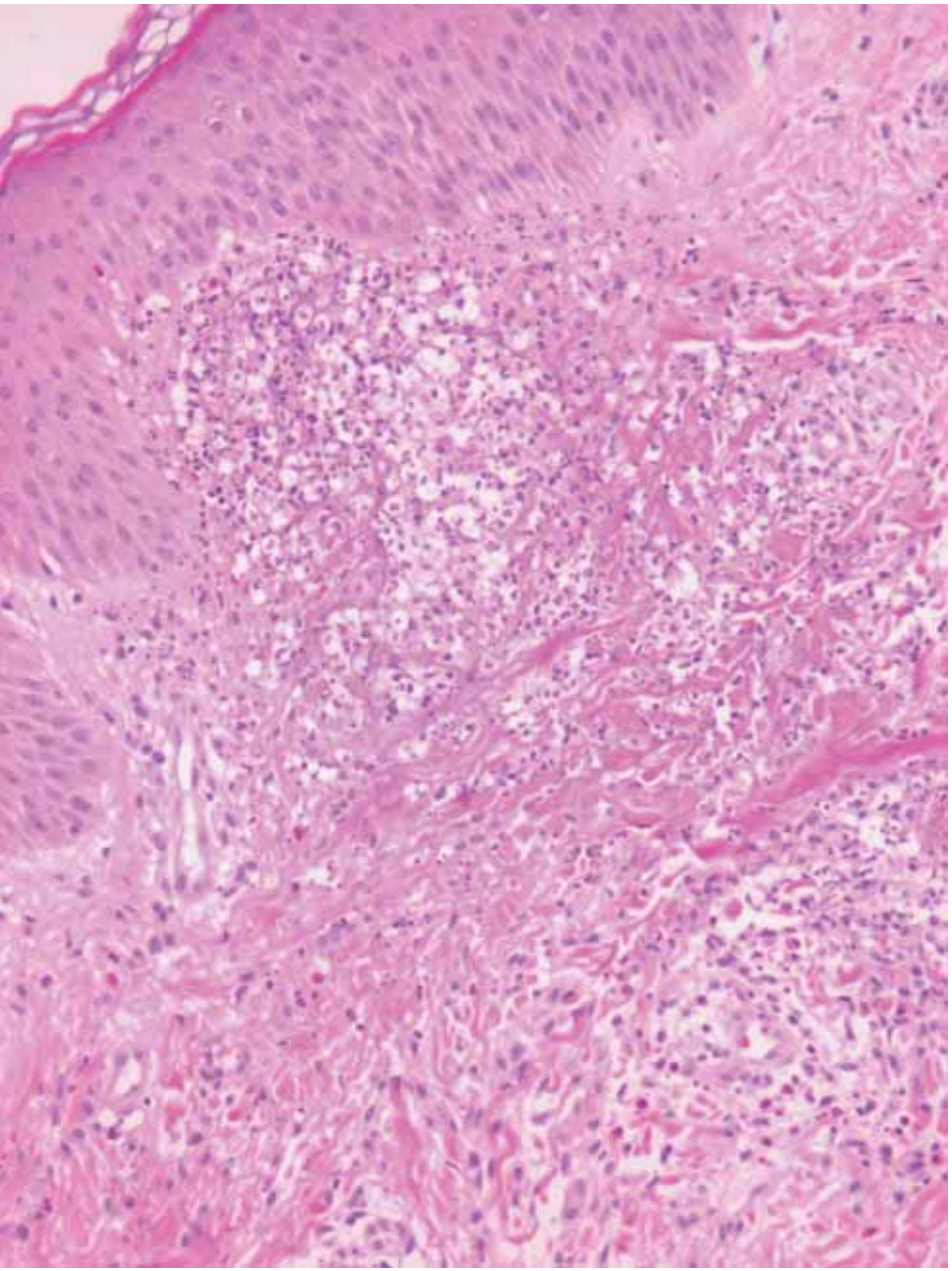


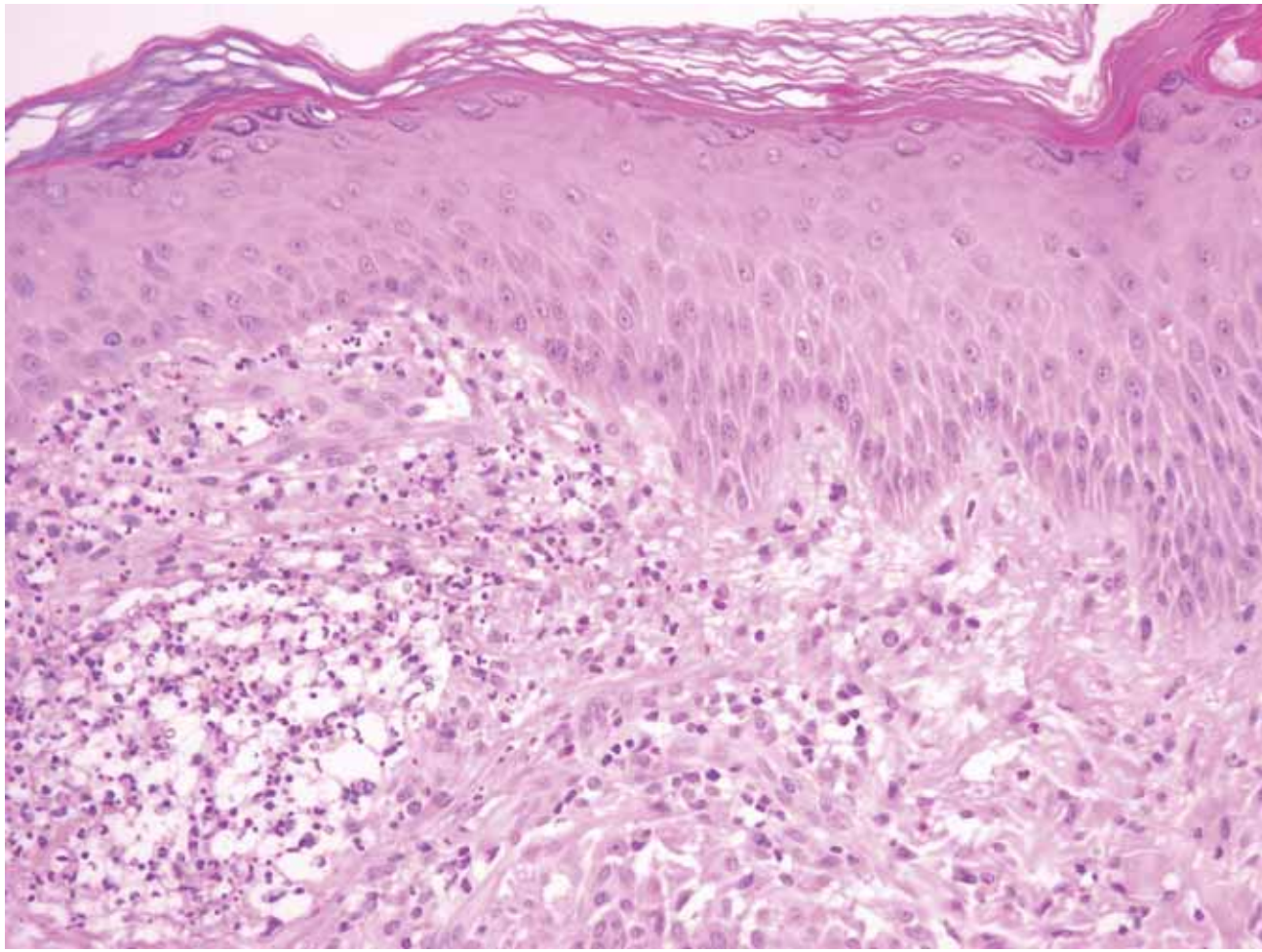


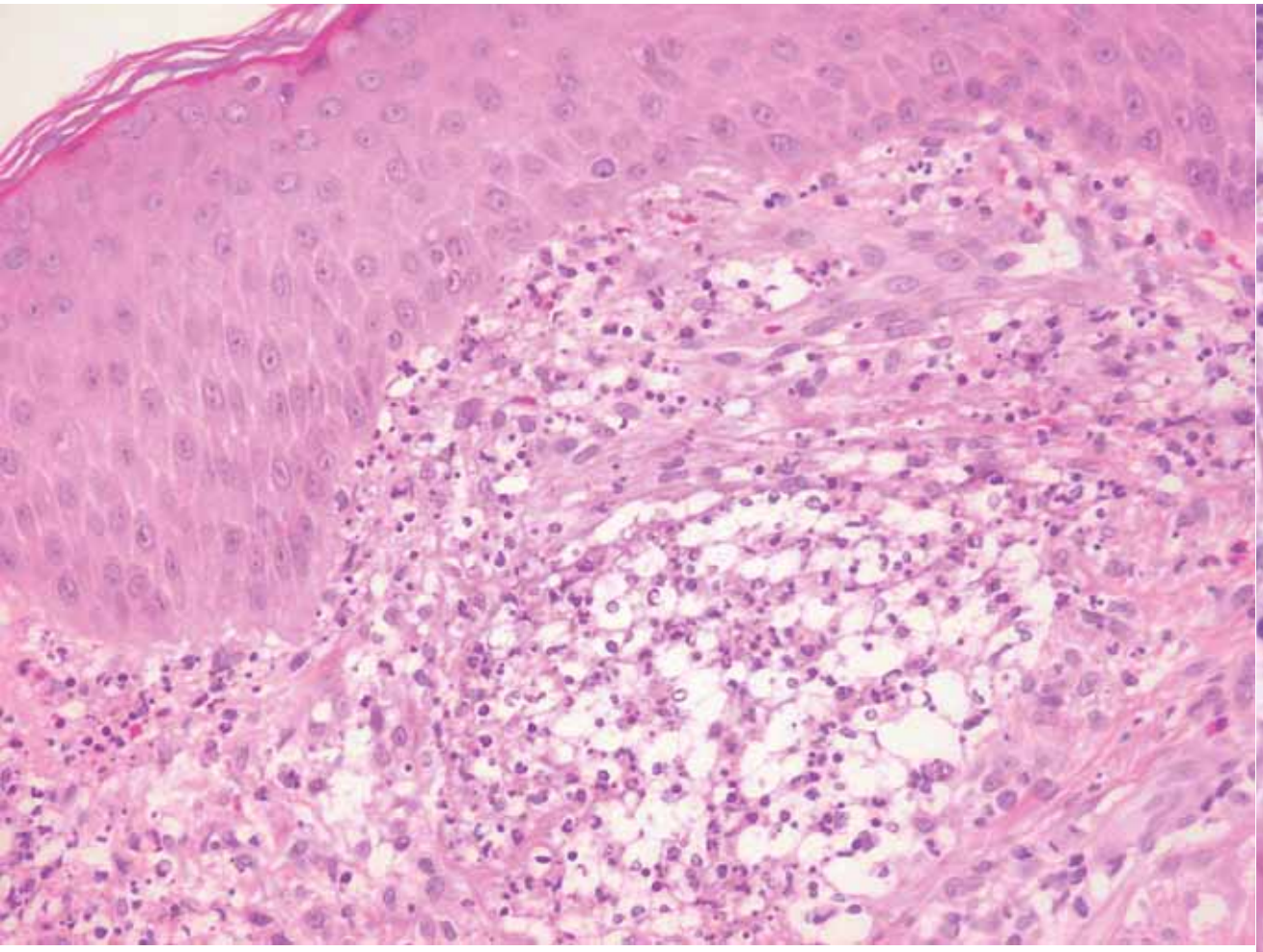


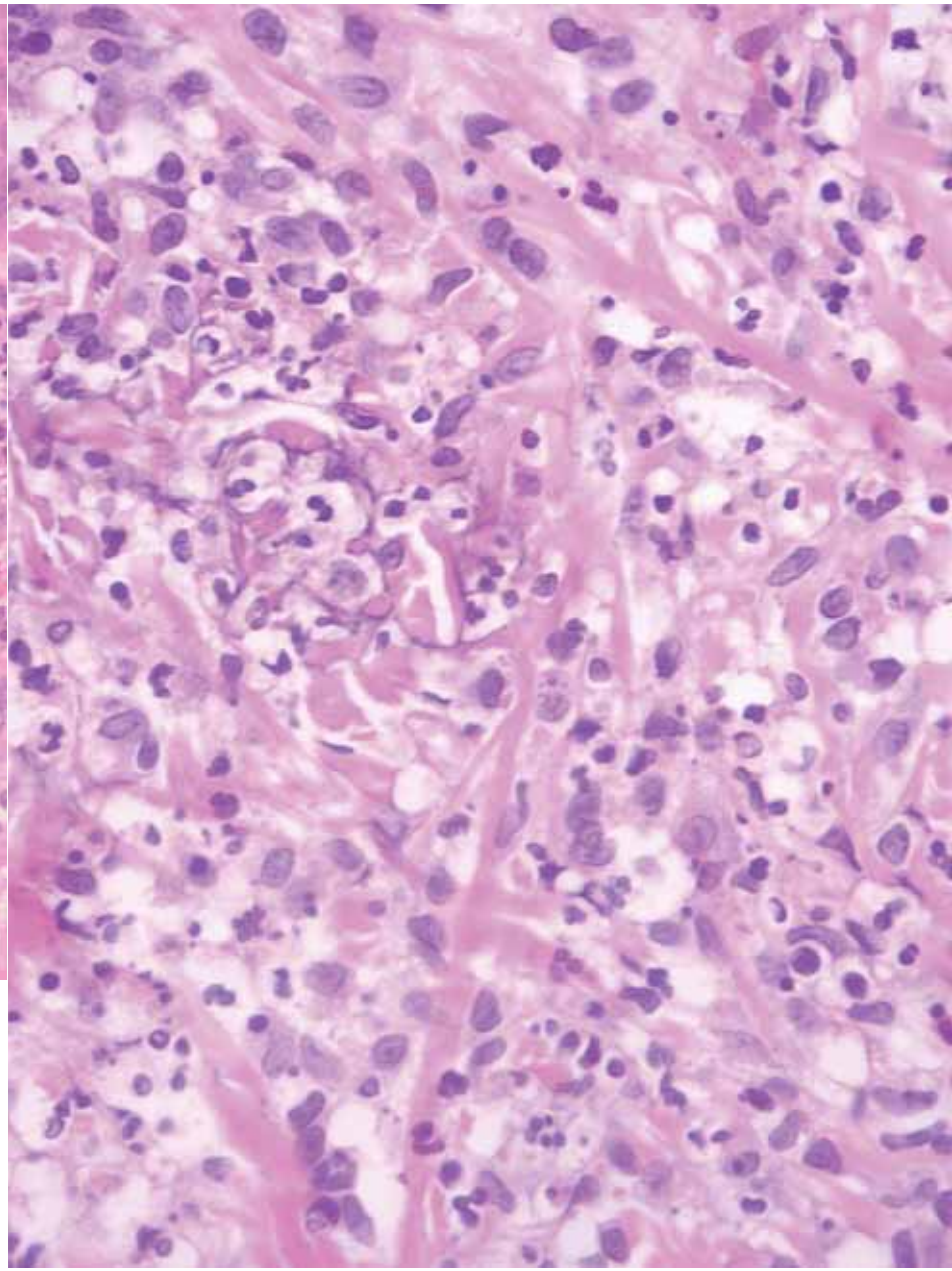


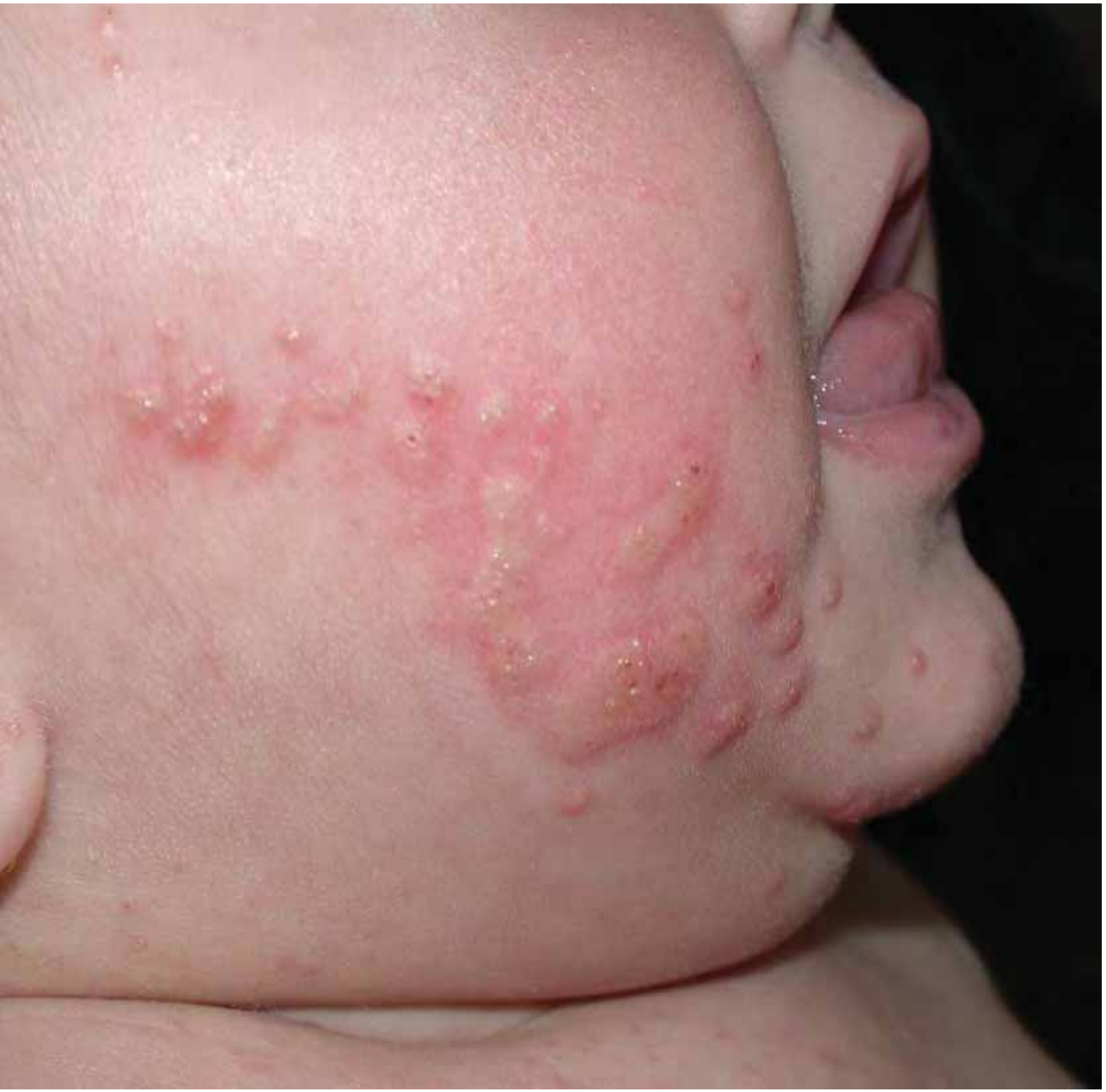


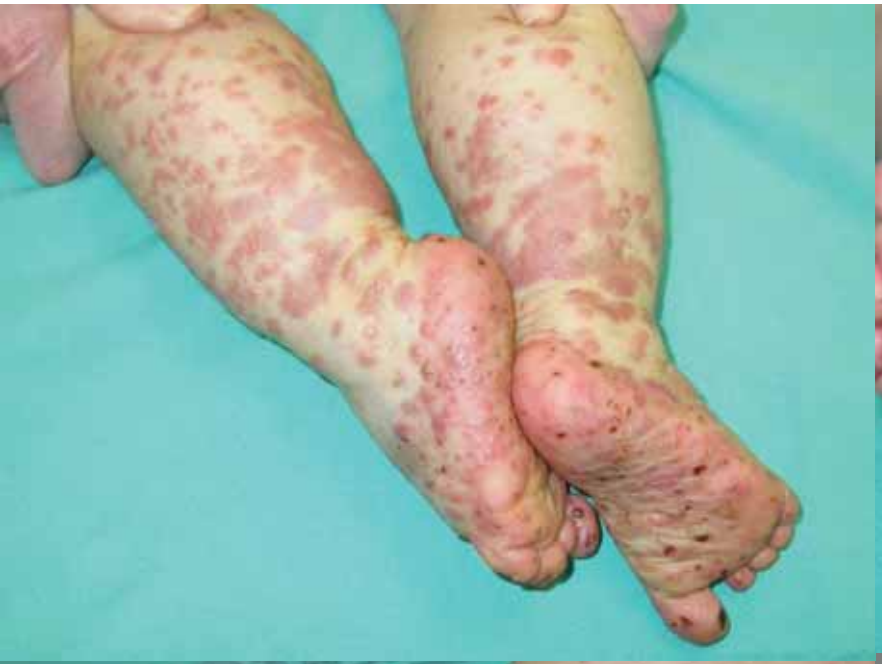
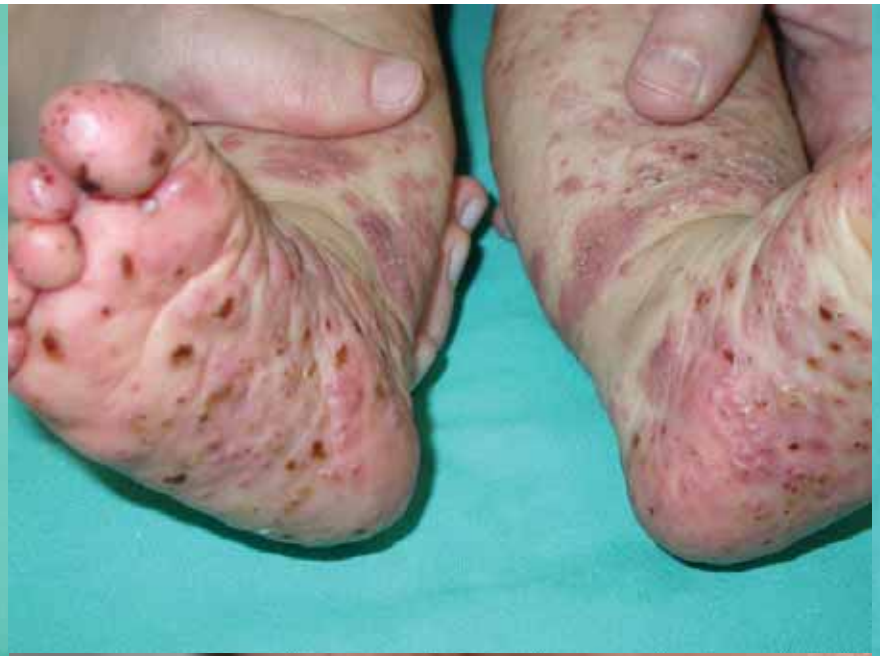
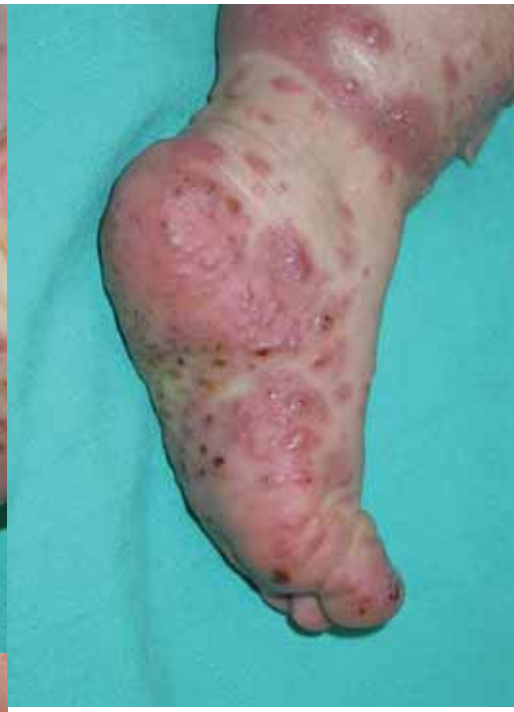
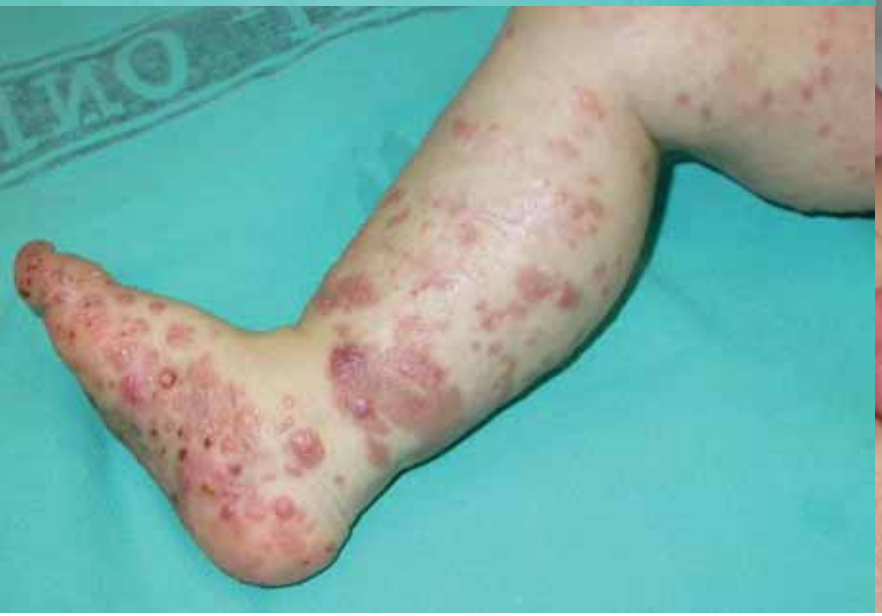
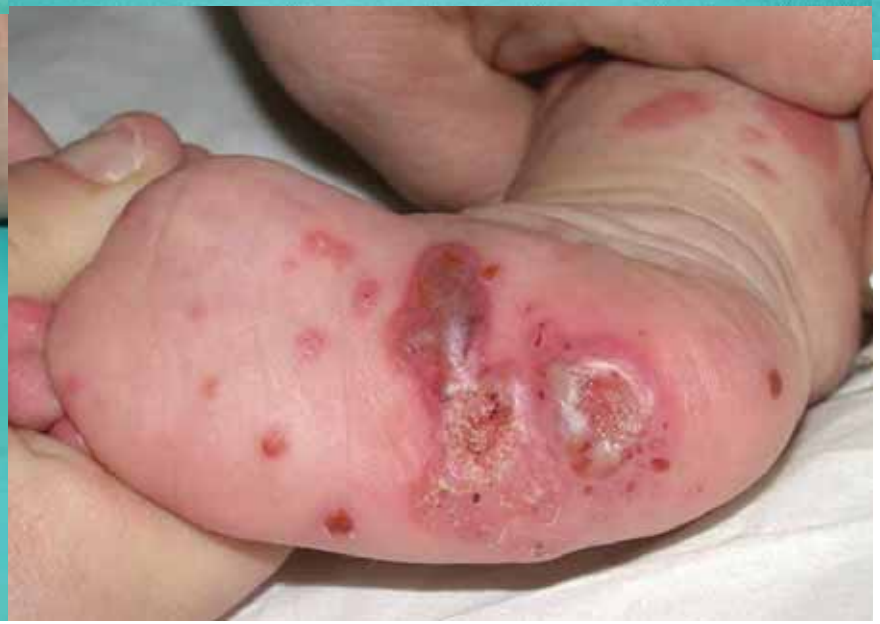


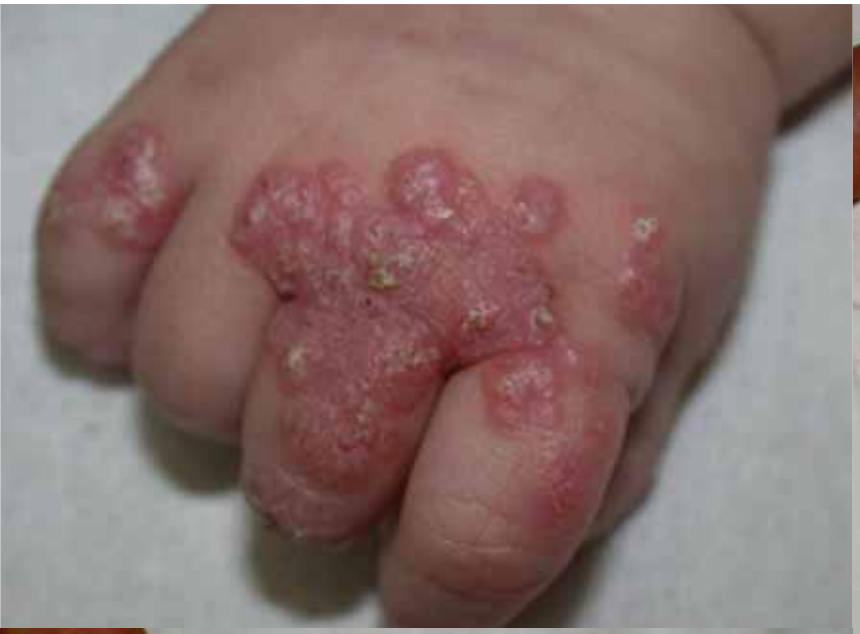
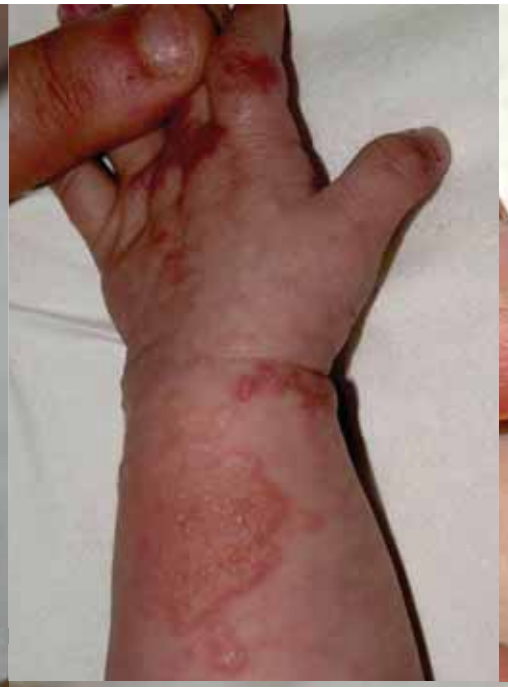
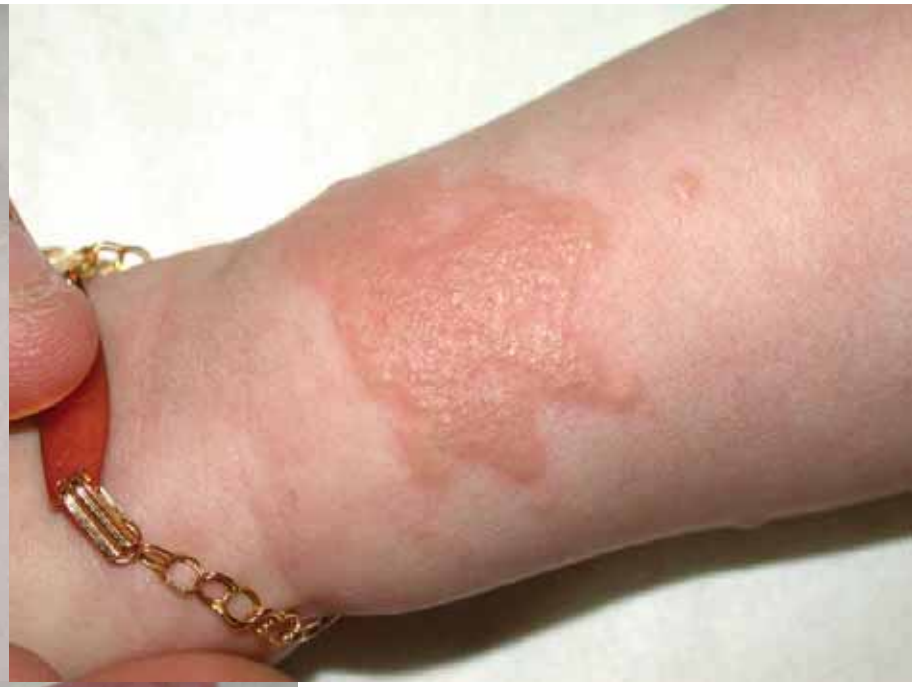
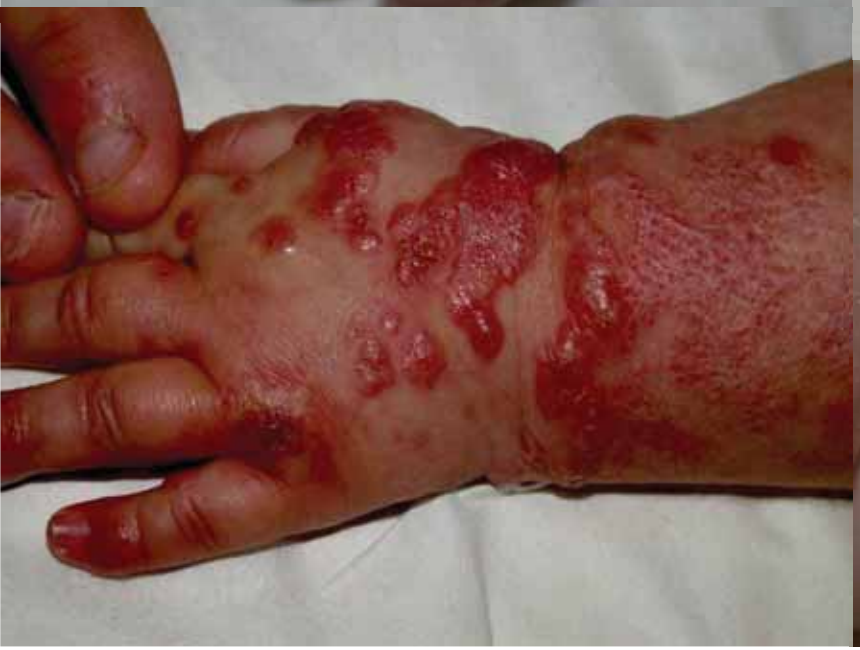
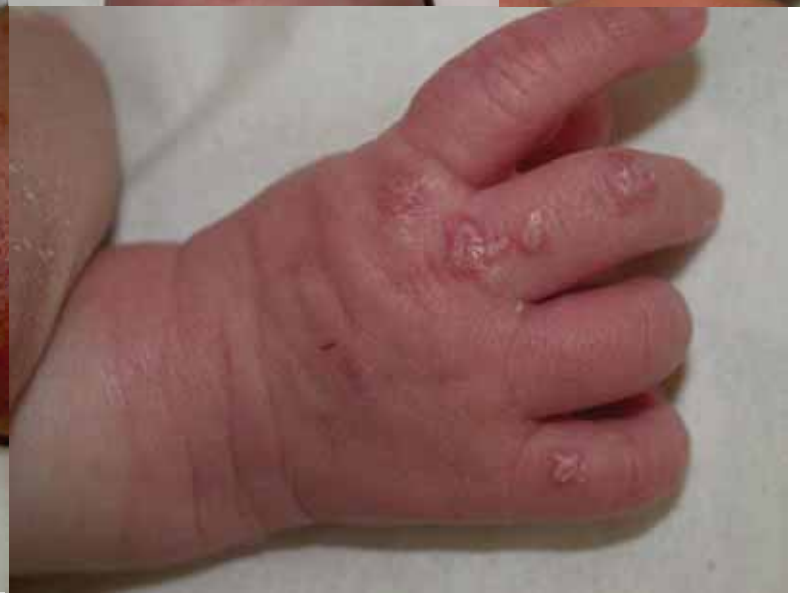








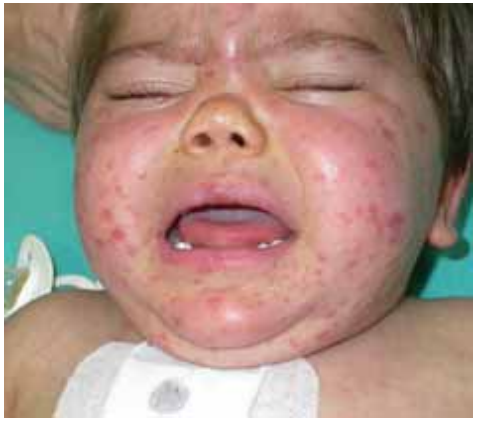






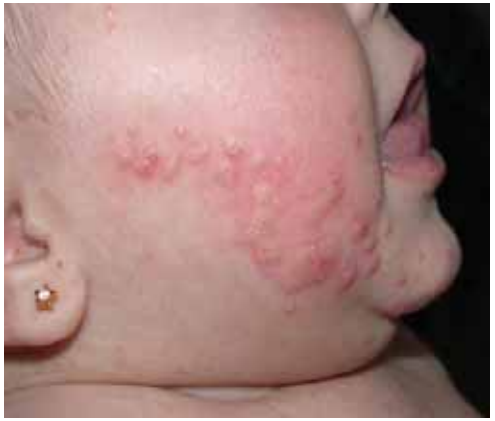






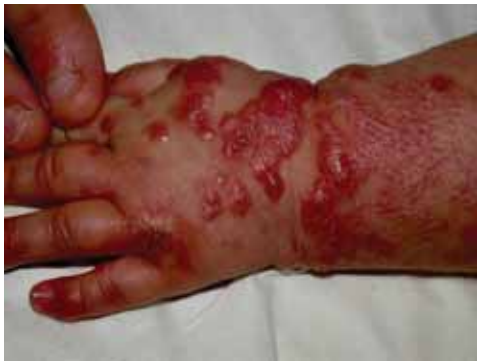
Pediatric Dermatology Vol. 24 No. 3 211–215, 2007

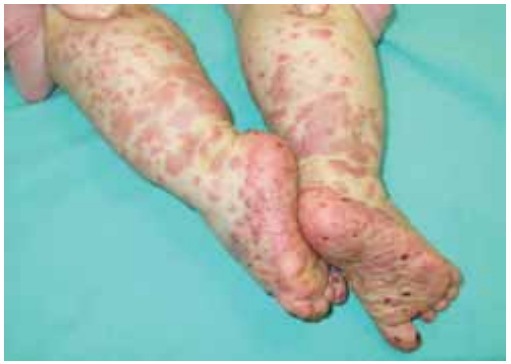
Perforating Neutrophilic and Granulomatous Dermatitis of the Newborn—A Clue to Immunodeficiency

Antonio Torrelo, M.D.,* Angel Vera, M.D.,† Mar Portugués, M.D.,‡ Inmaculada de Prada, M.D.,¶ Andrés Sanz, M.D.,# Isabel Colmenero, M.D.,¶ Ander Zulaica, M.D.,‡ Raúl de Lucas, M.D., Javier Fraga, M.D.,†† Javier Pedraz, M.D.,* Sindo Fontán, M.D.,‡‡ and Antonio Zambrano, M.D.,***









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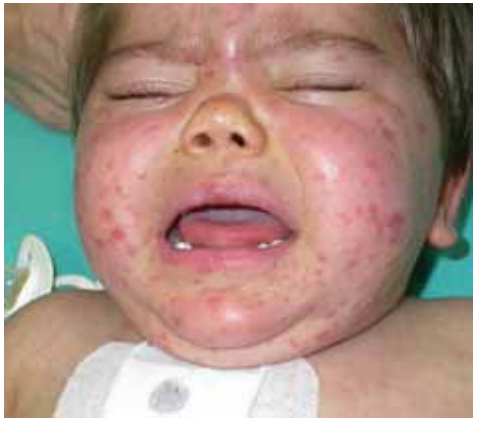
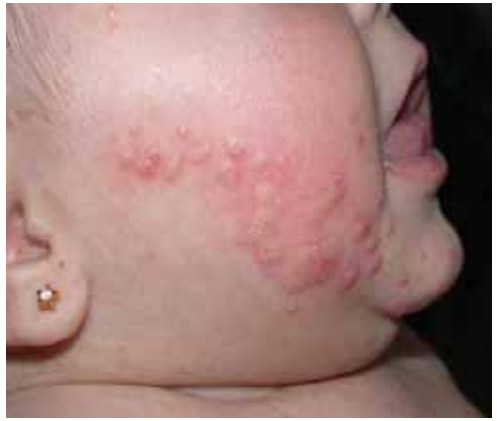
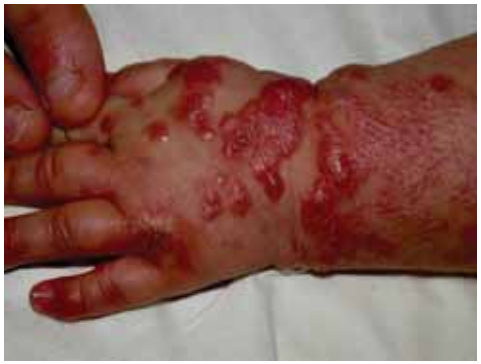
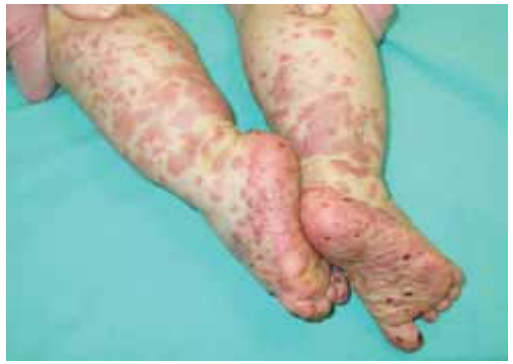


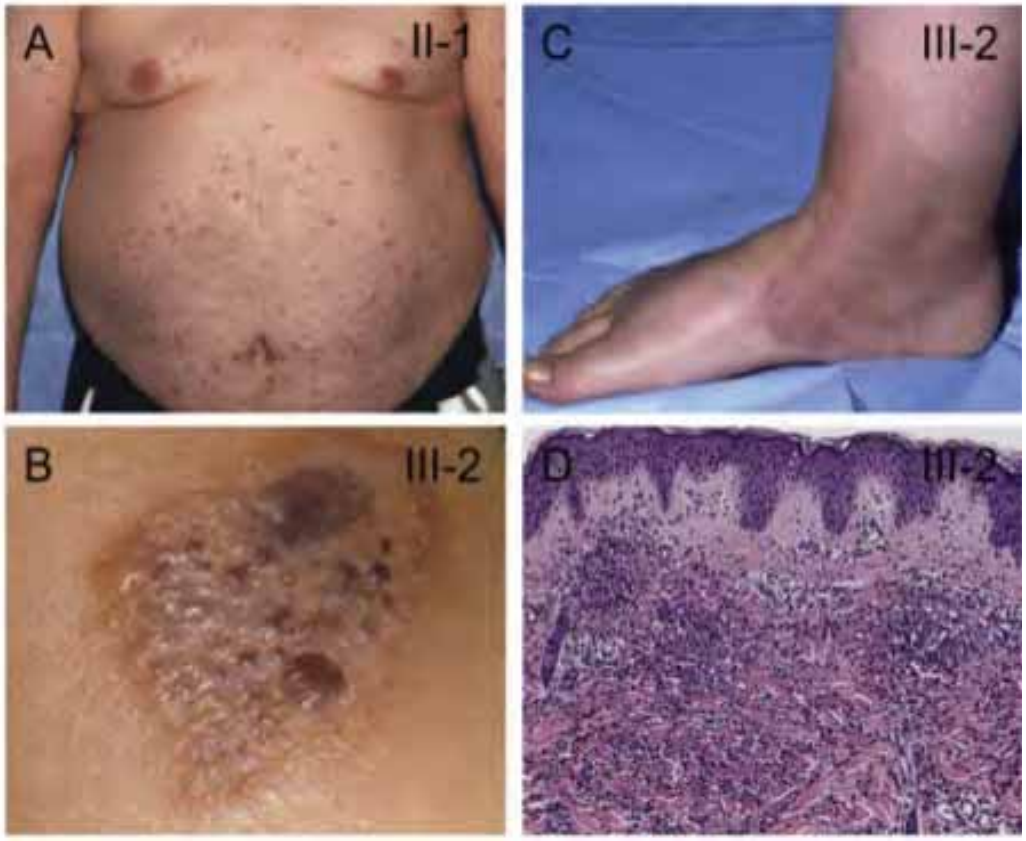






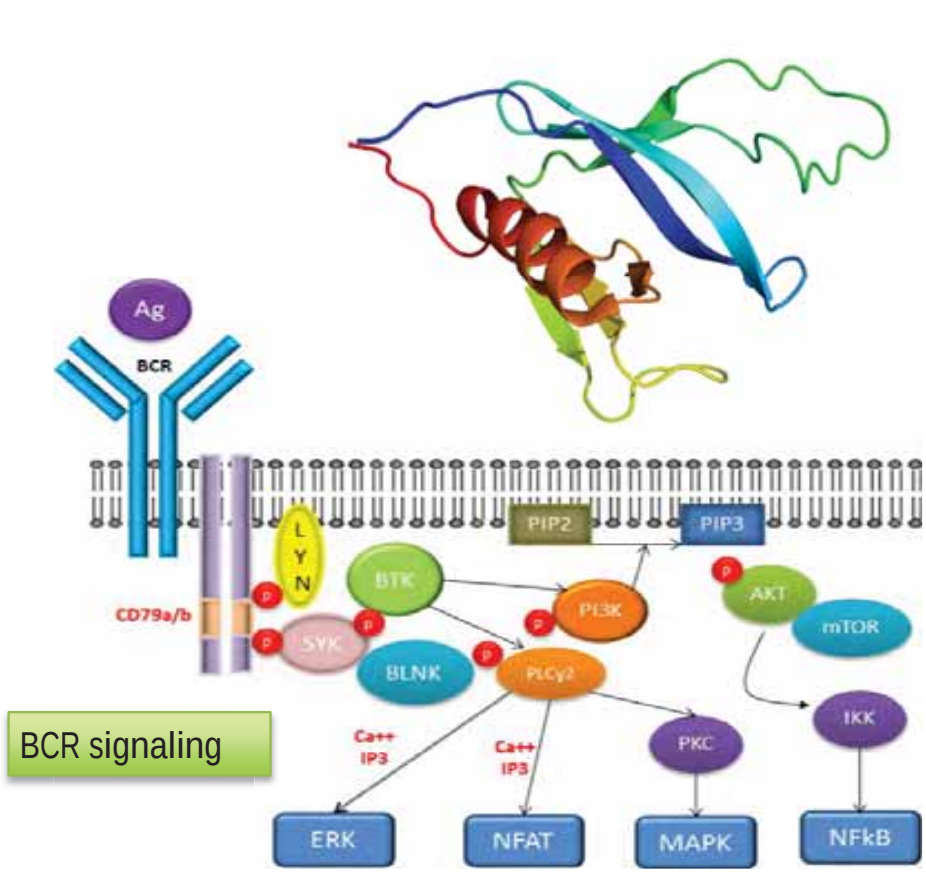
A Hypermorphic Missense Mutation in *PLCG2*, Encoding Phospholipase Cγ2, Causes a Dominantly Inherited Autoinflammatory Disease with Immunodeficiency

Qing Zhou,[1,8] Geun-Shik Lee,[1,2,8] Jillian Brady,[1] Shrimati Datta,[3] Matilda Katan,[4] Afzal Sheikh,[1] Marta S. Martins,[4] Tom D. Bunney,[4] Brian H. Santich,[5] Susan Moir,[5] Douglas B. Kuhns,[6] Debra A. Long Priel,[6] Amanda Ombrello,[1] Deborah Stone,[1] Michael J. Ombrello,[1] Javed Khan,[7] Joshua D. Milner,[3] Daniel L. Kastner,[1,*] and Ivona Aksentijevich[1,*]



1-Phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma-2

Phospholipase Cγ2



BCR signaling

Perforating neutrophilic and granulomatous dermatits of the newborn

APLAID syndrome: Autoinflammation and PCLG2-associated antibody deficiency and immune dysregulation

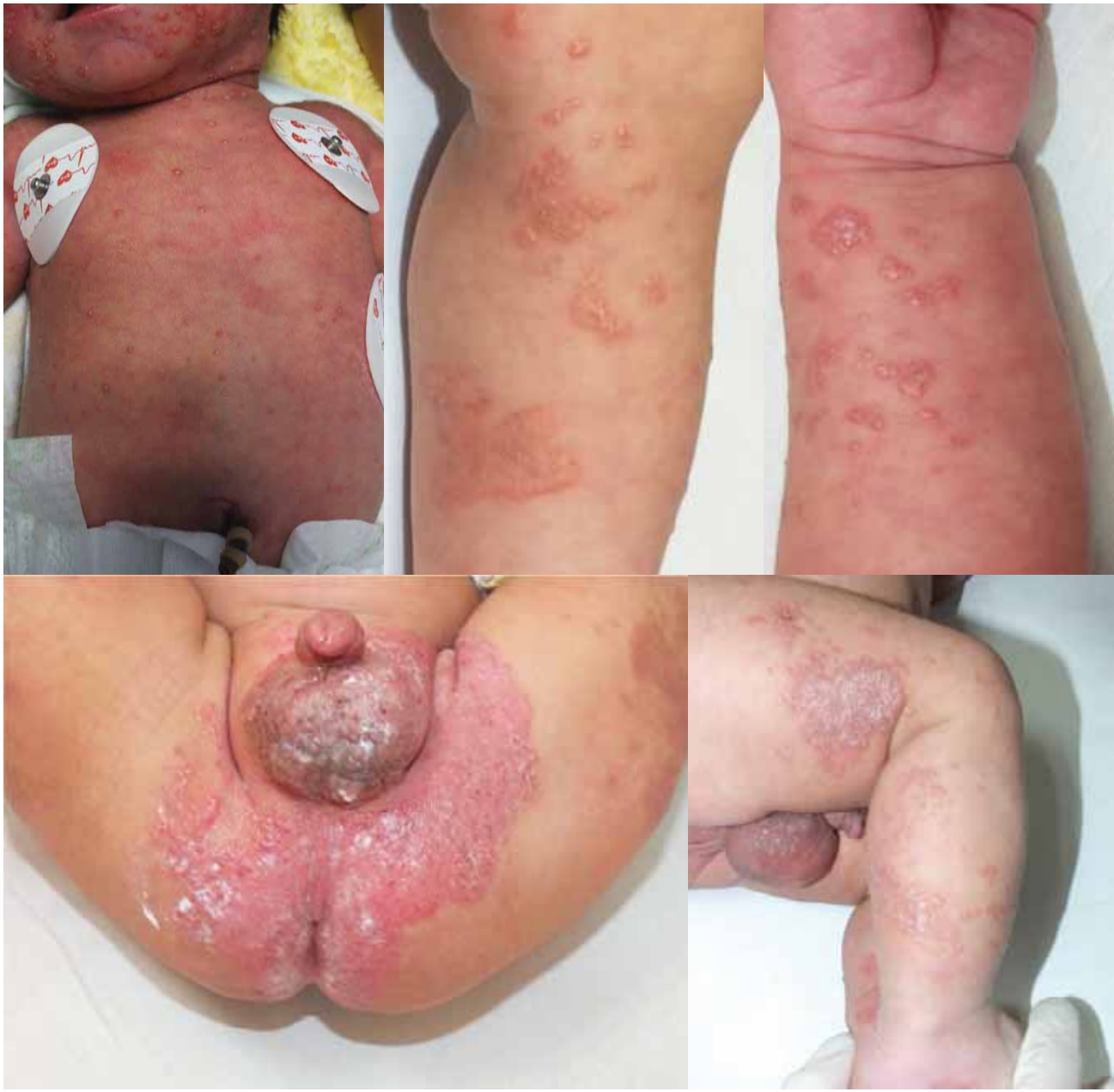
GOF (hypermorphic)

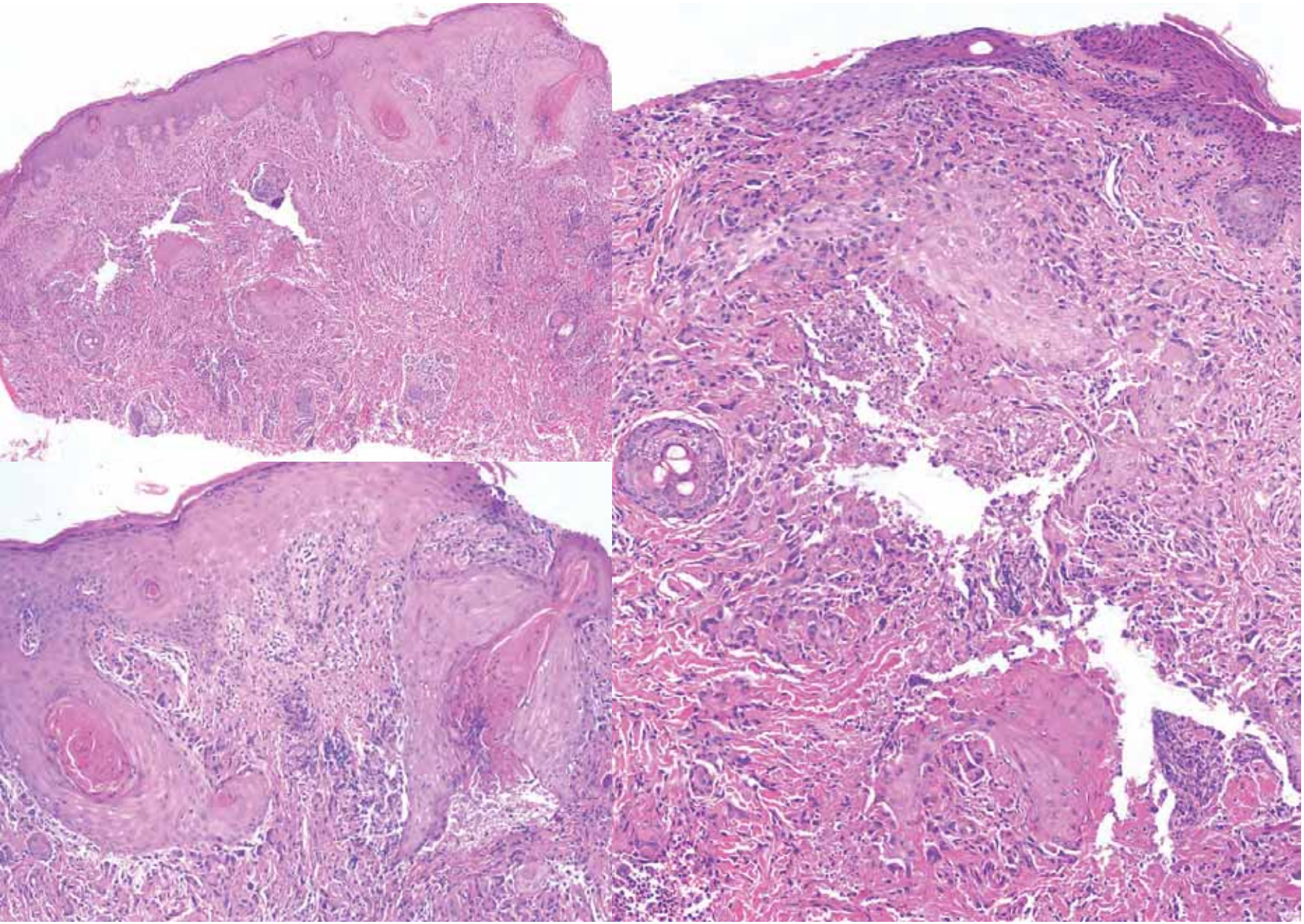
GOF (deletion of inhibitory)

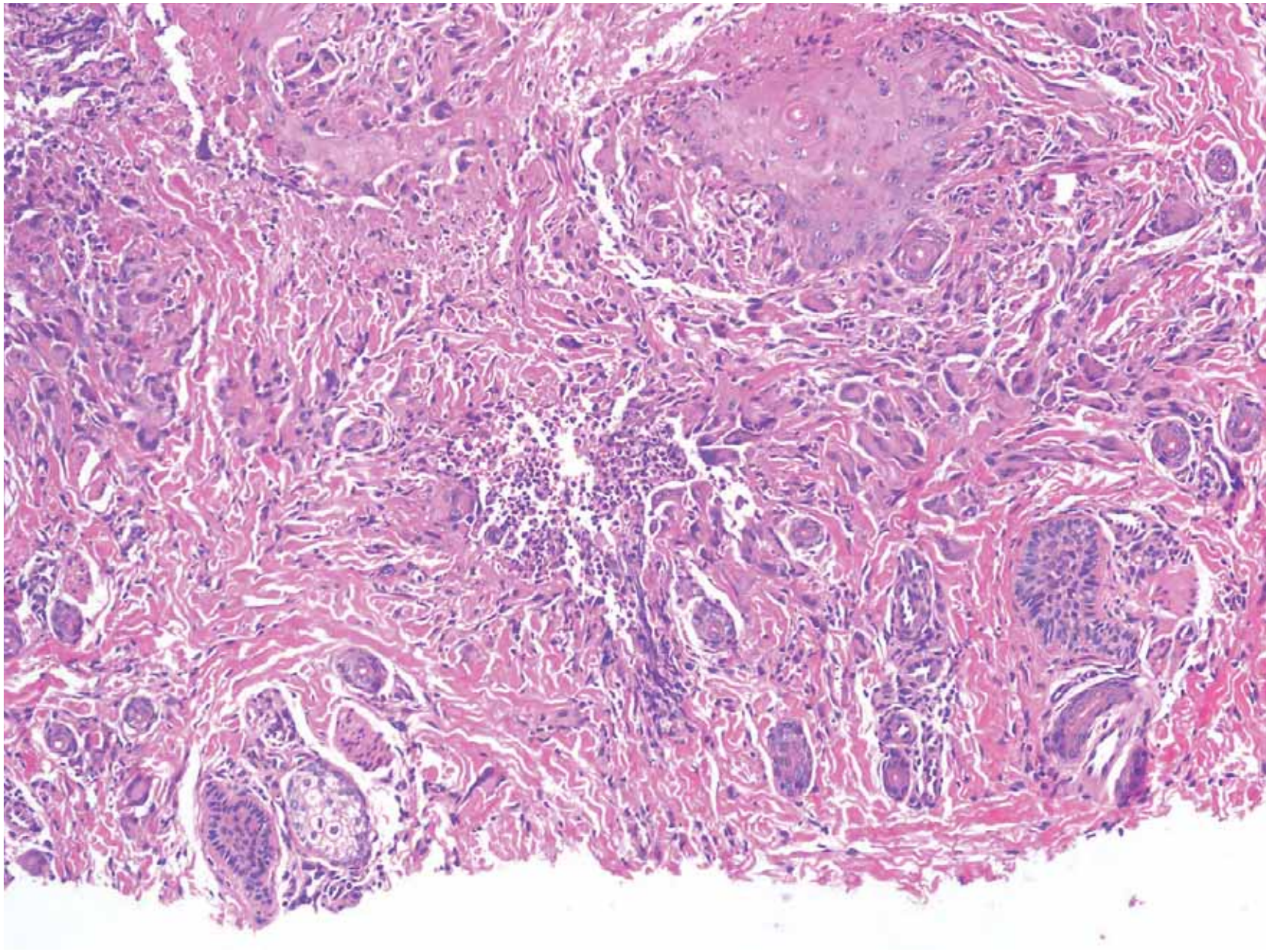
PLAID syndrome: PCLG2-associated antibody deficiency and immune dysregulation

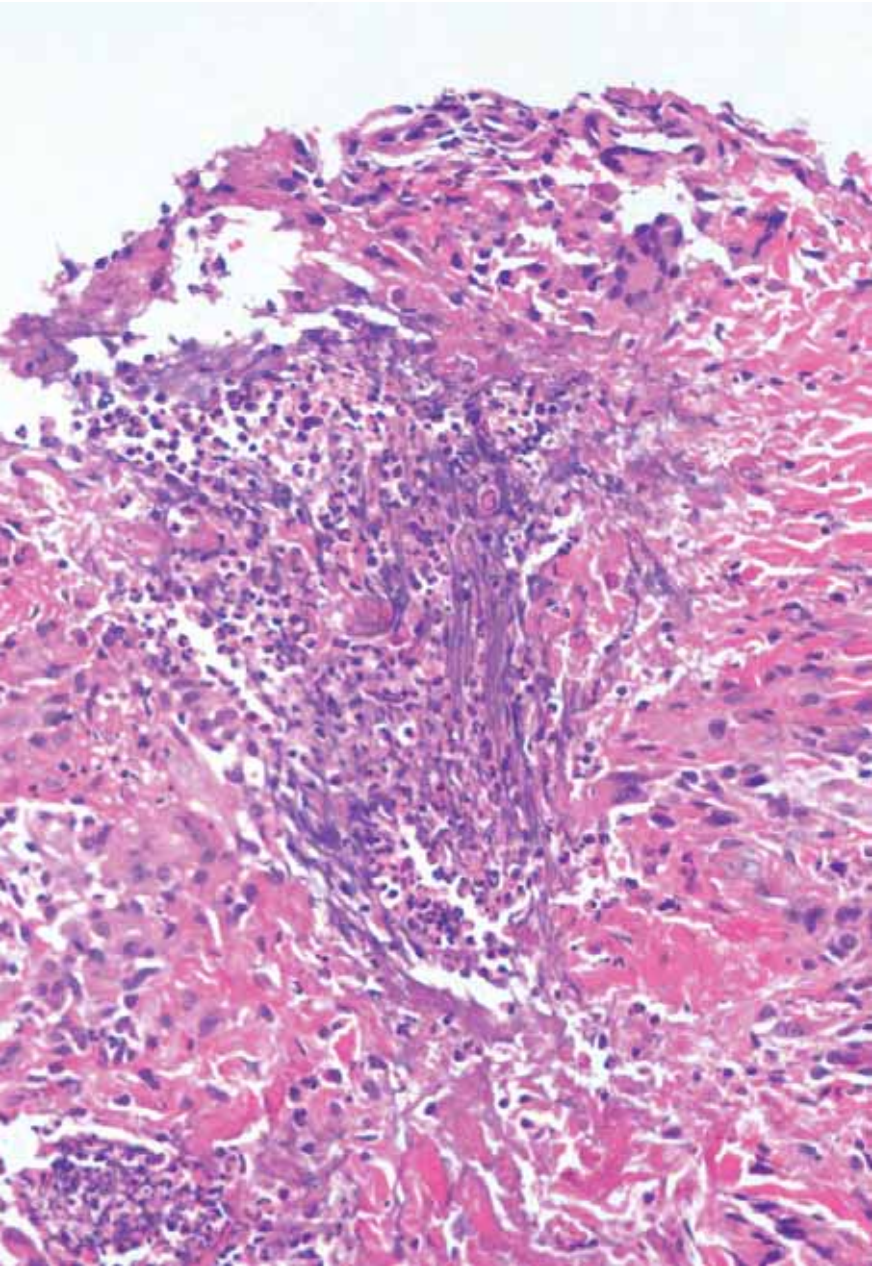
Cold urticaria

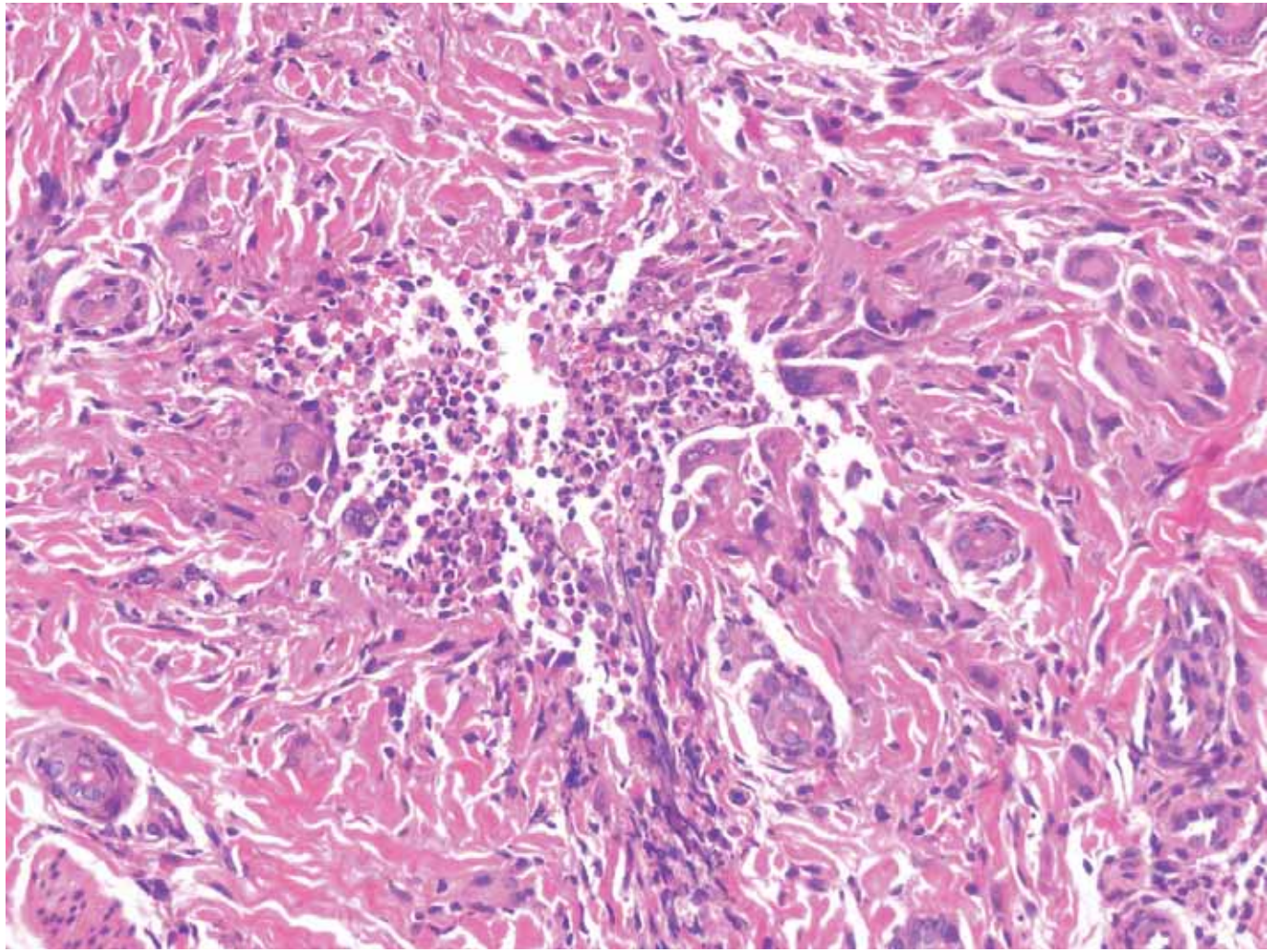
Mª Teresa García Romero, México











Genes analizados: Secuenciación completa de la región codificante del gen *PLCG2*

Resultado:

Cr:Posición	Gen	Cambio	Variante	Efecto	Cigosidad	ID dbSNP	Significado clínico
16:81953156	*PLCG2*	G > C	p.(Ala708Pro) c.2122G>C	Cambio de sentido	Heterocigosis		Probablemente patogénica

Variantes detectadas*(1):

Cr:Posición	Gen	Cambio	Variante	Efecto	Cigosidad	ID dbSNP	Significado clínico
16:81819768	PLCG2	T > C	p.(Ala58=) c.174T>C	Variante sinónima	Homocigosis	rs1143685, rs4586425	Benigna
16:81888152	PLCG2	A > G	p.(Leu99=) c.297A>G	Variante sinónima	Heterocigosis	rs1143686	Benigna
16:81929488	PLCG2	C > T	p.(Asp383=) c.1149C>T	Variante sinónima	Heterocigosis	rs1143688, rs17626801	Benigna
16:81941319	PLCG2	C > T	p.(Ala499=) c.1497C>T	Variante sinónima	Heterocigosis	rs1143689, rs4243221	Benigna
16:81953081	PLCG2	T > C	c.2055-8T>C	Variante en región aceptora de splicing	Heterocigosis	rs12448130	Benigna
16:81953156	PLCG2	G > C	p.(Ala708Pro) c.2122G>C	Cambio de sentido	Heterocigosis		Probablemente patogénica
16:81960783	PLCG2	G > A	p.(Gln838Gln) c.2514G>A	Variante sinónima	Heterocigosis	rs115583707	Probablemente benigna
16:81971403	PLCG2	T > C	p.(Asn1031=) c.3093T>C	Variante sinónima	Heterocigosis	rs1071644	Benigna

**Anotación asociada a las patologías establecidas en la base de datos OMIM (1), al menos que se indique específicamente la patología.*

ORIGINAL ARTICLE

Severe Autoinflammatory Manifestations and Antibody Deficiency Due to Novel Hypermorphic *PLCG2* Mutations

Andrea Martin-Nalda[1,2] · Claudia Fortuny[3,4,1] · Lourdes Rey[5] · Tom D. Bunney[6] · Laia Alsina[4,7,8] · Ana Esteve-Solé[4,7,8] · Daniel Bull[9] · Maria Carmen Anton[10] · María Basagaña[11] · Ferran Casals[12] · Angela Deyà[4,7,8] · Marina García-Prat[1,2] · Ramon Gimeno[13] · Manel Juan[10,14,15] · Helios Martínez-Banaclocha[16] · Juan J Martínez-García[16] · Anna Mensa-Vilaró[10] · Raquel Rabionet[4,17] · Nieves Martín-Begue[18] · Francesc Rudilla[19,20] · Jordi Yagüe[10,14,15] · Xavier Estivill[21] · Vicente García-Patos[22] · Ramon M. Pujol[23] · Pere Soler-Palacín[1,2,24] · Matilda Katan[6] · Pablo Pelegrín[16] · Roger Colobran[2,25,26] · Asun Vicente[27] · Juan I. Arostegui[10,14,15]

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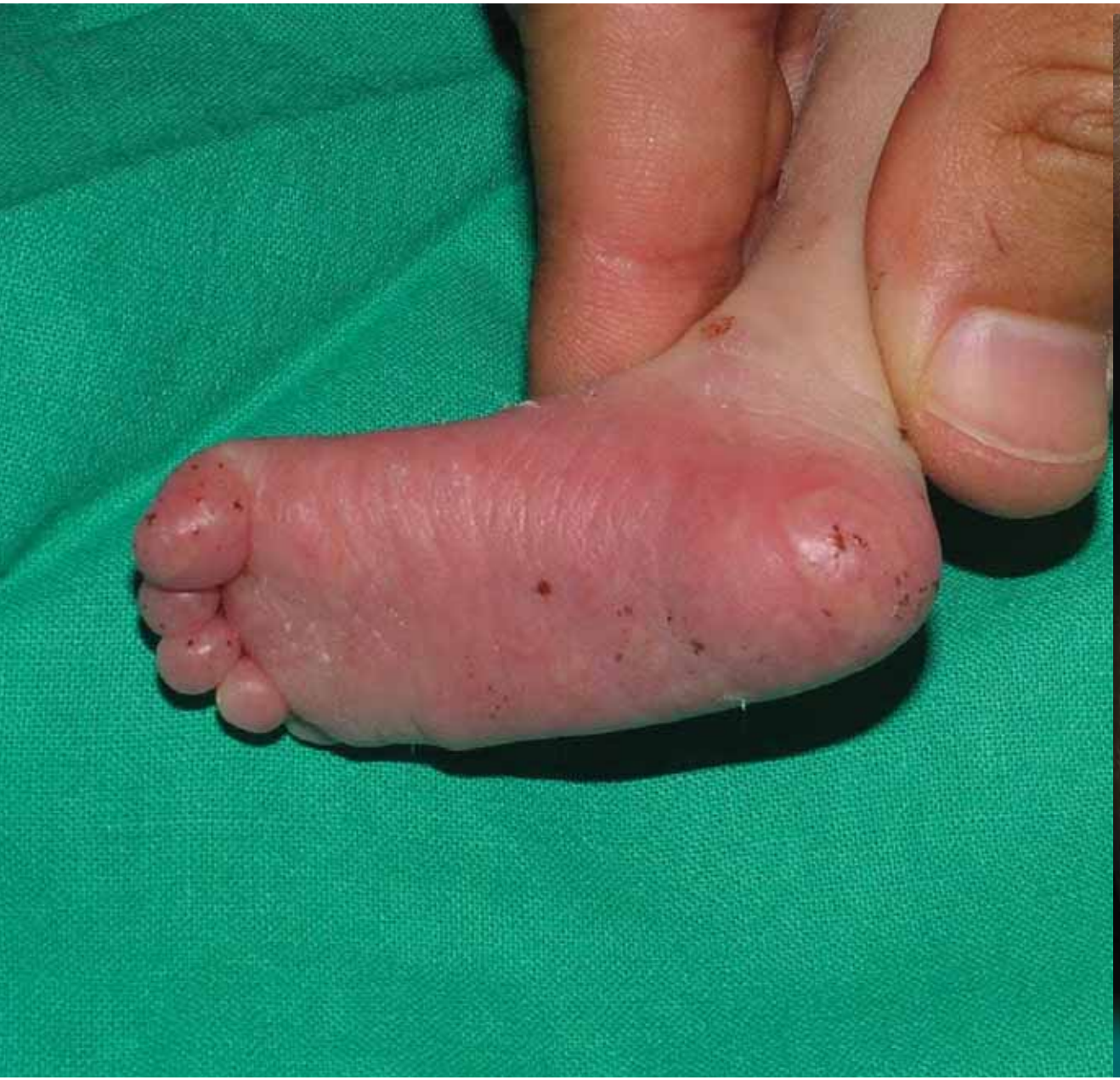
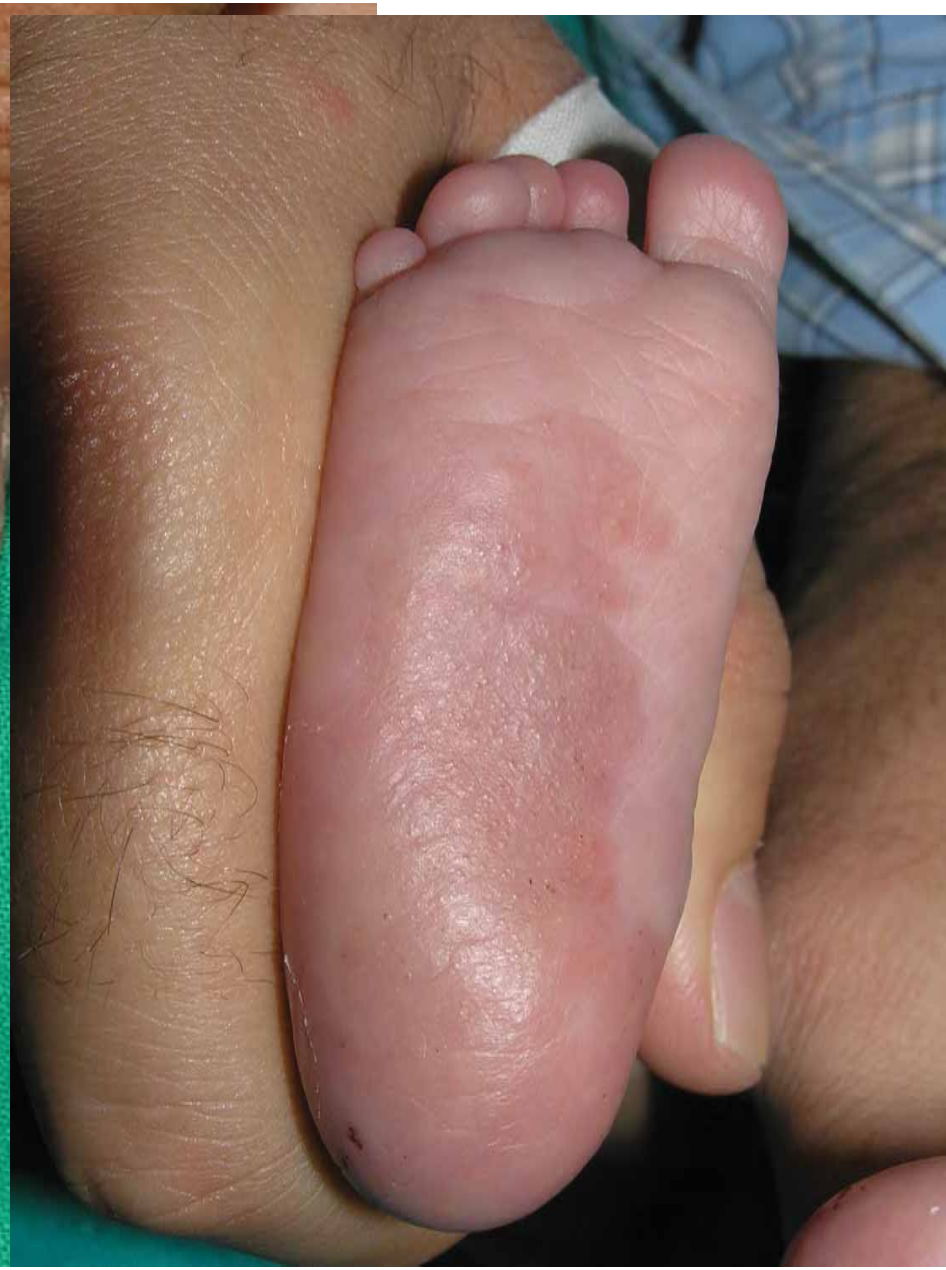
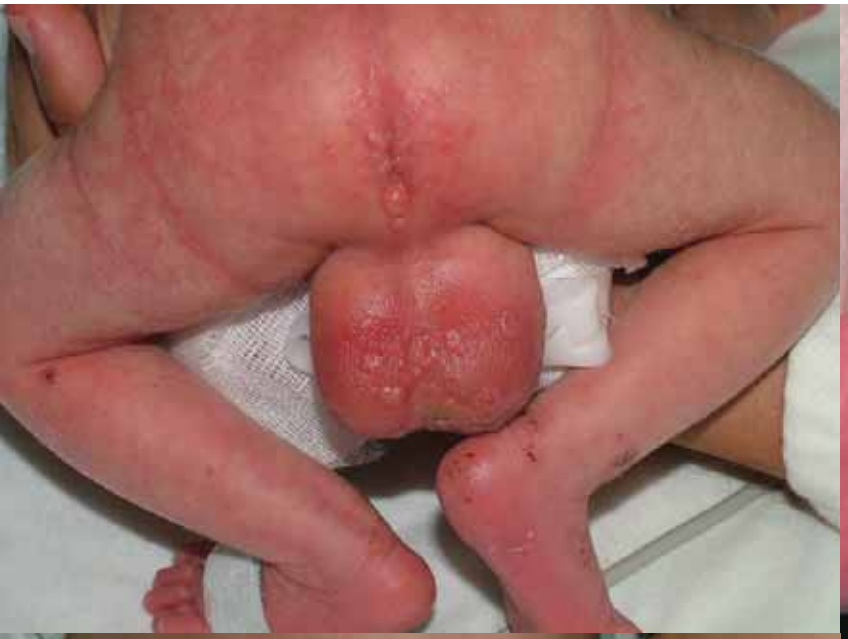
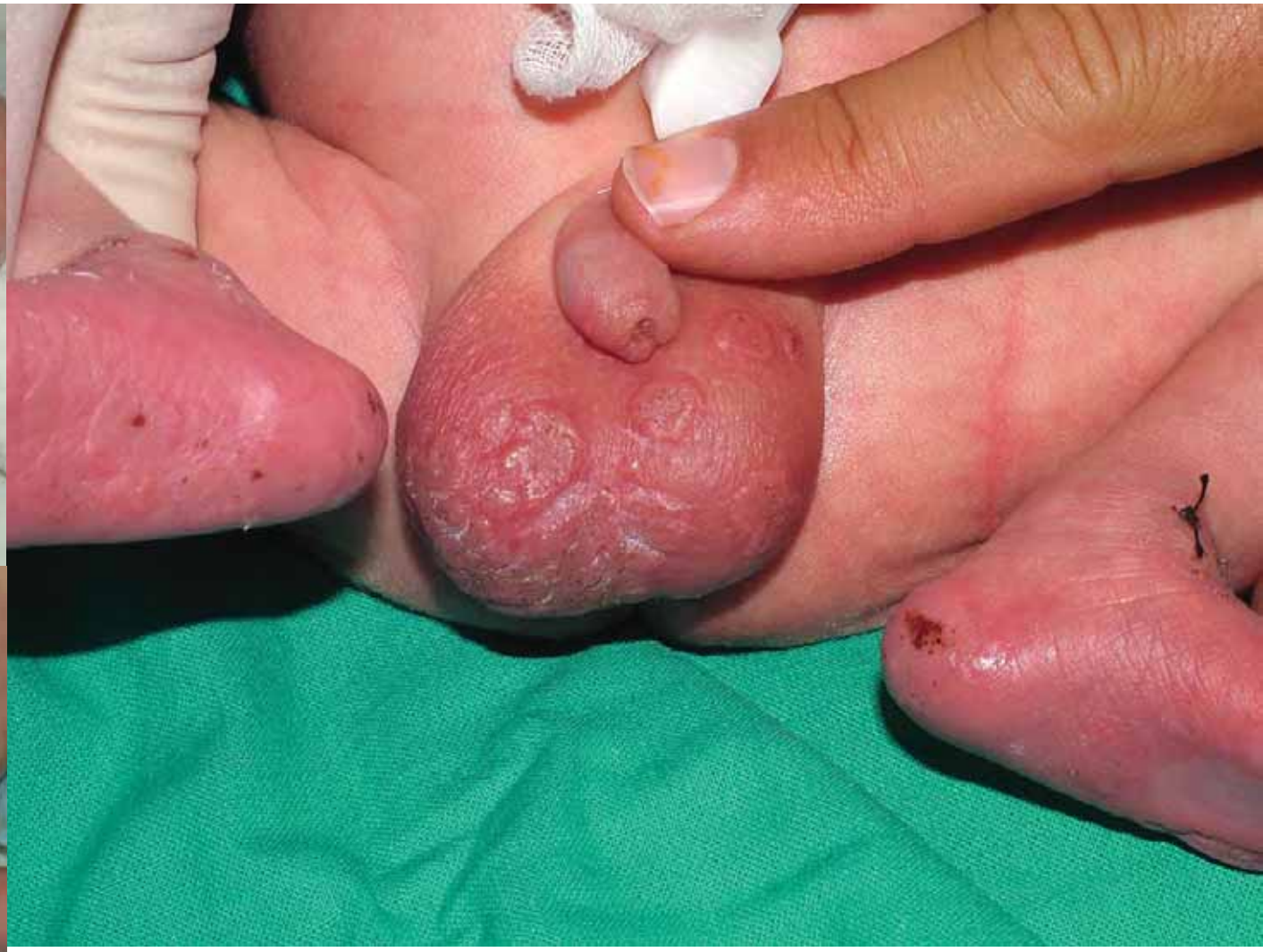
Abstract
Autoinflammatory diseases (AIDs) were first described as clinical disorders characterized by recurrent episodes of seemingly unprovoked sterile inflammation. In the past few years, the identification of novel AIDs expanded their phenotypes toward more complex clinical pictures associating vasculopathy, autoimmunity, or immunodeficiency. Herein, we describe two unrelated patients suffering since the neonatal period from a complex disease mainly characterized by severe sterile inflammation, recurrent bacterial infections, and marked humoral immunodeficiency. Whole-exome sequencing detected a novel, de novo heterozygous *PLCG2* variant in each patient (p.Ala708Pro and p.Leu845_Leu848del). A clear enhanced PLCγ2 activity for both variants was demonstrated by both ex vivo calcium responses of the patient's B cells to IgM stimulation and in vitro assessment of PLC activity. These data supported the autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation (APLAID) diagnosis in both patients. Immunological evaluation revealed a severe decrease of immunoglobulins and B cells, especially class-switched memory B cells, with normal T and NK cell counts. Analysis of bone marrow of one patient revealed a reduced immature B cell fraction compared with controls. Additional investigations showed that both *PLCG2* variants activate the NLRP3-inflammasome through the alternative pathway instead of the canonical pathway. Collectively, the evidences here shown expand APLAID diversity toward more severe phenotypes than previously reported including dominantly inherited agammaglobulinemia, add novel data about its genetic basis, and implicate the alternative NLRP3-inflammasome activation pathway in the basis of sterile inflammation.

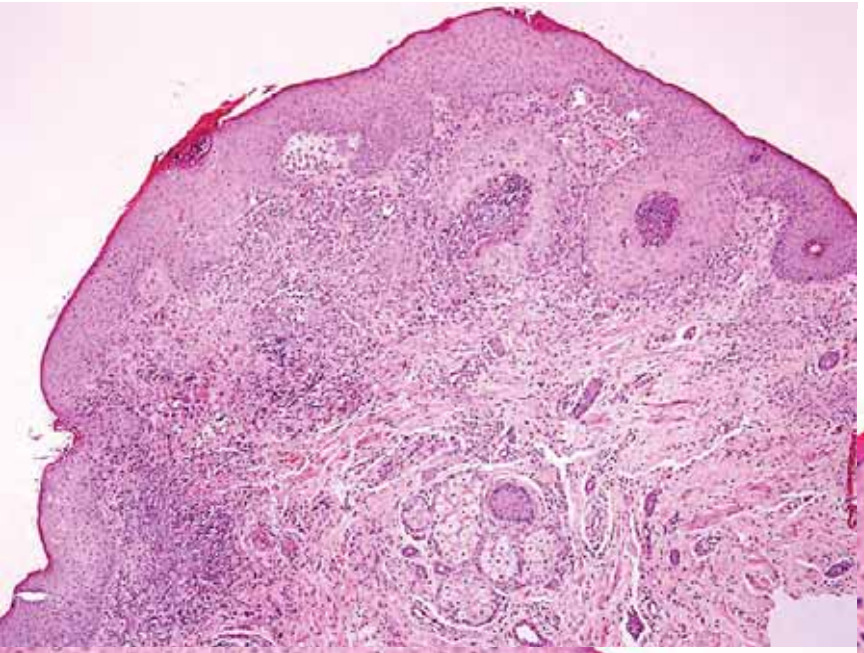
Keywords Autoinflammatory diseases · APLAID · PLCγ2 · inflammasome · caspase-1 · interleukin-1 · agammaglobulinemia

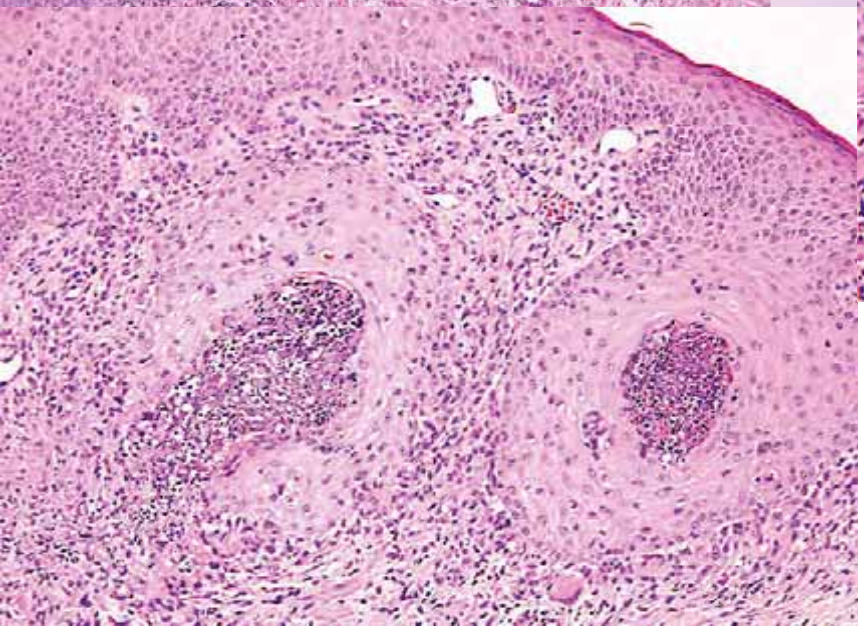


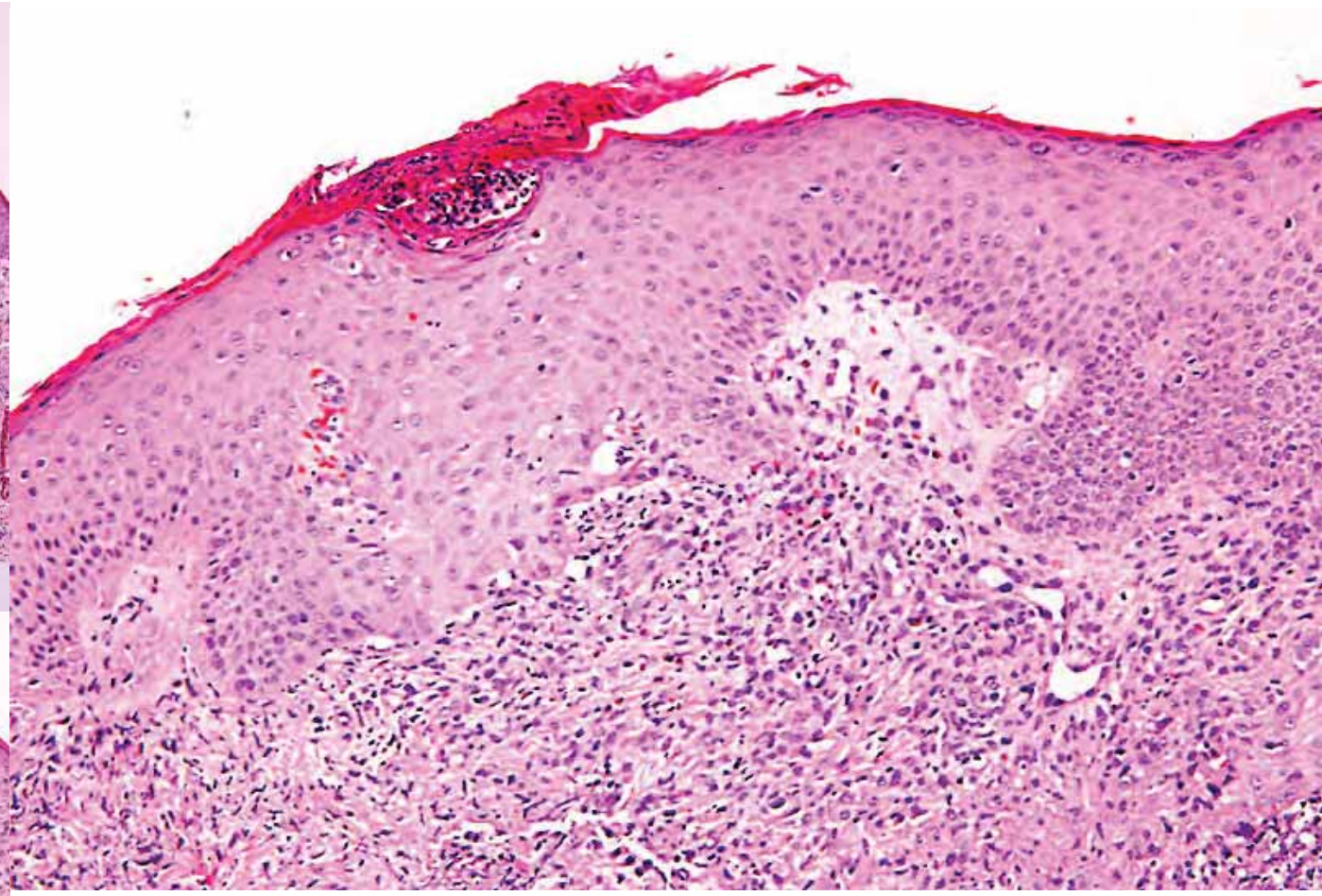


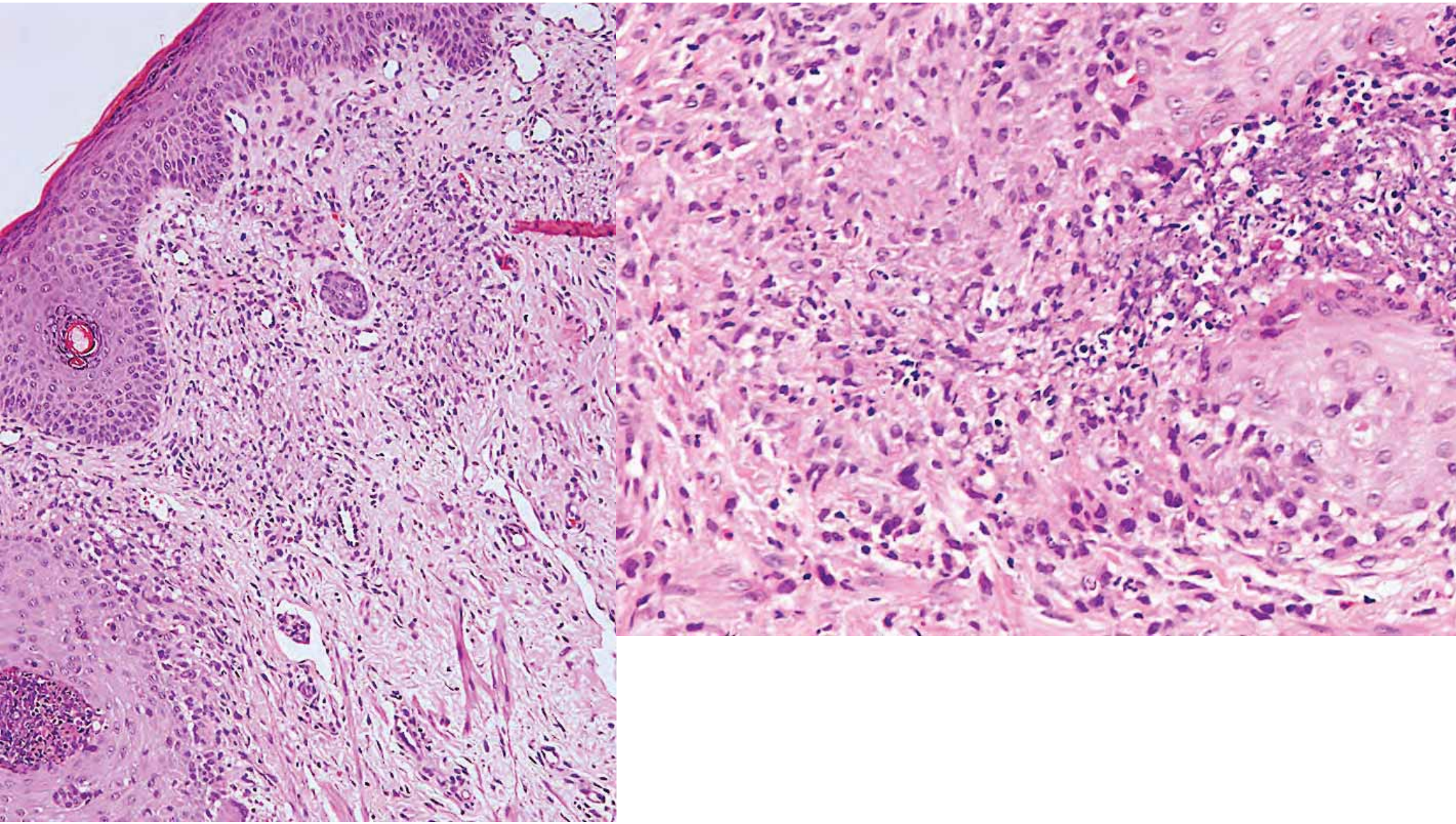


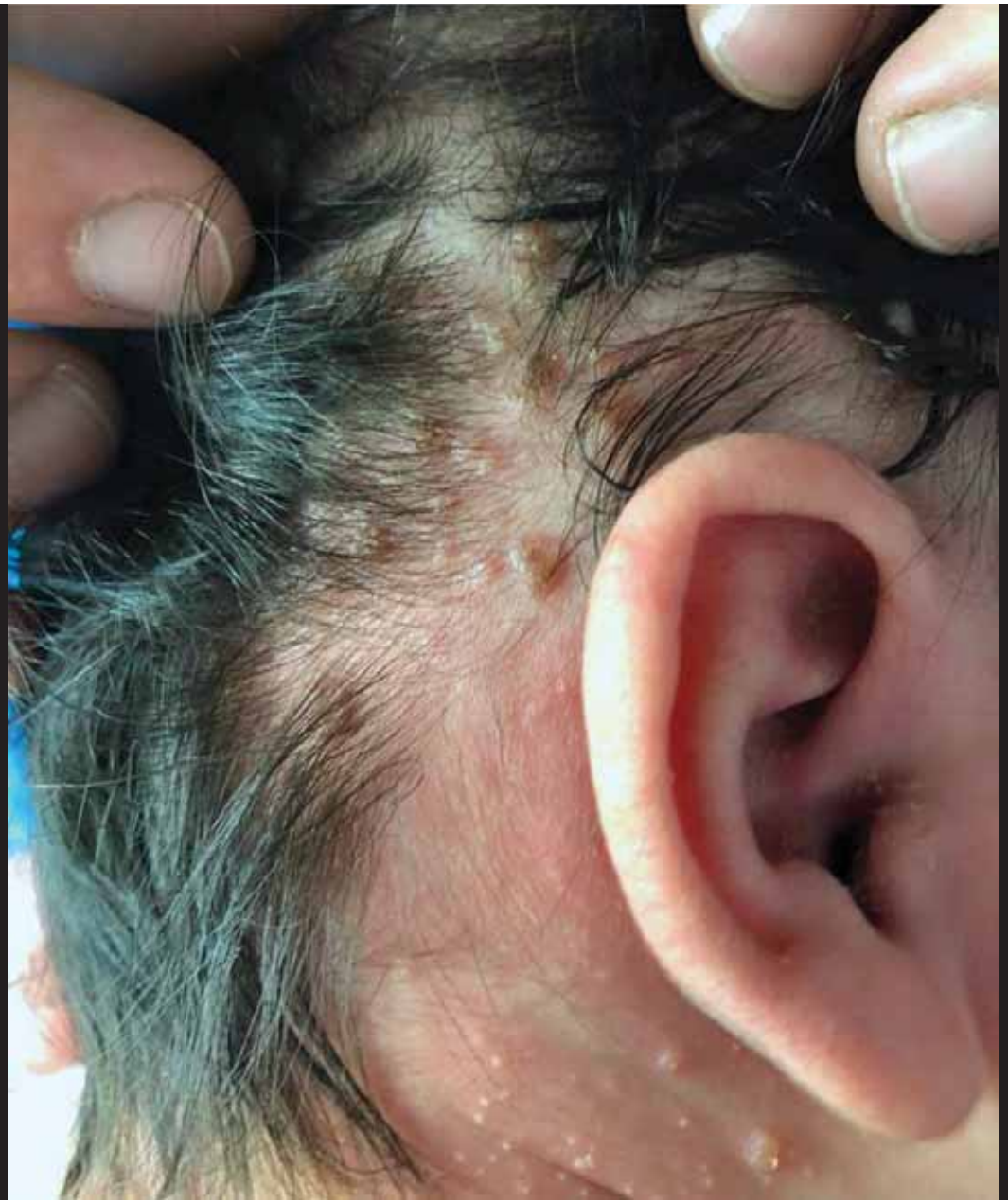


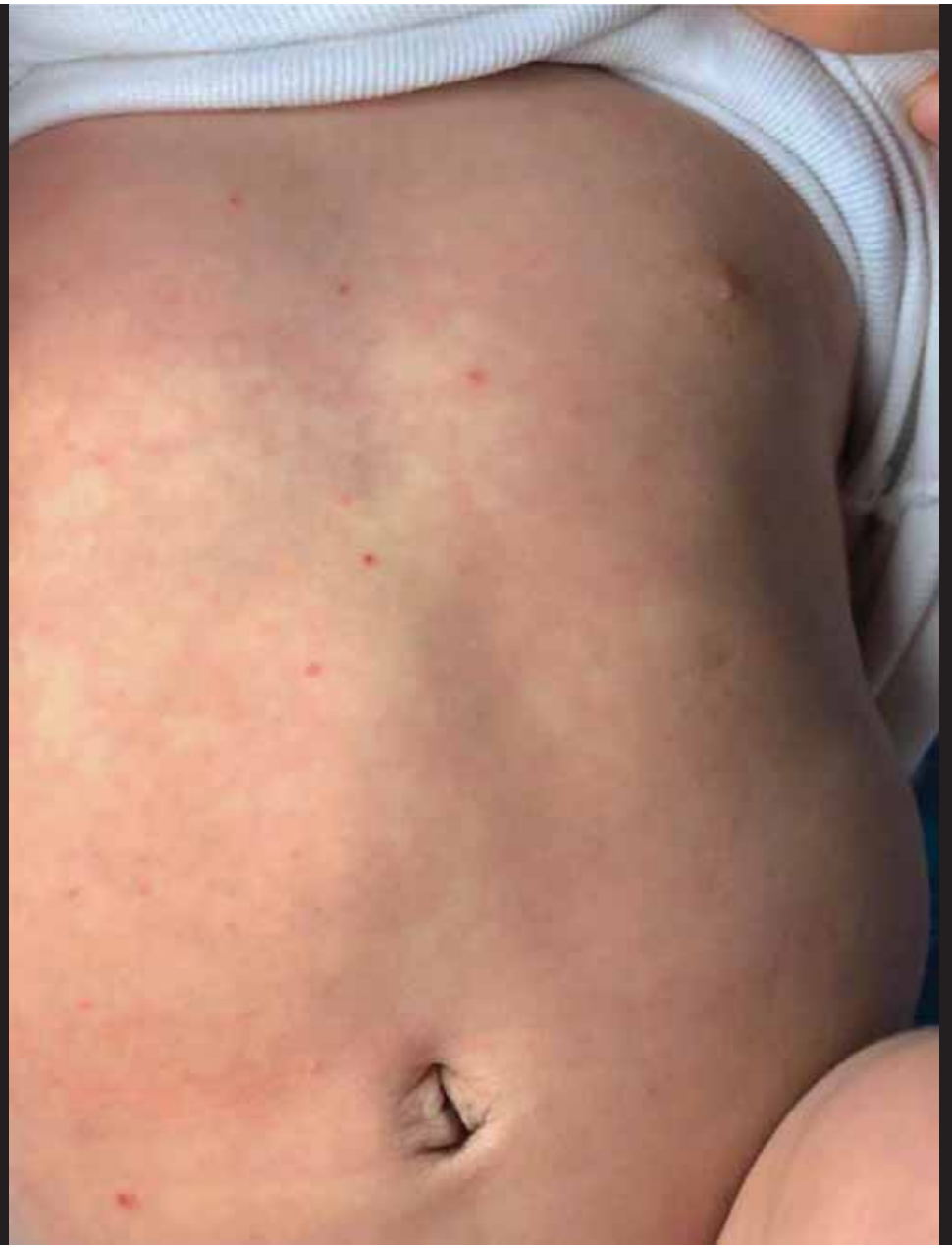


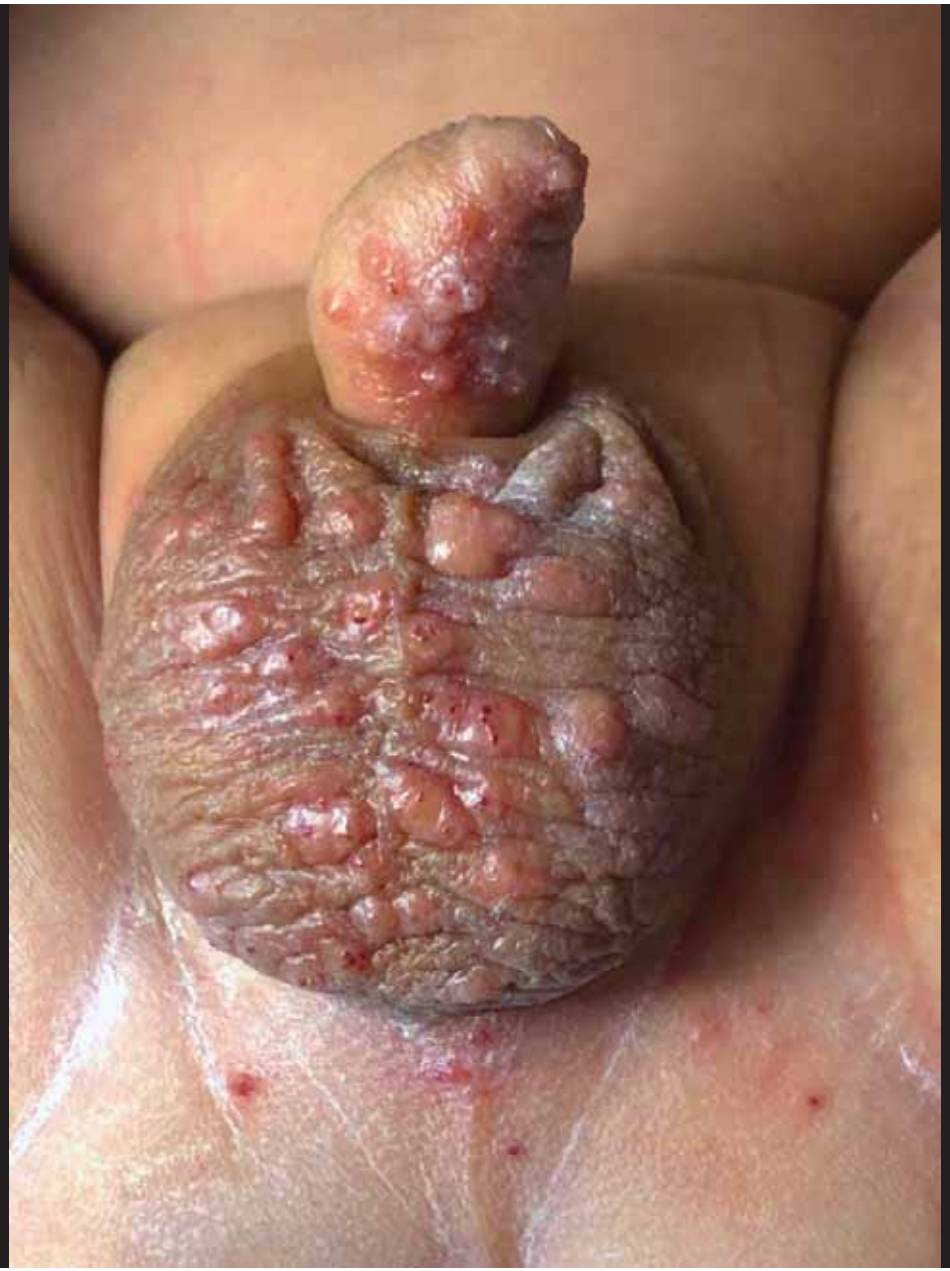


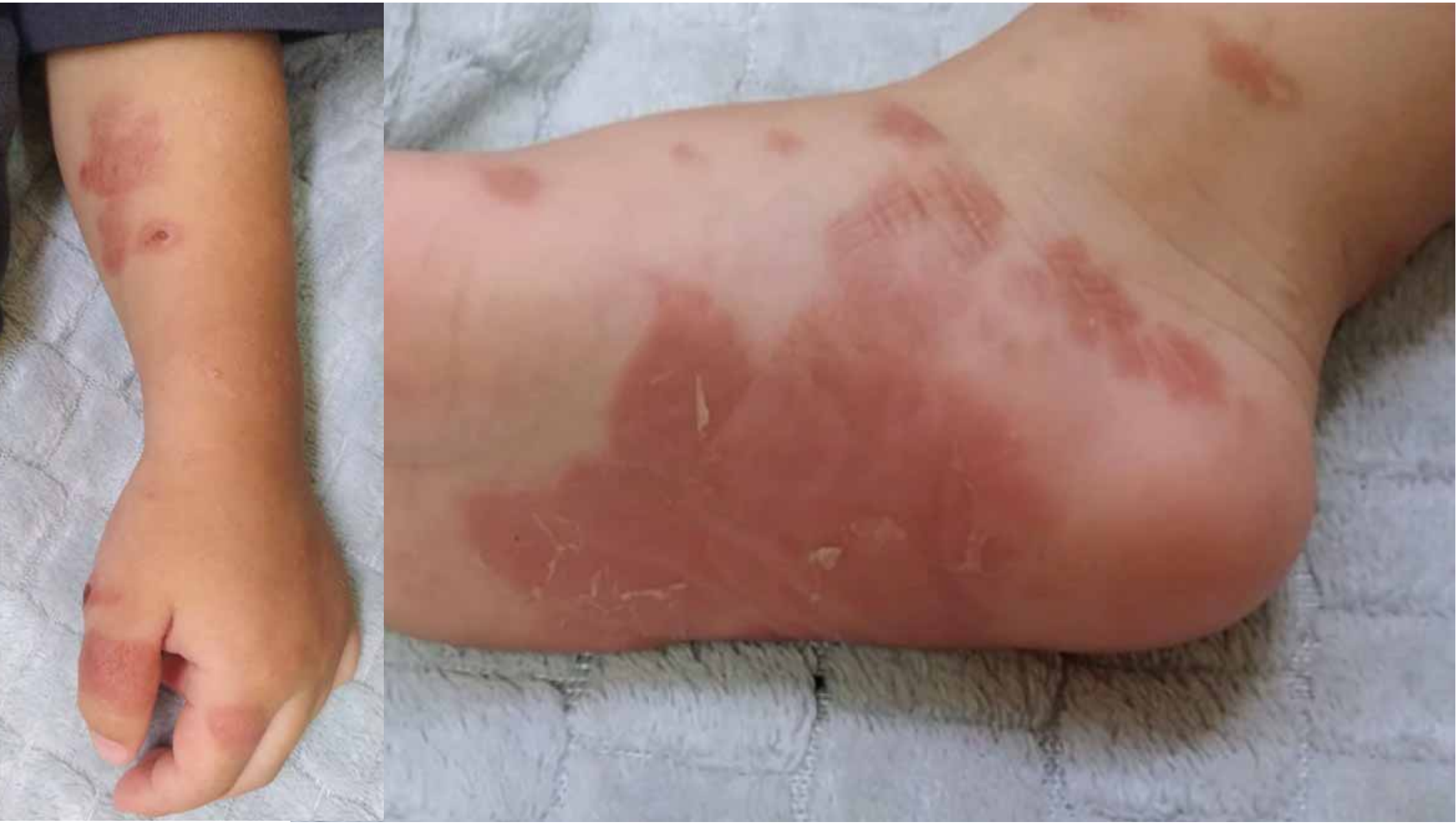


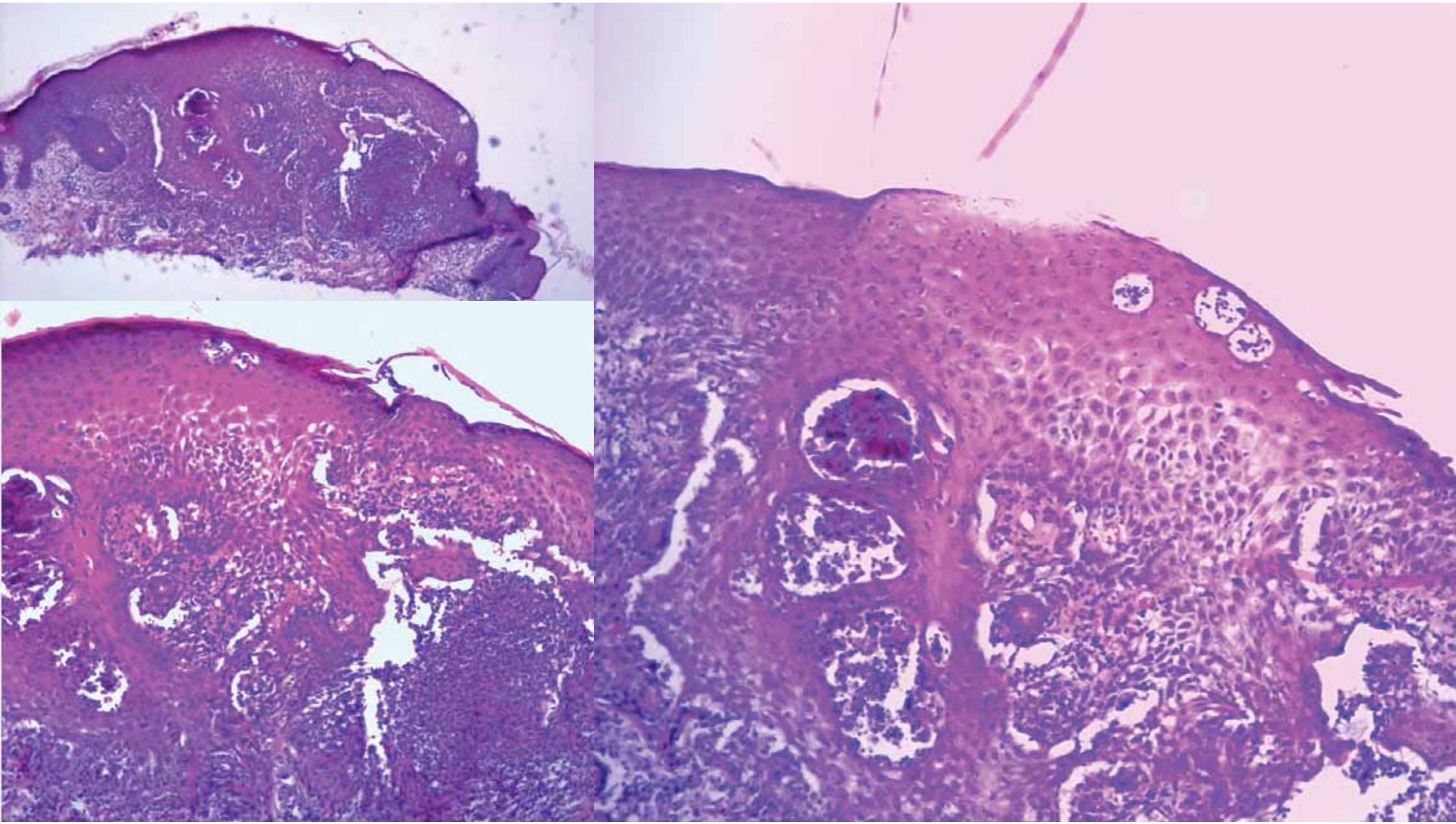


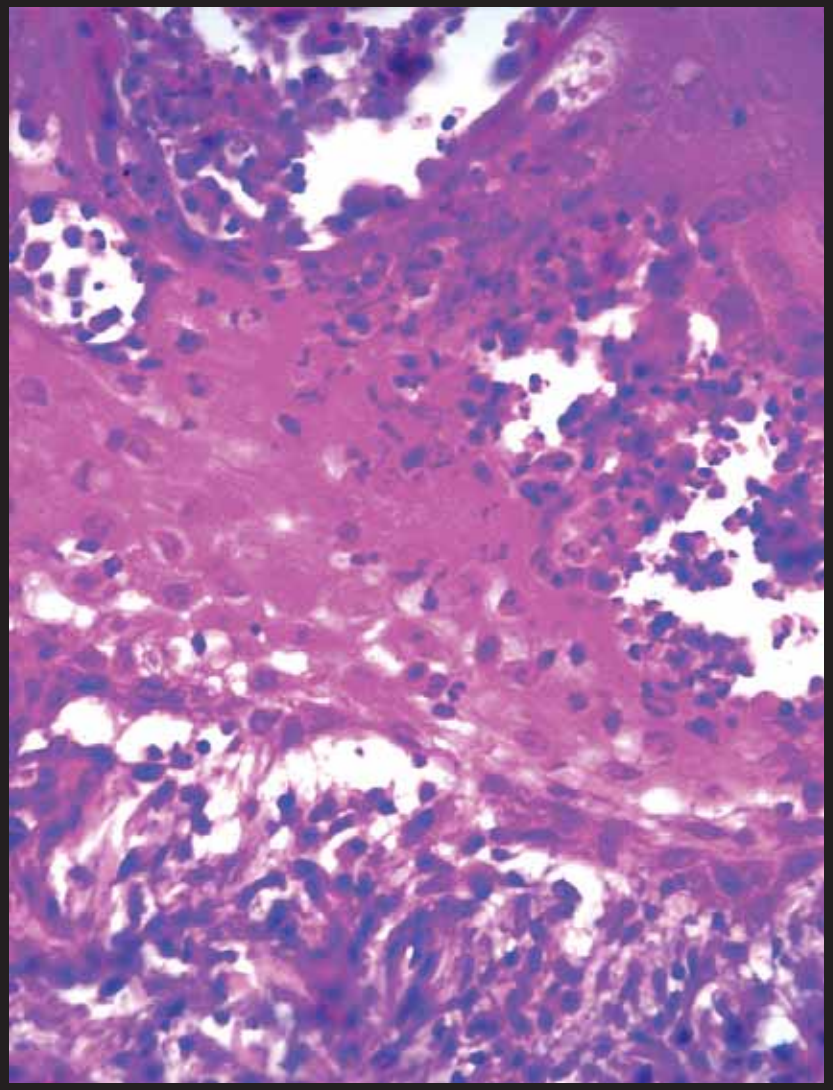


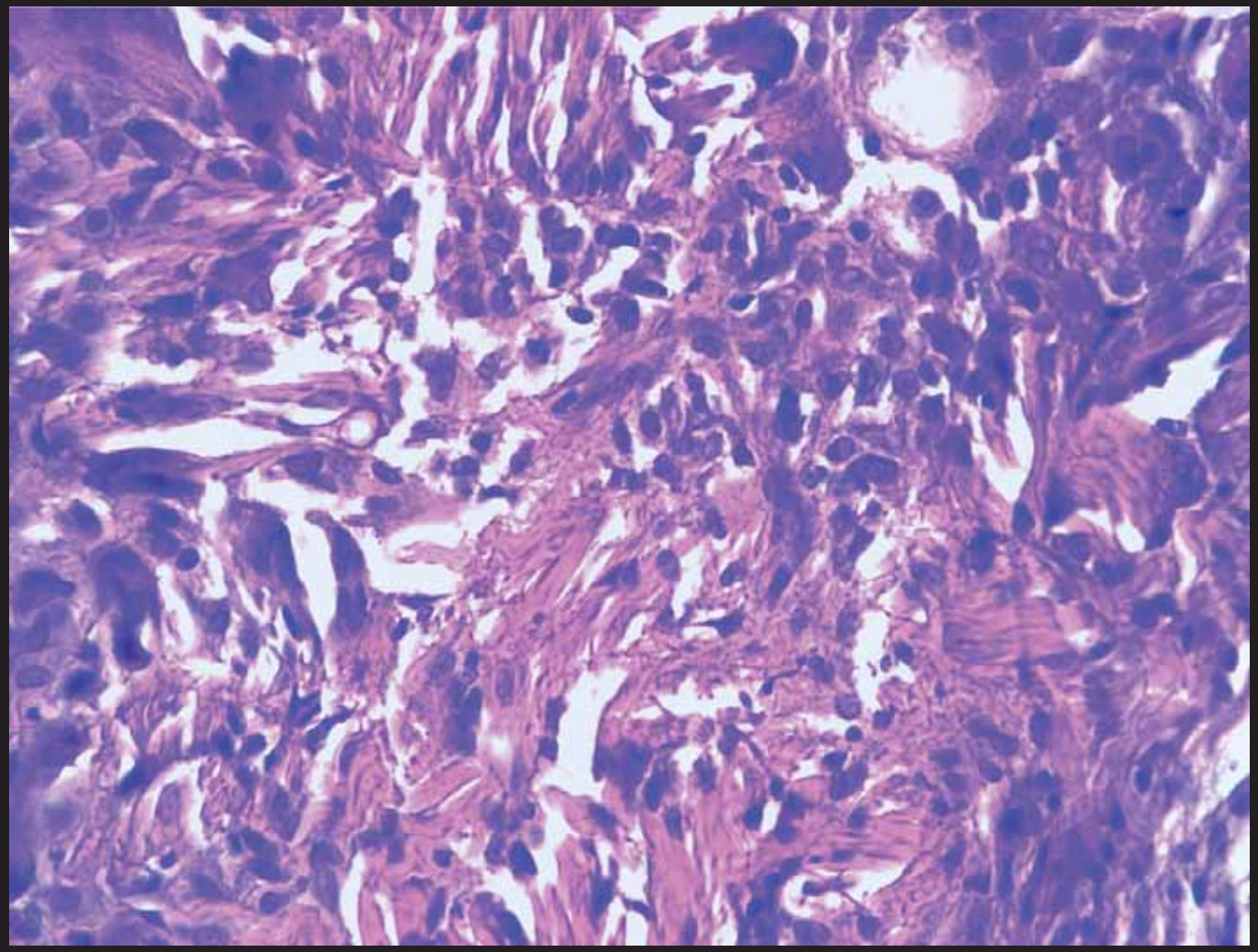






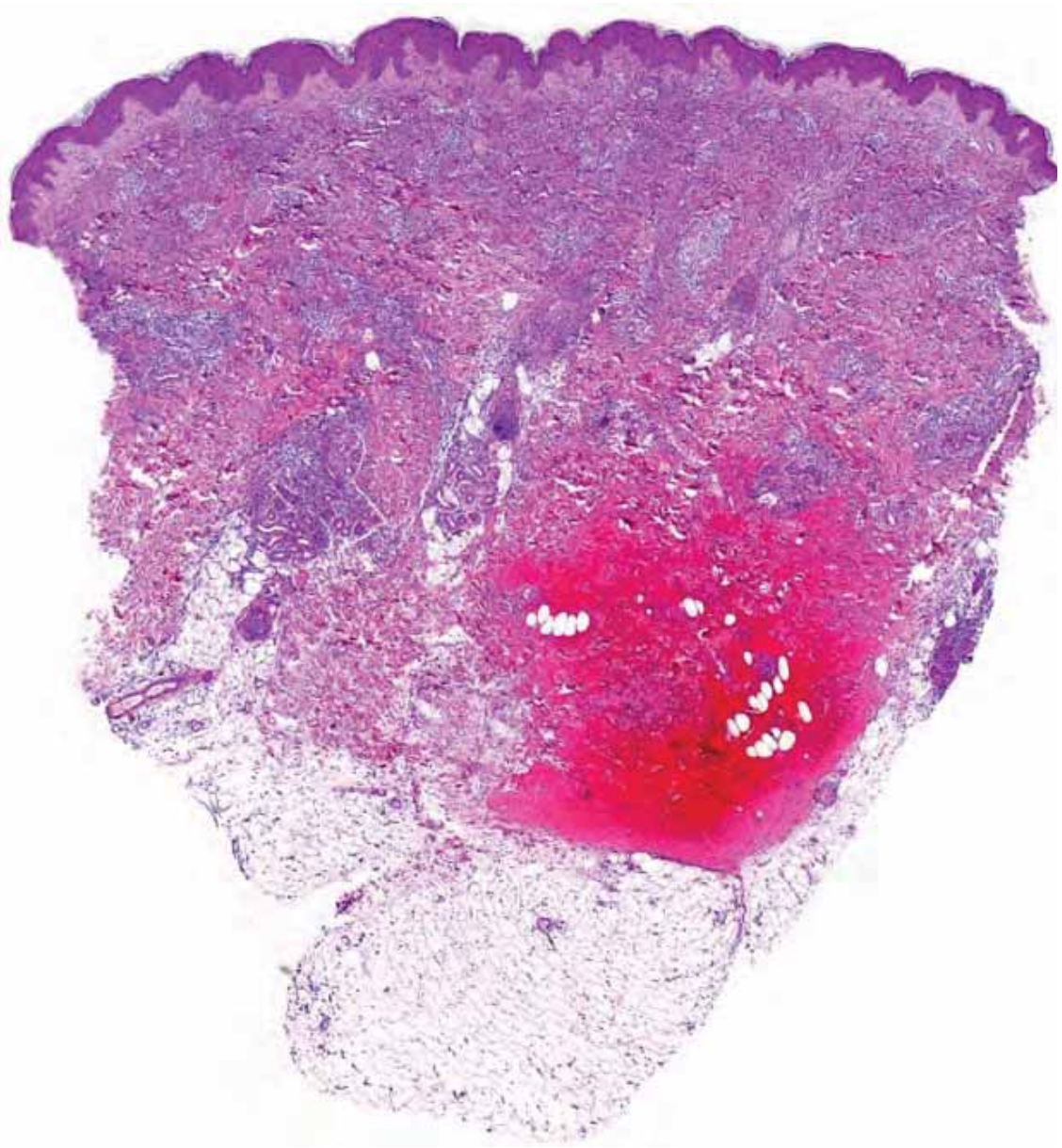


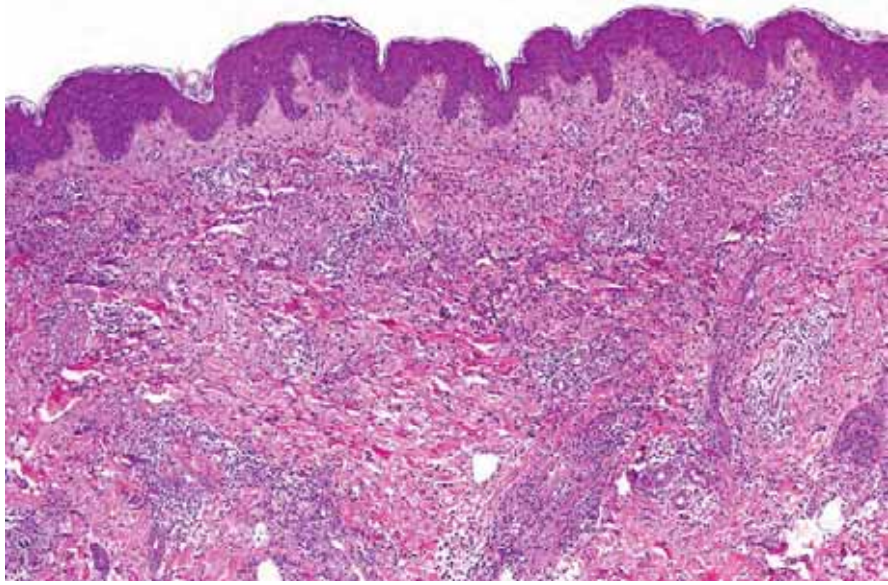


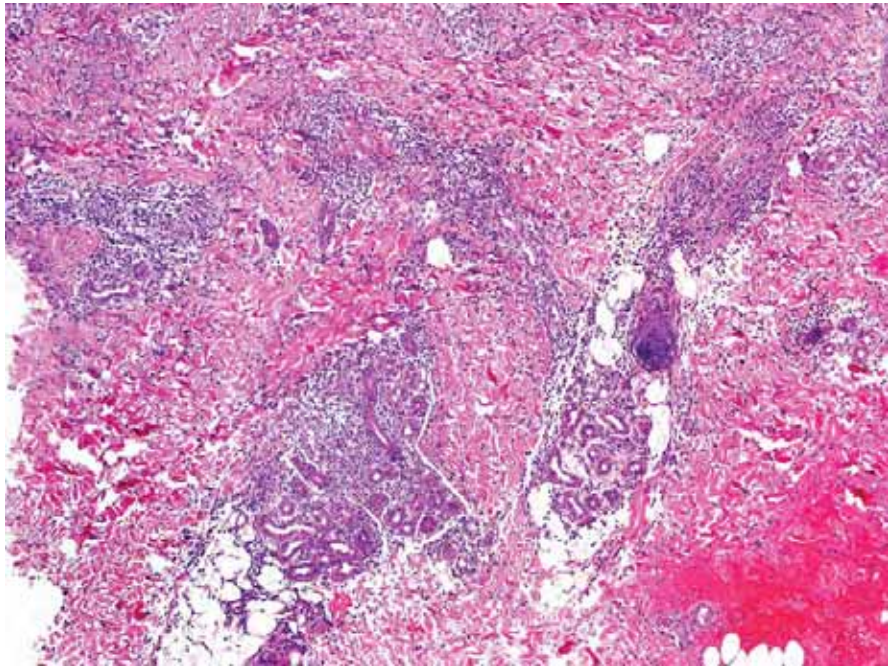
Dermatopathologic clue #2

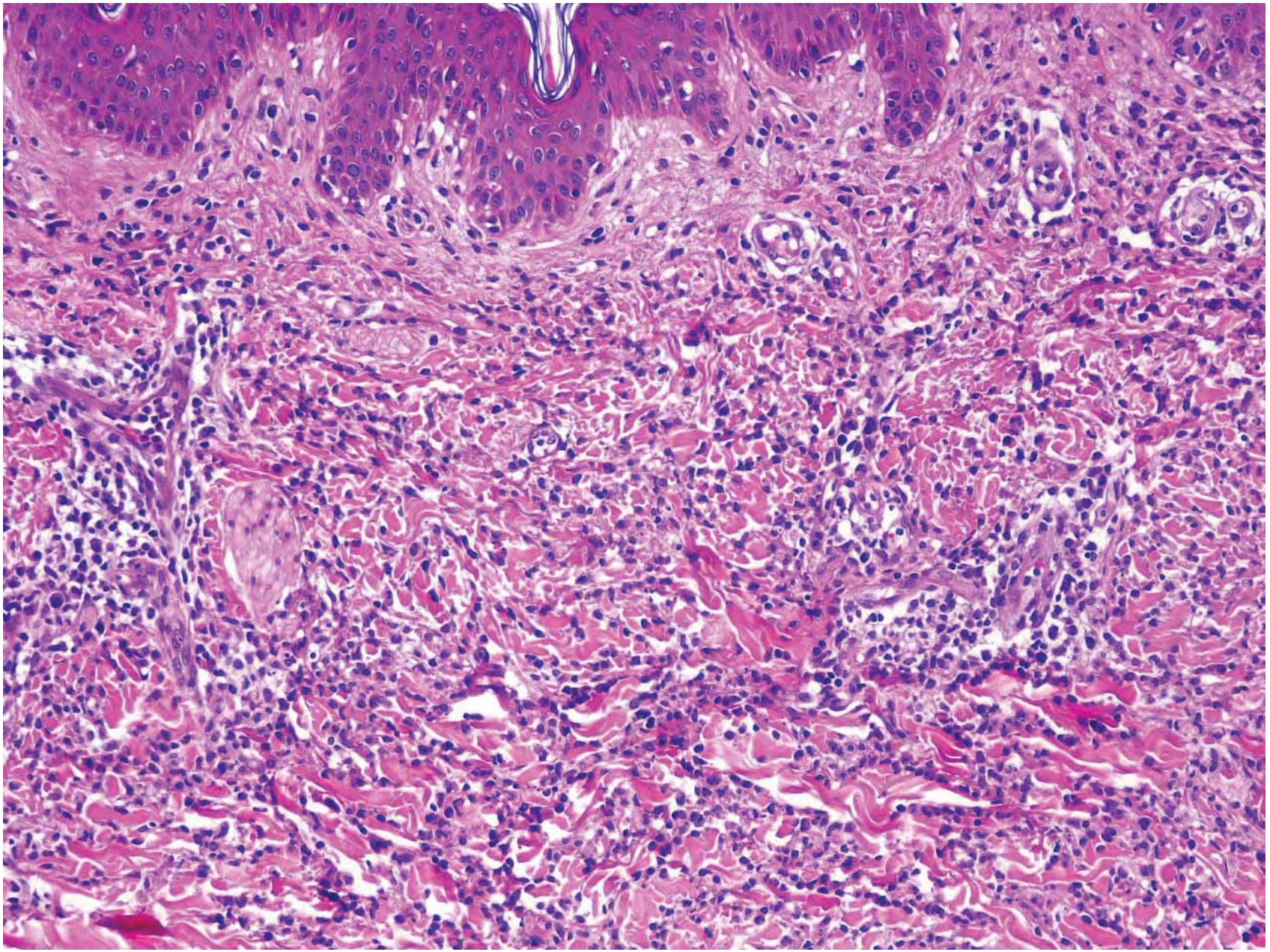
Perforating neutrophilic granulomatous dermatitis newborn

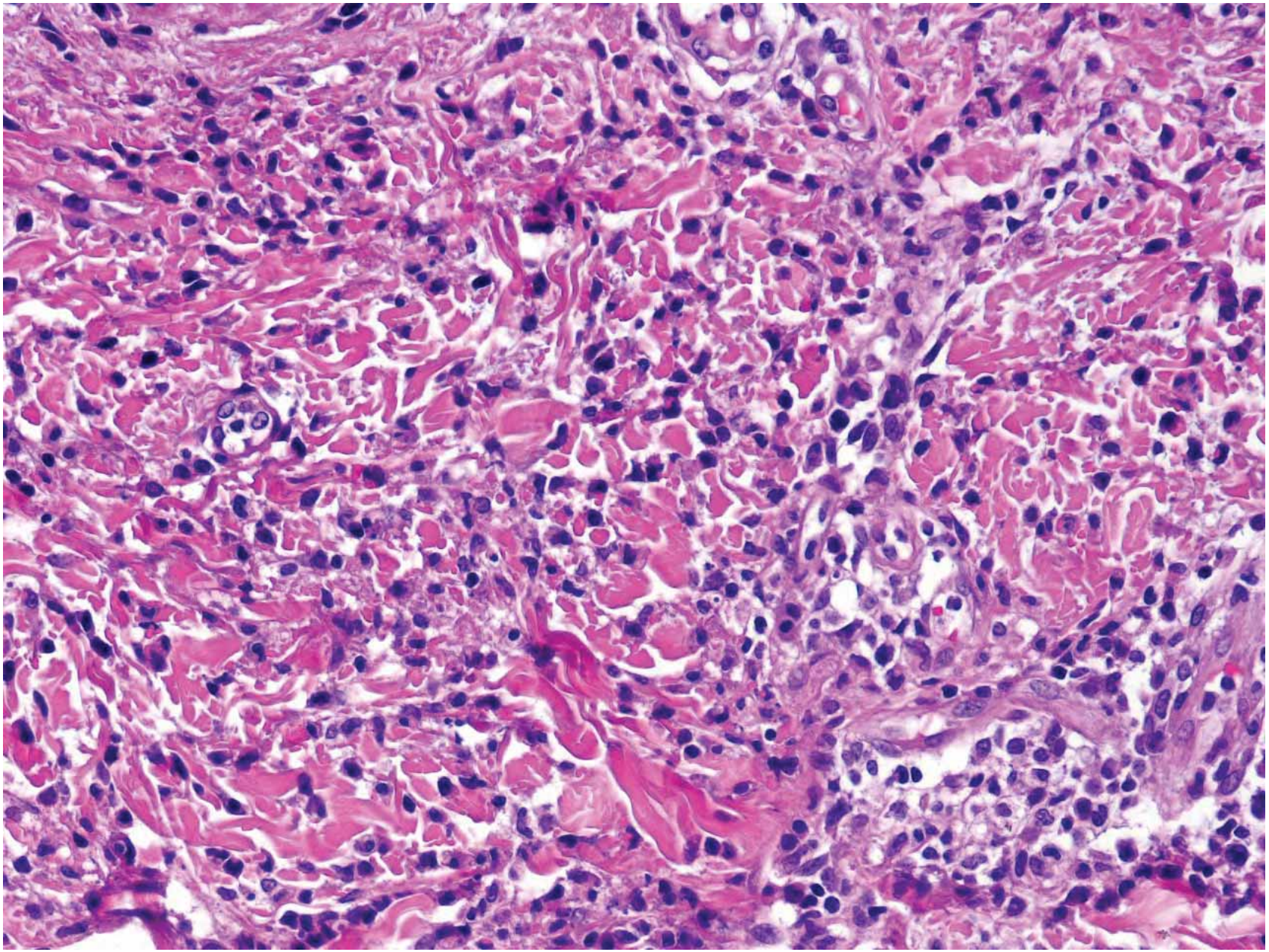
APLAID (PLCG2) – AID with immunodeficiency

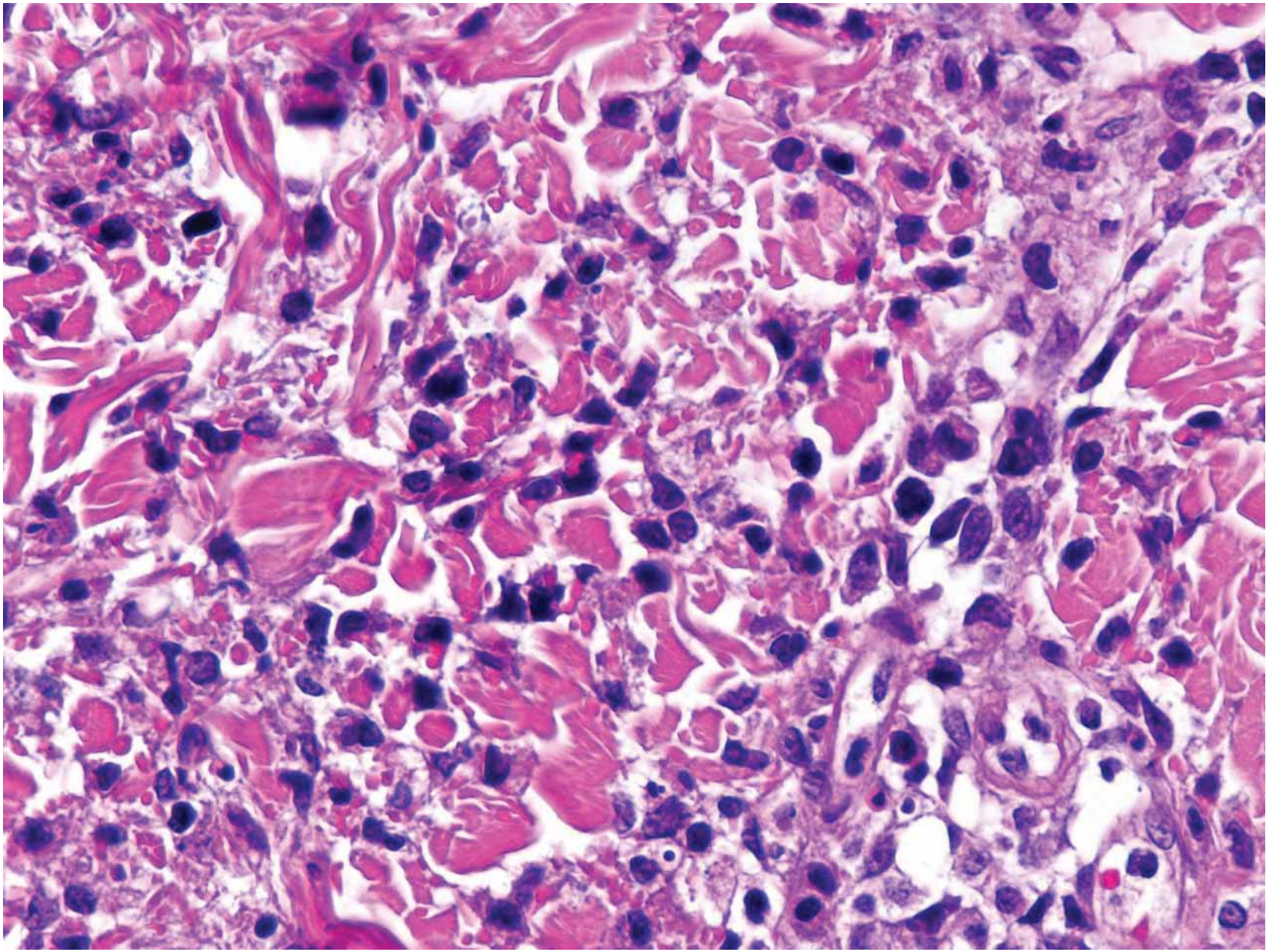


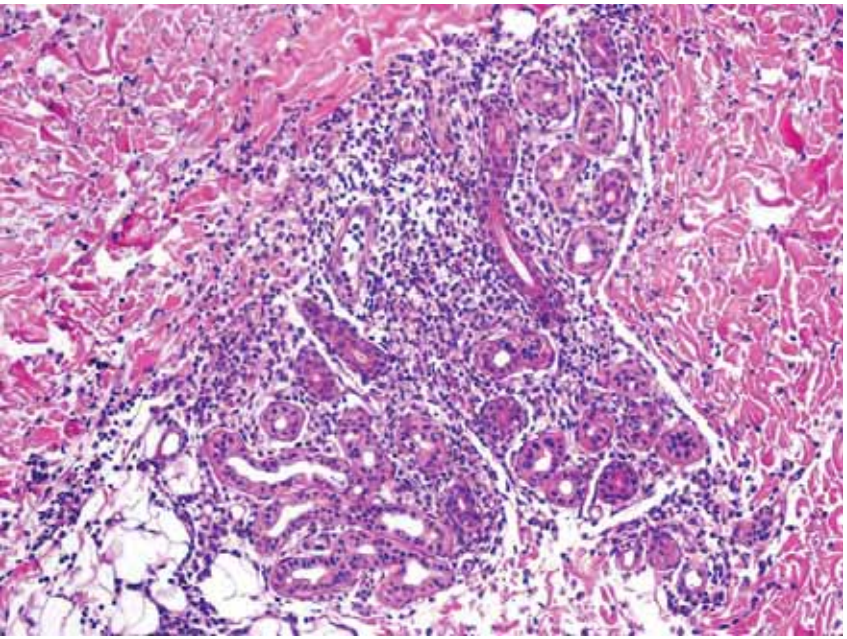


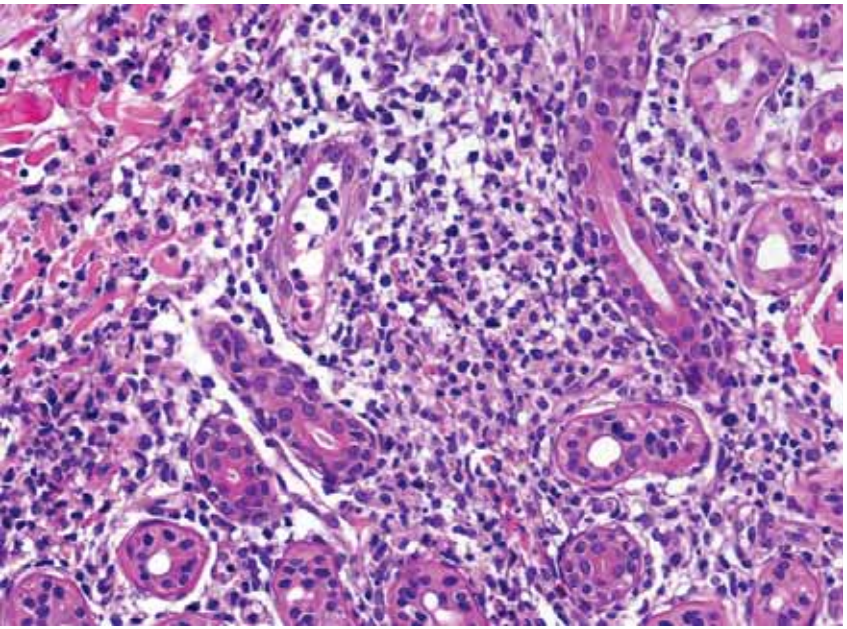


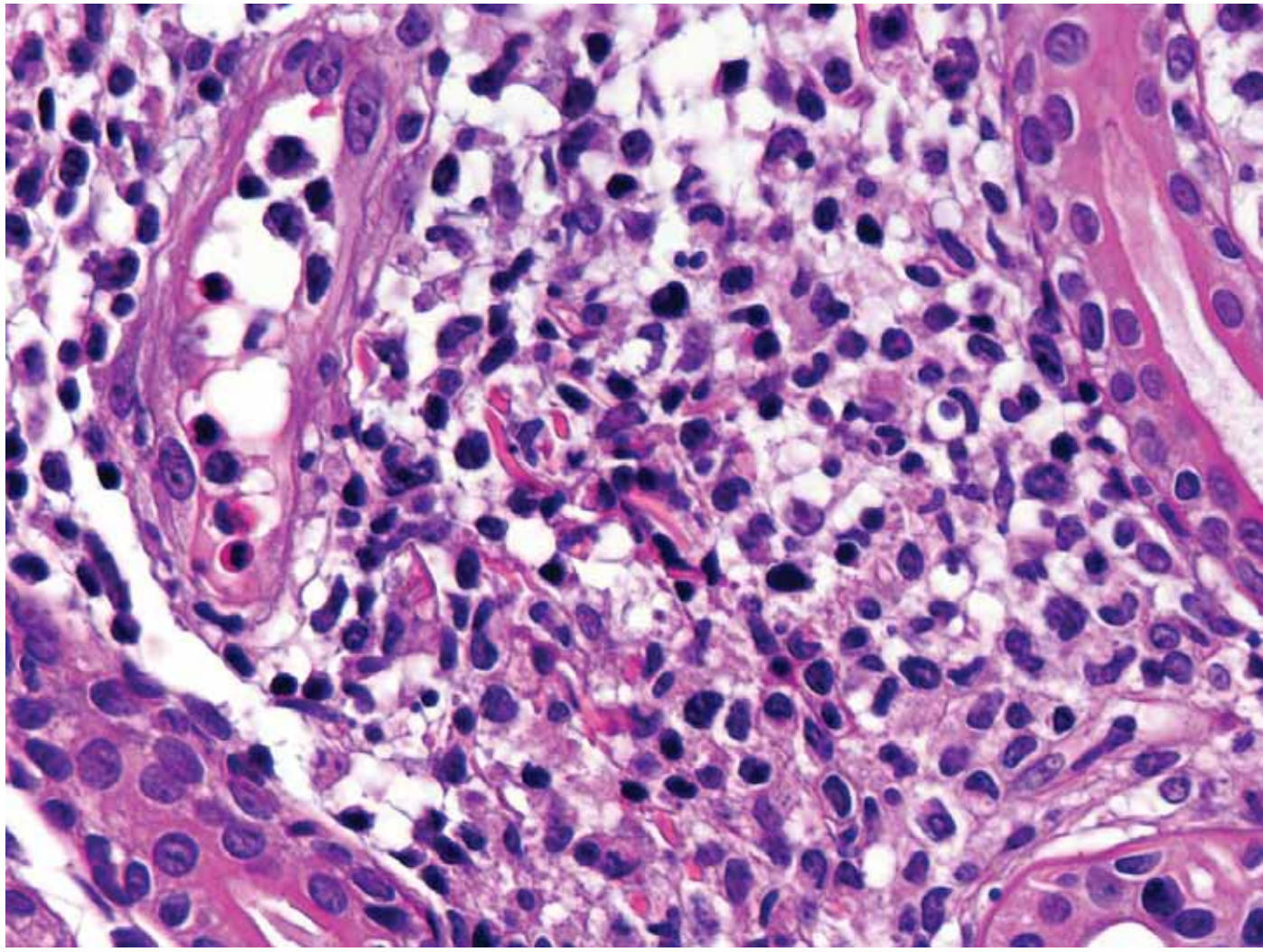


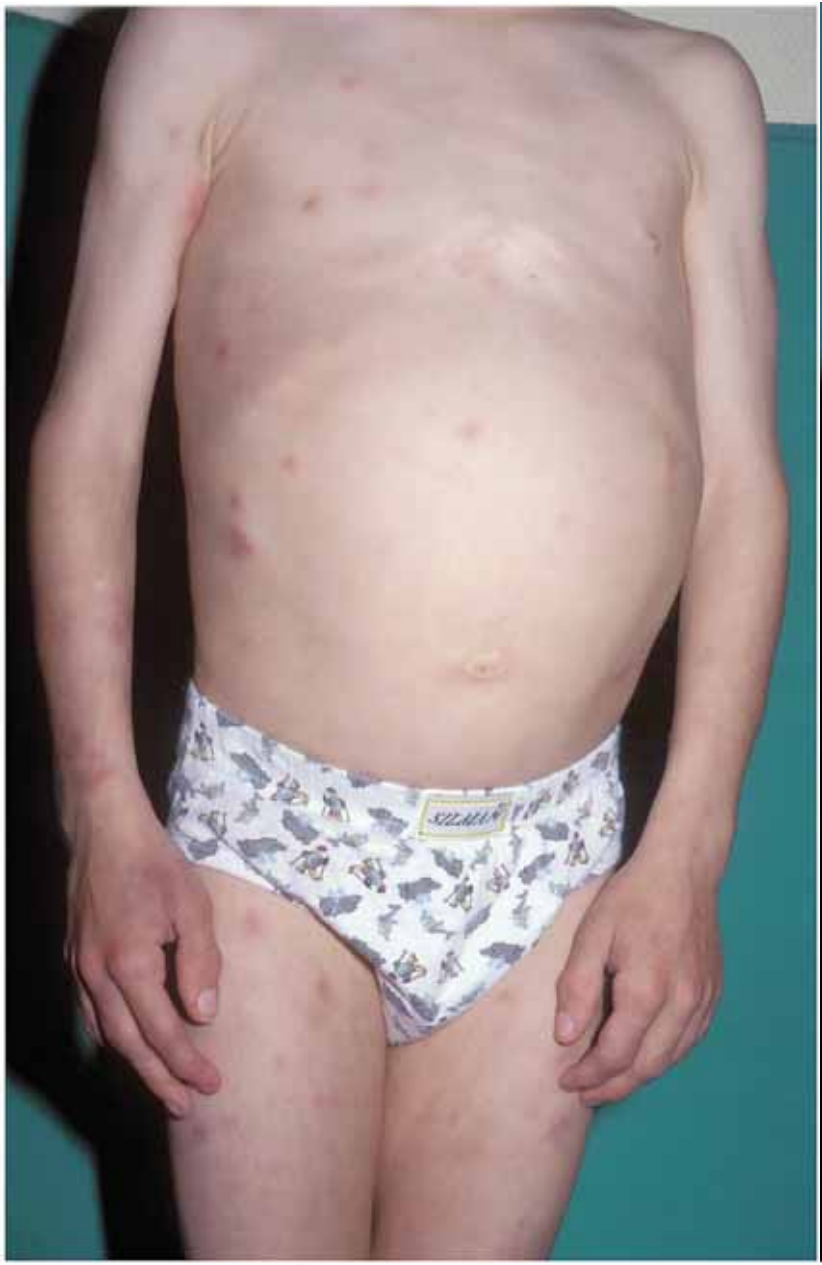


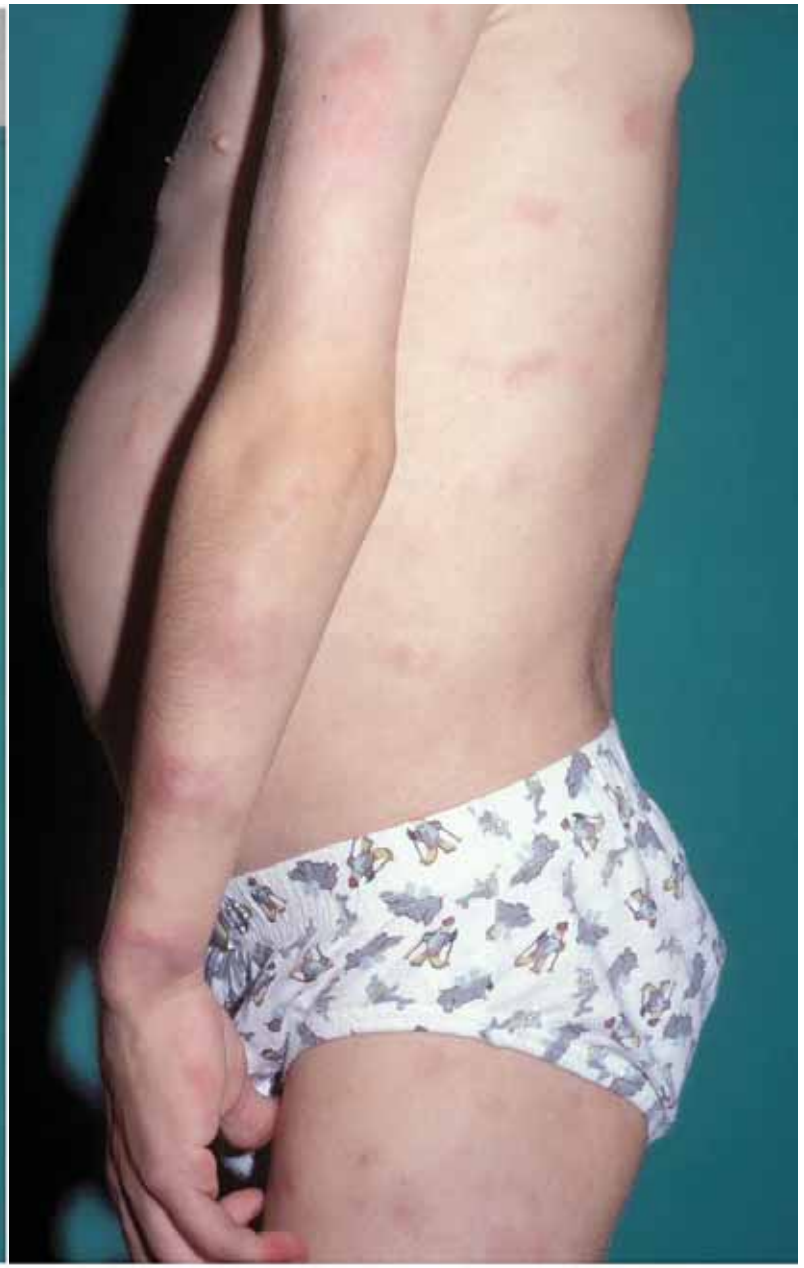


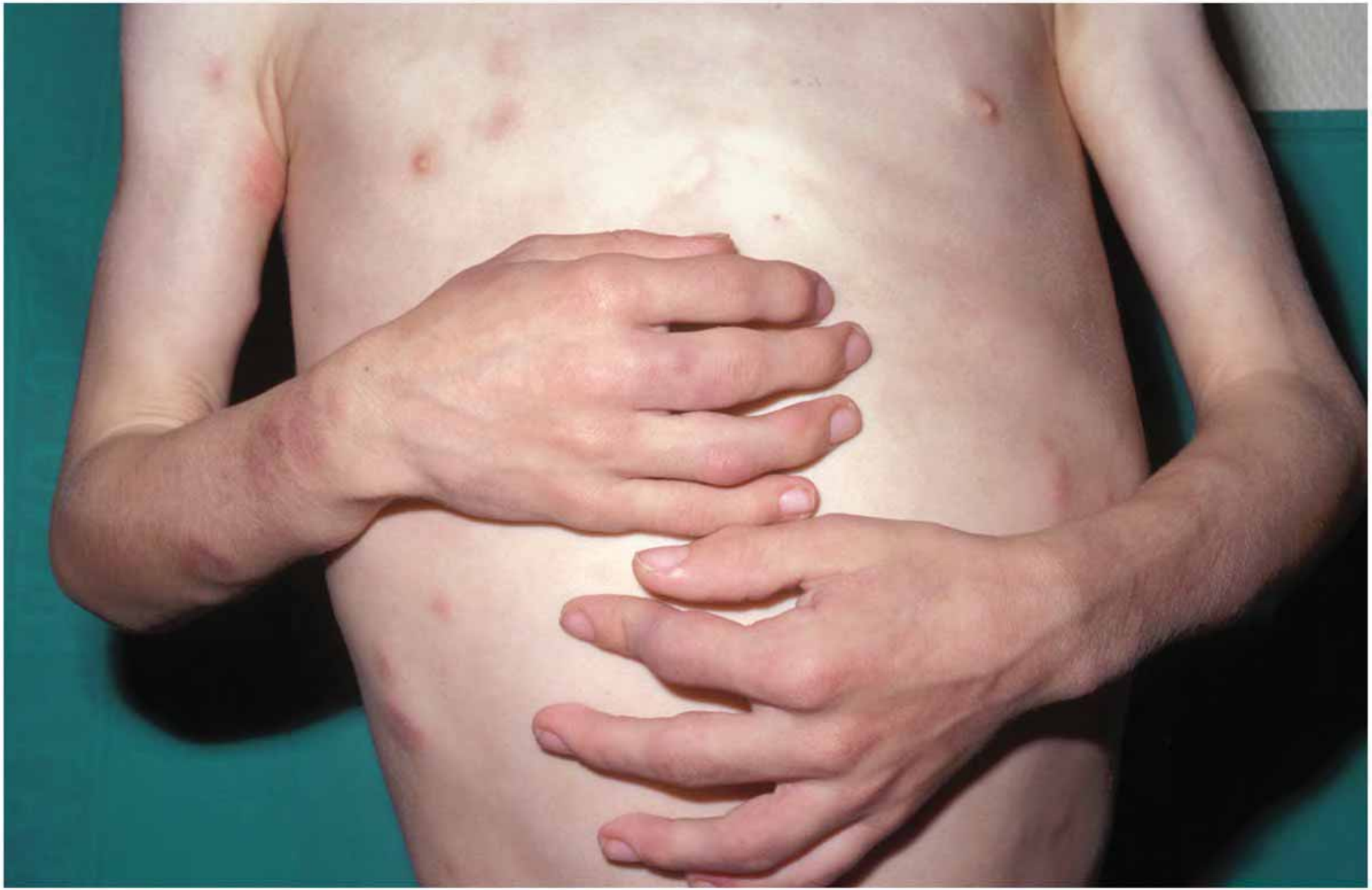


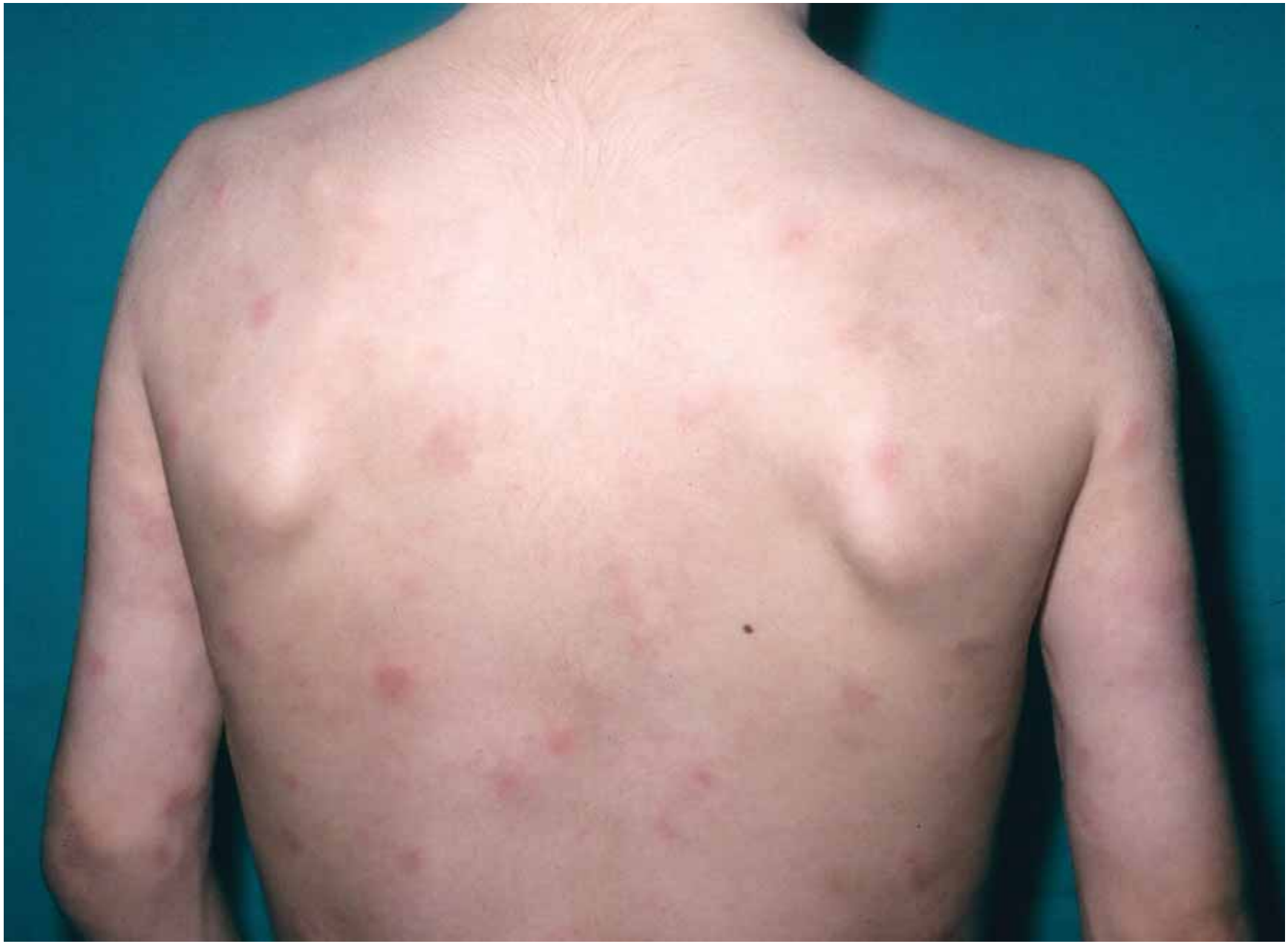


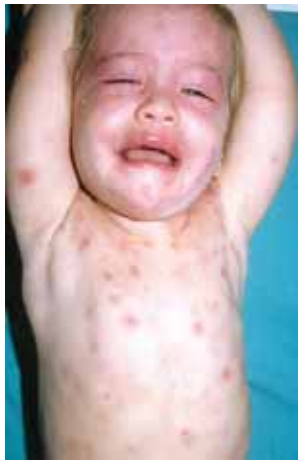


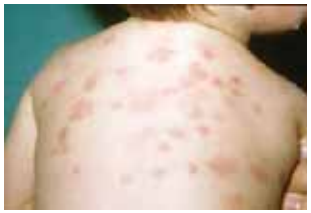


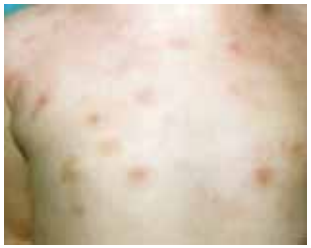


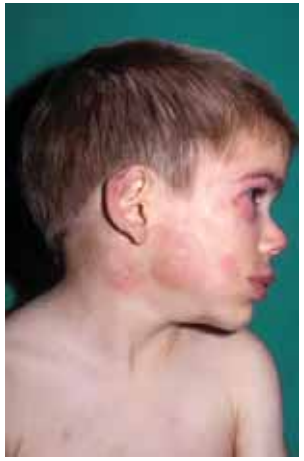










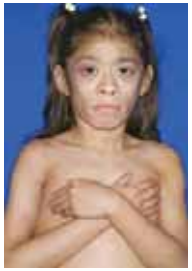


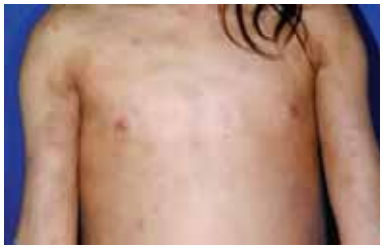
Chronic *a*typical *n*eutrophilic *d*ermatosis with *l*ipodystrophy and *e*levated temperature (CANDLE) syndrome

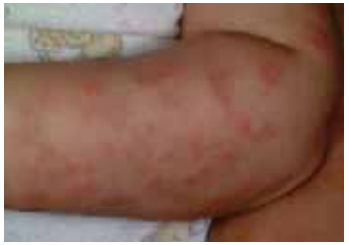
Antonio Torrelo, MD,[a] Sapna Patel, MD,[b] Isabel Colmenero, MD,[c] Dolores Gurbindo, MD,[d] Francisco Lendínez, MD,[c] Angela Hernández, MD,[a] Juan Carlos López-Robledillo, MD,[f] Ali Dadban, MD,[g] Luis Requena, MD,[h] and Amy S. Paller, MD[b]

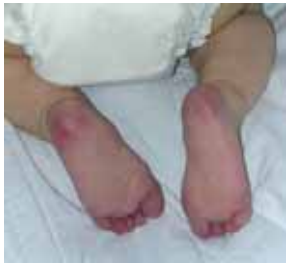
Madrid and Almería, Spain; Chicago, Illinois; and Amiens, France

Several syndromes manifest as recurrent daily fevers, skin lesions, and multisystem inflammation. We describe 4 patients with early-onset recurrent fevers, annular violaceous plaques, persistent violaceous eyelid swelling, low weight and height, lipodystrophy, hepatomegaly, and a range of visceral inflammatory manifestations. Laboratory abnormalities included chronic anemia, elevated acute-phase reactants, and raised liver enzymes. Histopathologic examination of lesional skin showed atypical mononuclear infiltrates of myeloid lineage and mature neutrophils. Our patients have a distinctive early-onset, chronic inflammatory condition with atypical or immature myeloid infiltrates in the skin. We propose the acronym CANDLE (chronic *a*typical *n*eutrophilic *d*ermatosis with *l*ipodystrophy and *e*levated temperature) syndrome for this newly described disorder, which is probably genetic in origin. (J Am Acad Dermatol 2010;62:489-95.)









*C*hronic *a*typical *n*eutrophilic *d*ermatosis with *l*ipodystrophy and *e*levated temperature (CANDLE) syndrome

Antonio Torrelo, MD,[a] Sapna Patel, MD,[b] Isabel Colmenero, MD,[c] Dolores Gurbindo, MD,[d] Francisco Lendínez, MD,[e] Angela Hernández, MD,[a] Juan Carlos López-Robledillo, MD,[f] Ali Dadban, MD,[g] Luis Requena, MD,[h] and Amy S. Paller, MD[b]

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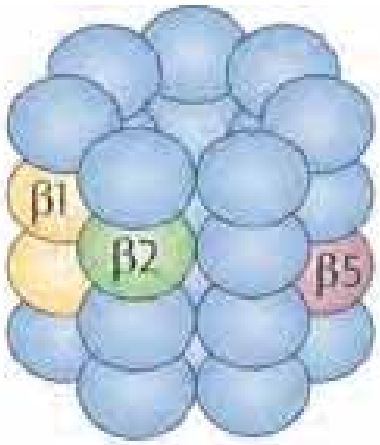
Chronic *a*typical *n*eutrophilic *d*ermatosis with *l*ipodystrophy and *e*levated temperature (CANDLE) syndrome

Antonio Torrelo, MD,[a] Sapna Patel, MD,[b] Isabel Colmenero, MD,[c] Dolores Gurbindo, MD,[d] Francisco Lendínez, MD,[e] Angela Hernández, MD,[a] Juan Carlos López-Robledillo, MD,[f] Ali Dadban, MD[g]

- First AID with lipodystrophy
- Firstly described human proteasome pathology
- First human disorder directly related to IFN1
- First digenic immunological disorder
- First AID targeted with JAKis

Proteasome - inmunoproteasome

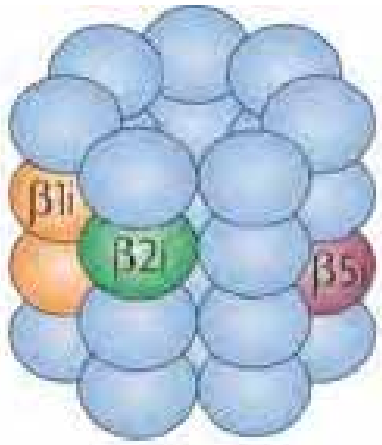


Constitutive proteasome

β1 (PSMB6, Y, δ)

β2 (PSMB7, Z, MC14)

β5 (PSMB5, X, MB1, ε)



Immunoproteasome

β1i (PSMB9, LMP2)

β2i (PSMB10, LMP10, MECL1)

β5i (PSMB8, LMP7)

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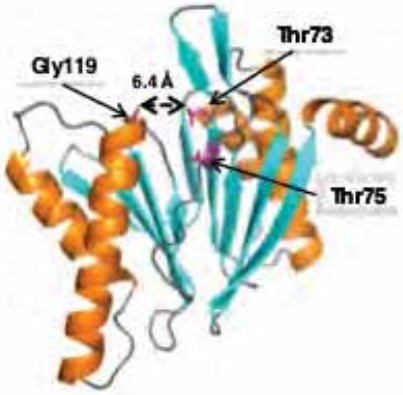
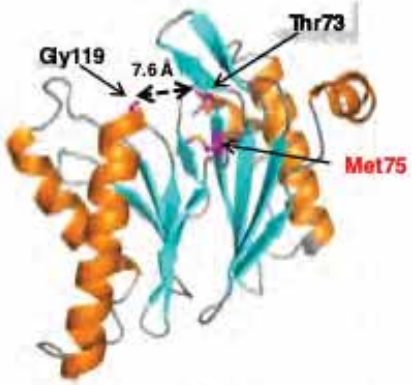


PSMB8 (wild-type)



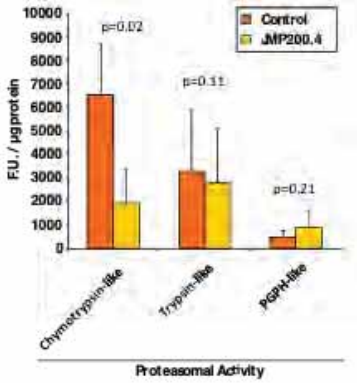
Mutant PSMB8 (Thr75Met)

Mutant PSMB8 (Cys135X)

Normal function

↓ catalytic activity

i-proteasomes do not ensemble



Interferonopathies

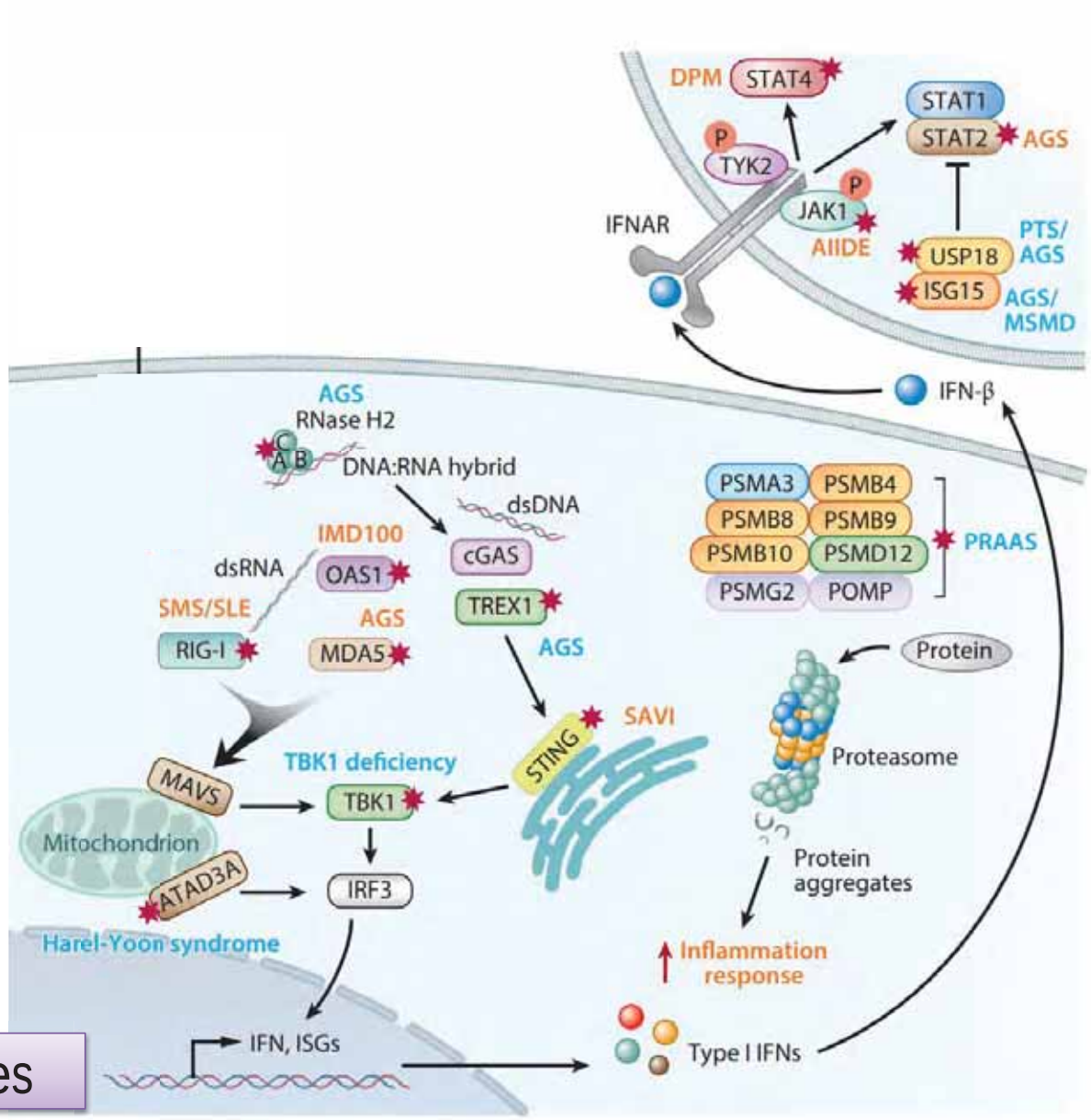
Constitutional release of type I IFNs

Neutrophilic dermatosis

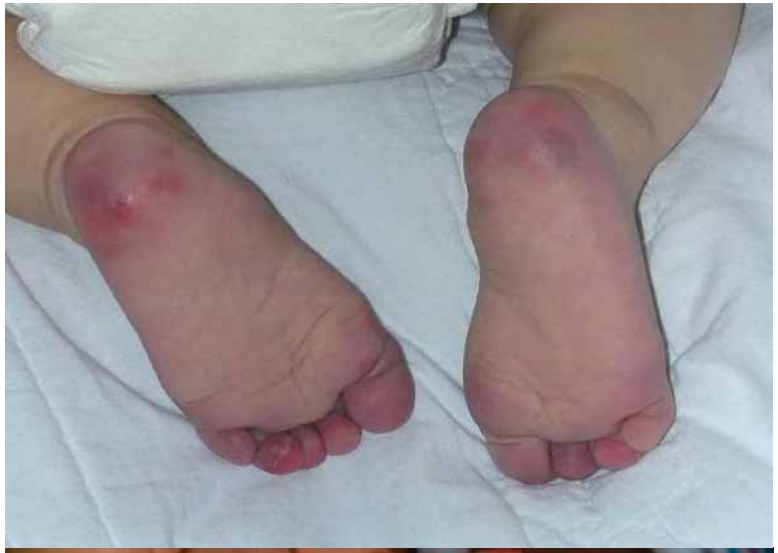
Vasculopathy

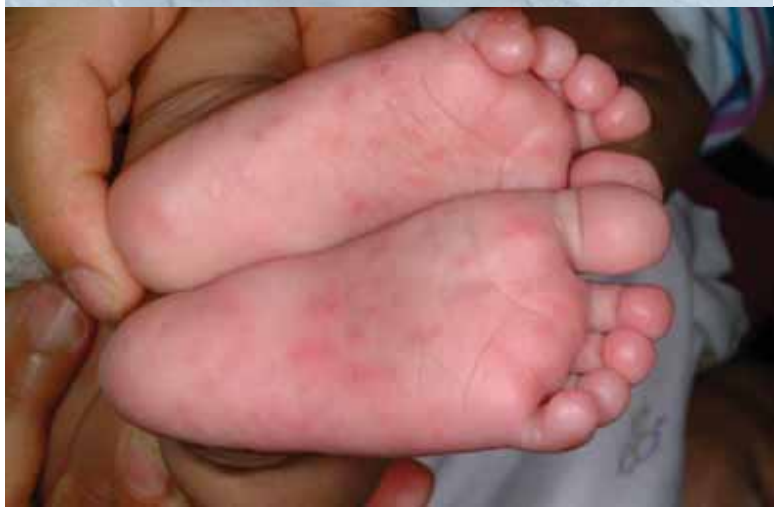
Neutrophilic panniculitis

Neutrophils & macrophages

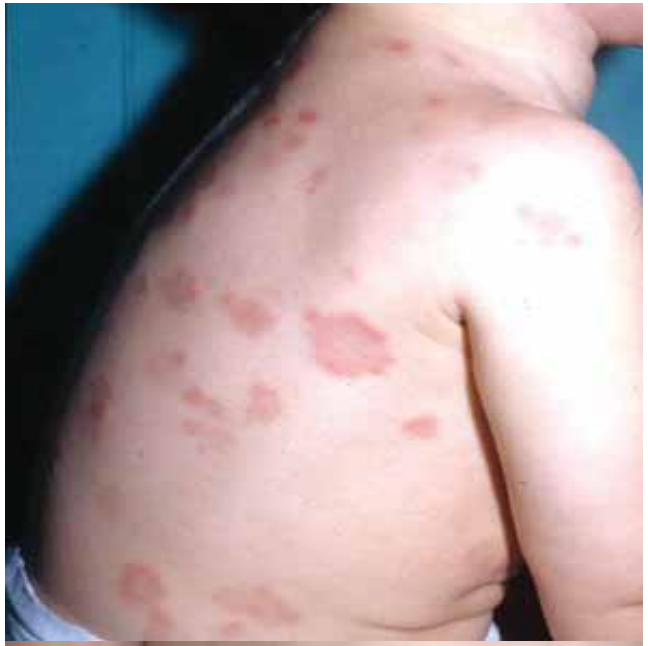


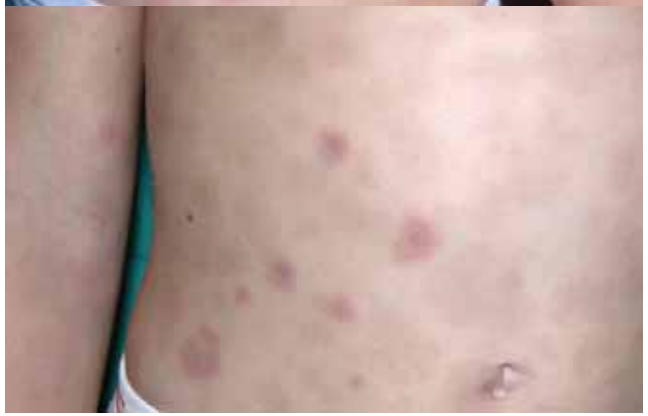
Pernio in infancy



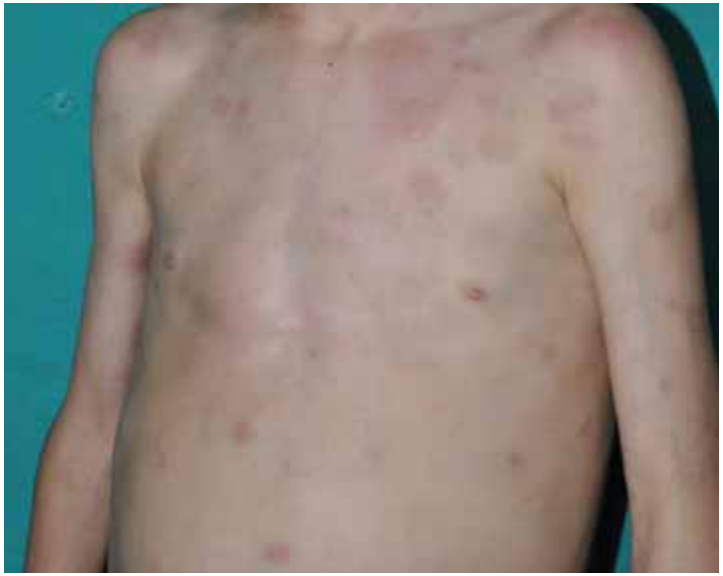


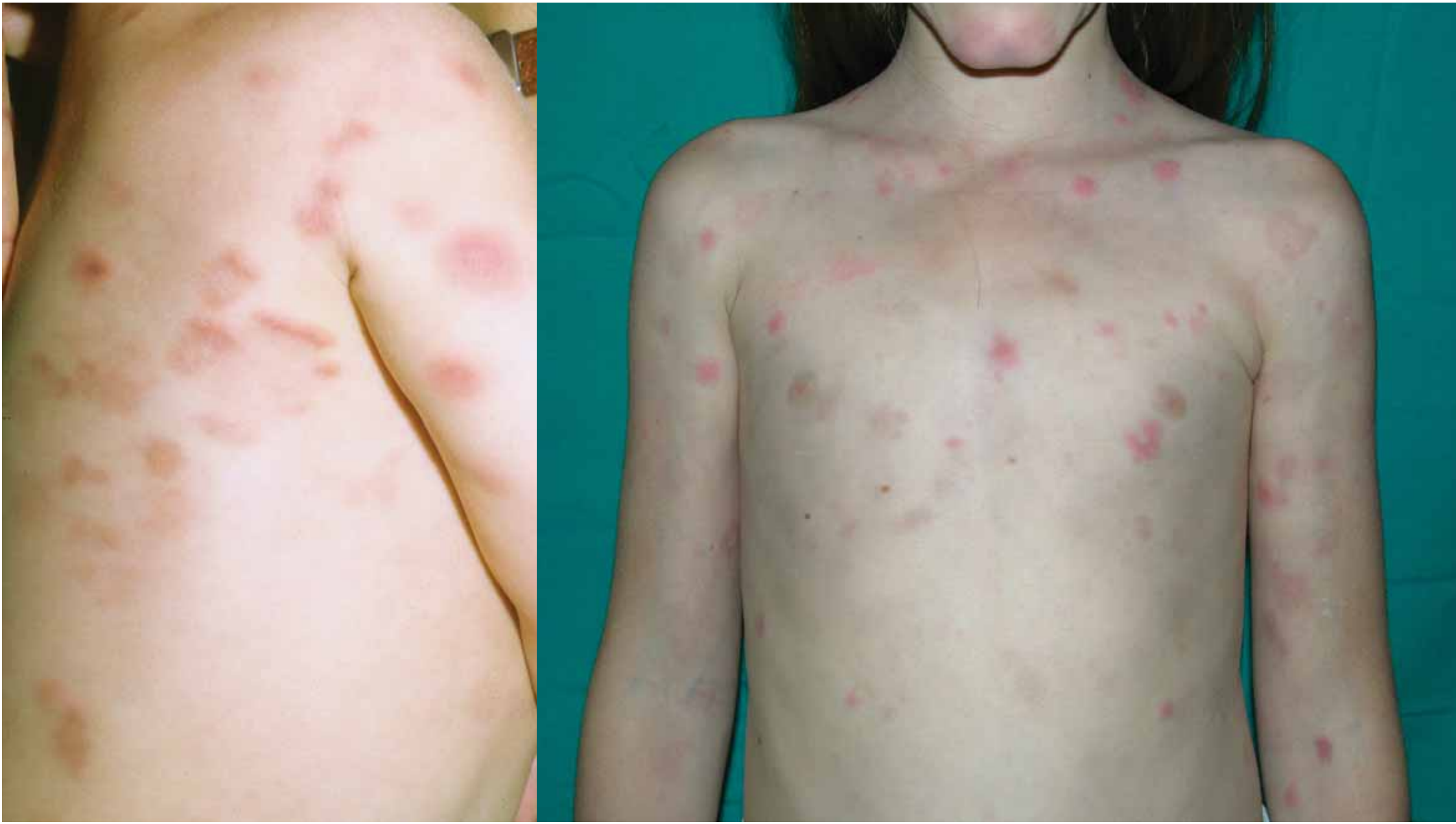
Purpuric rash

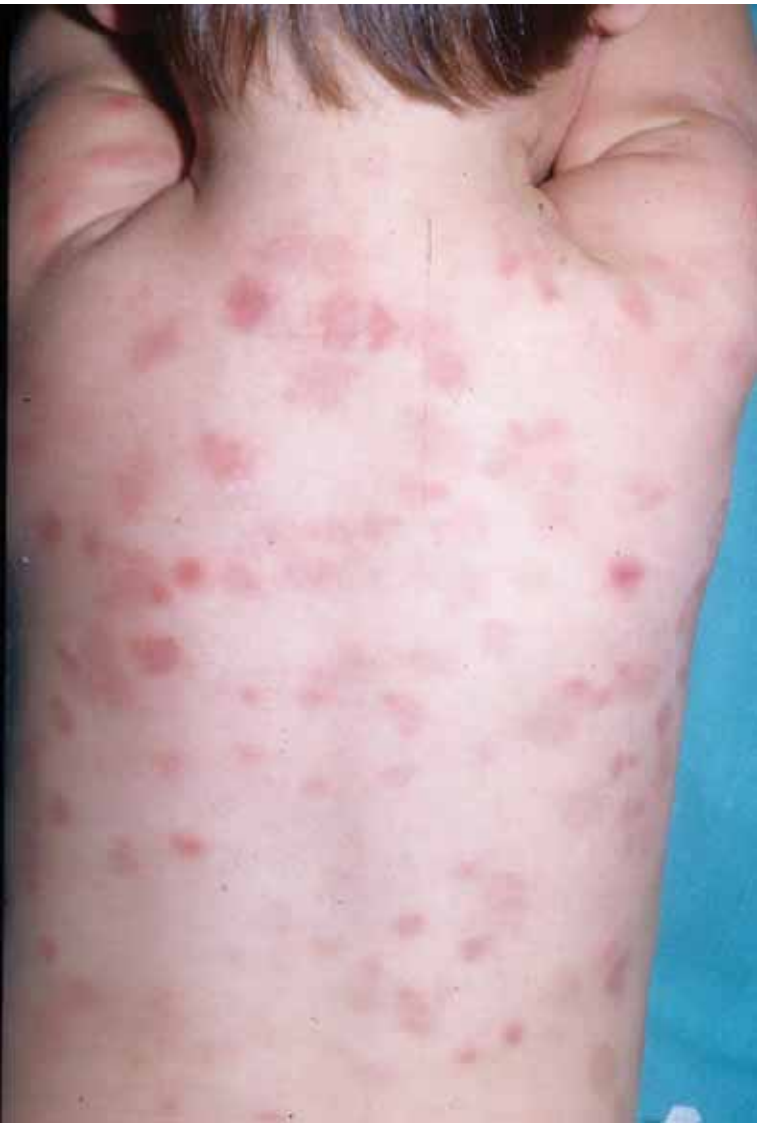


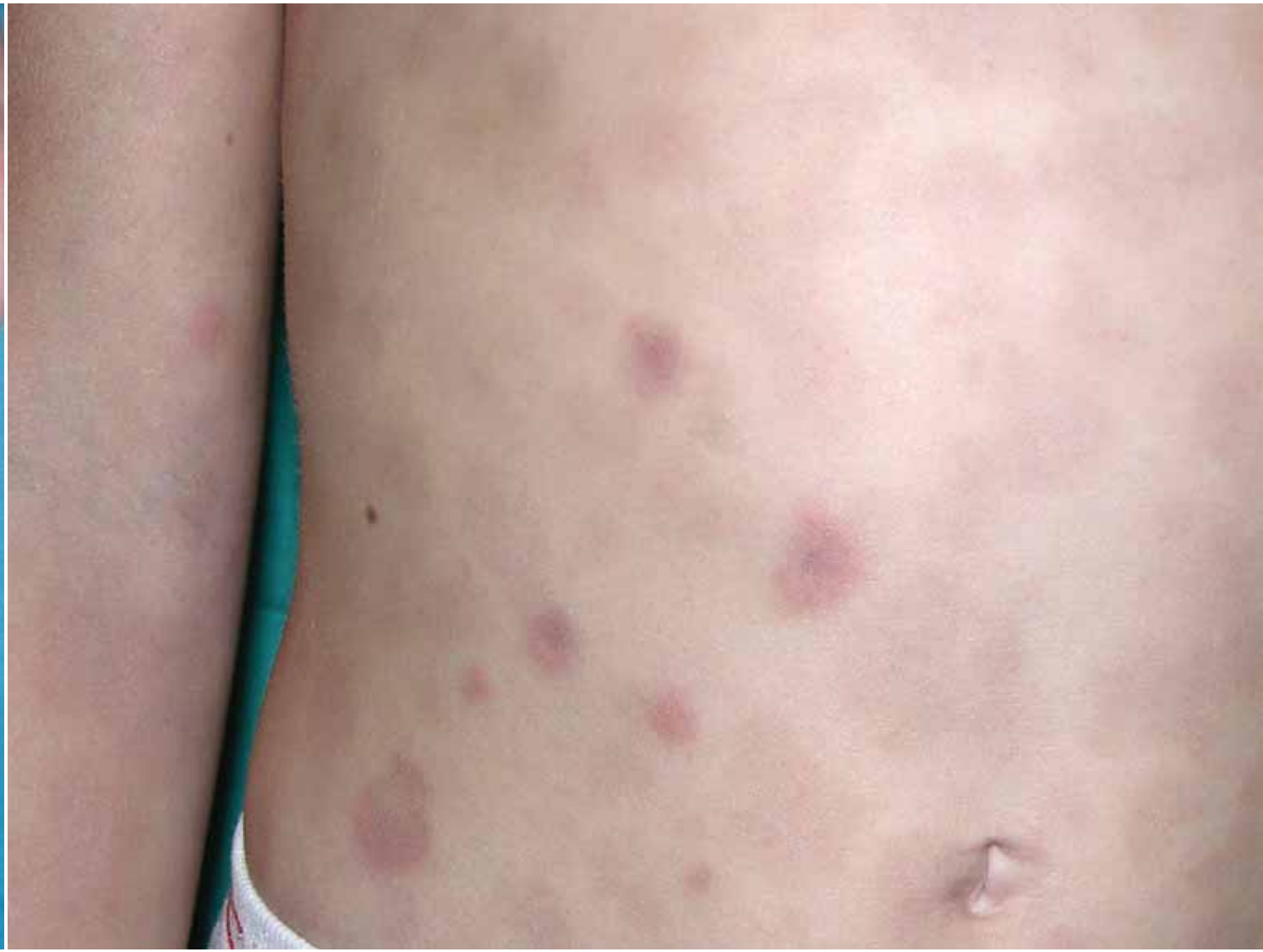


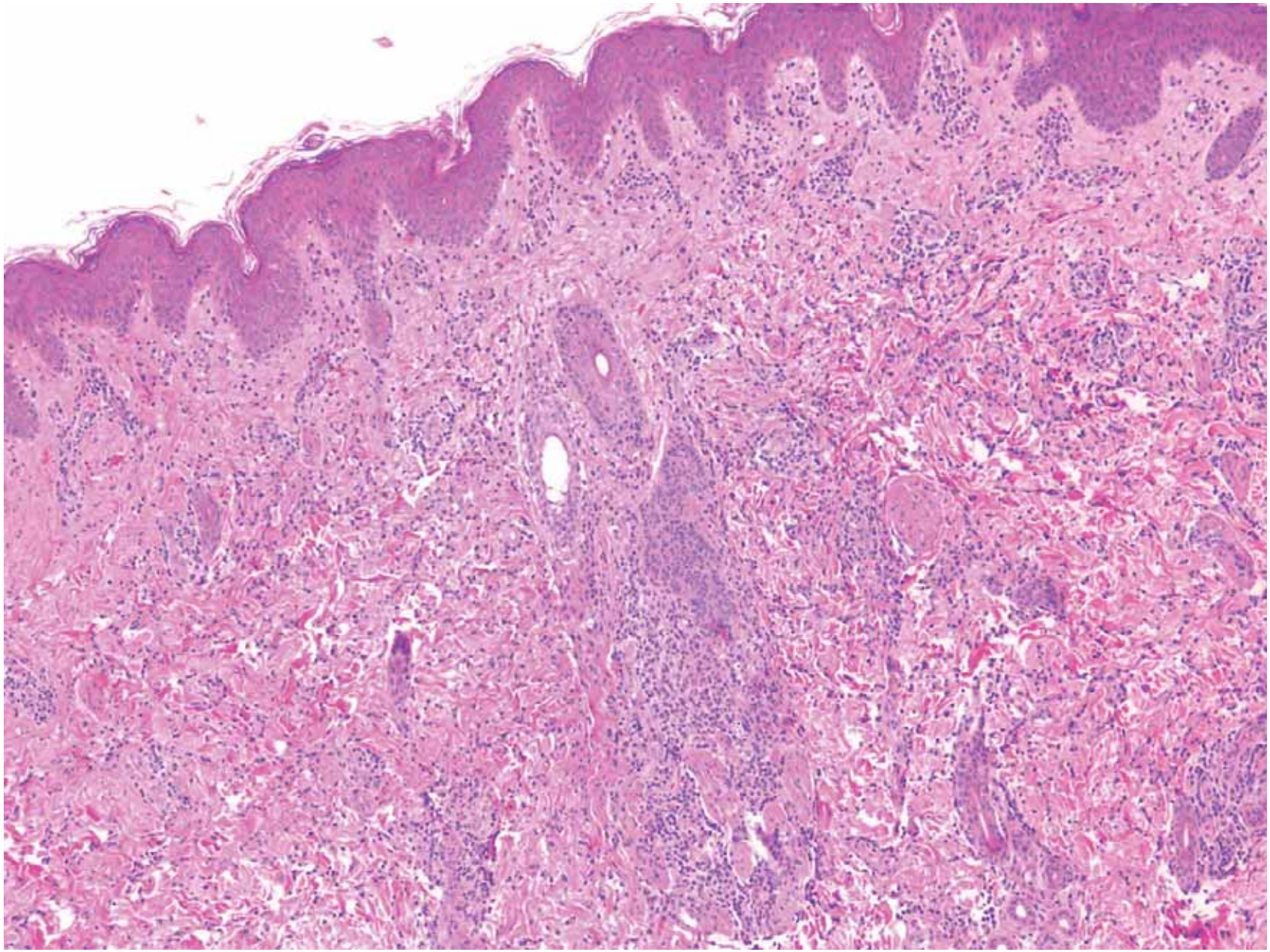
Lipodystrophy

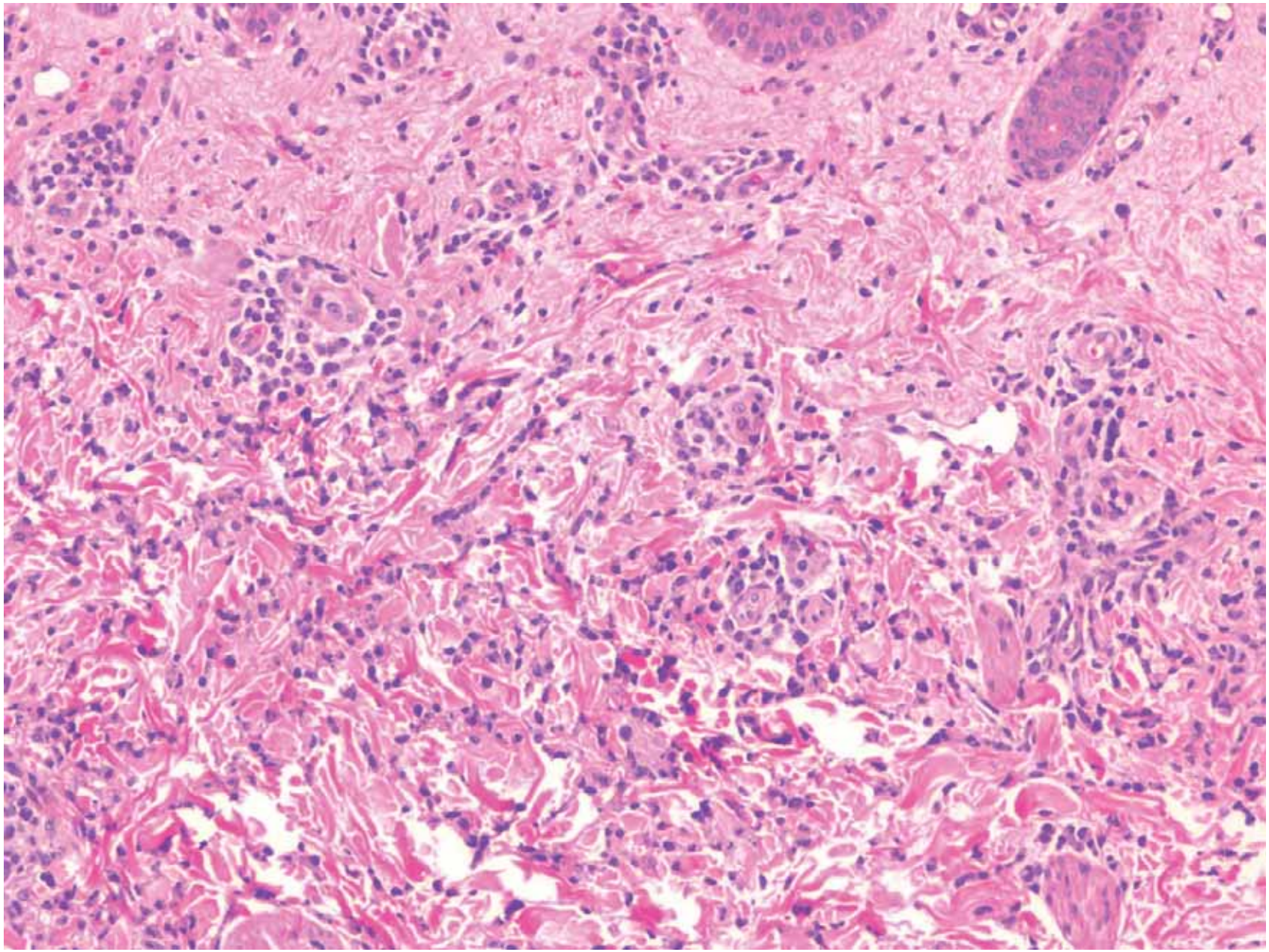


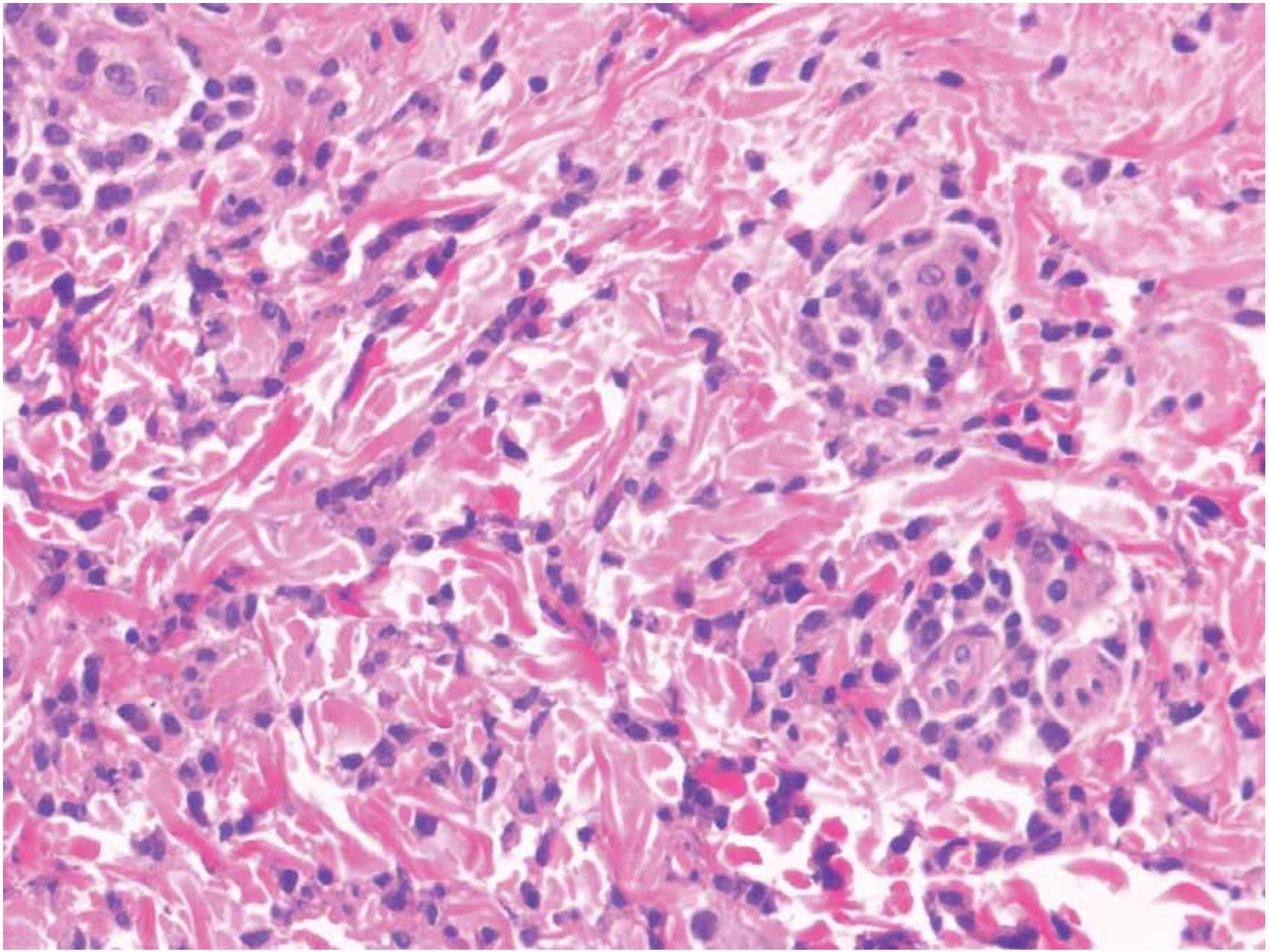


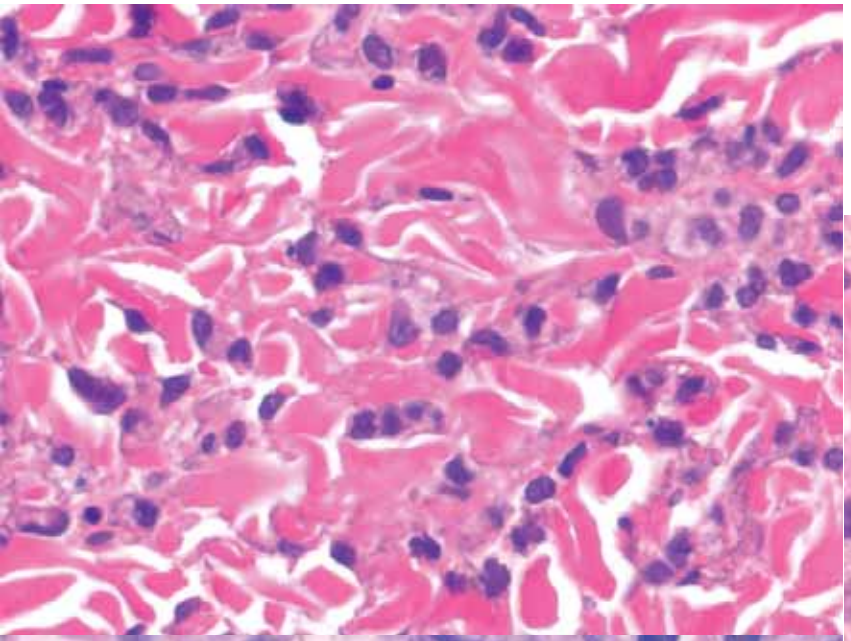


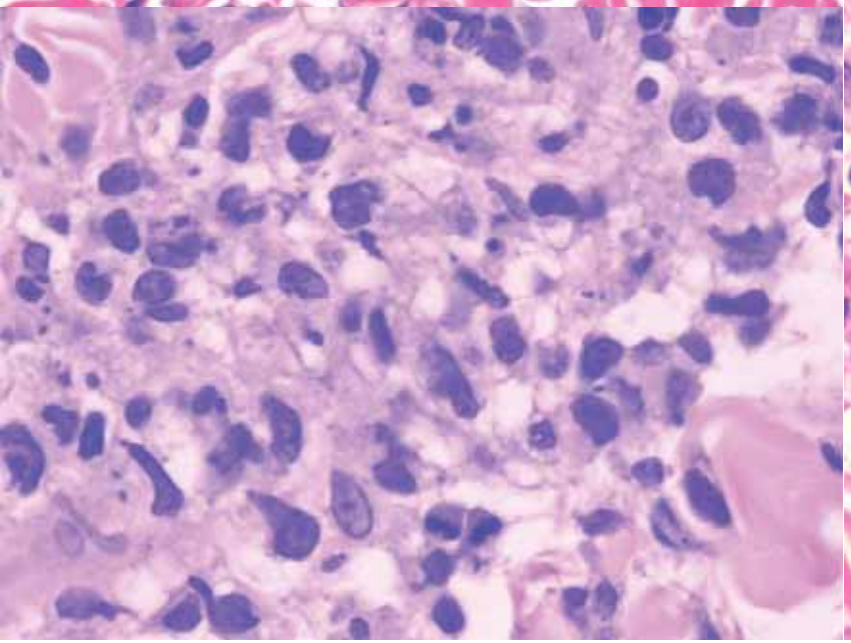


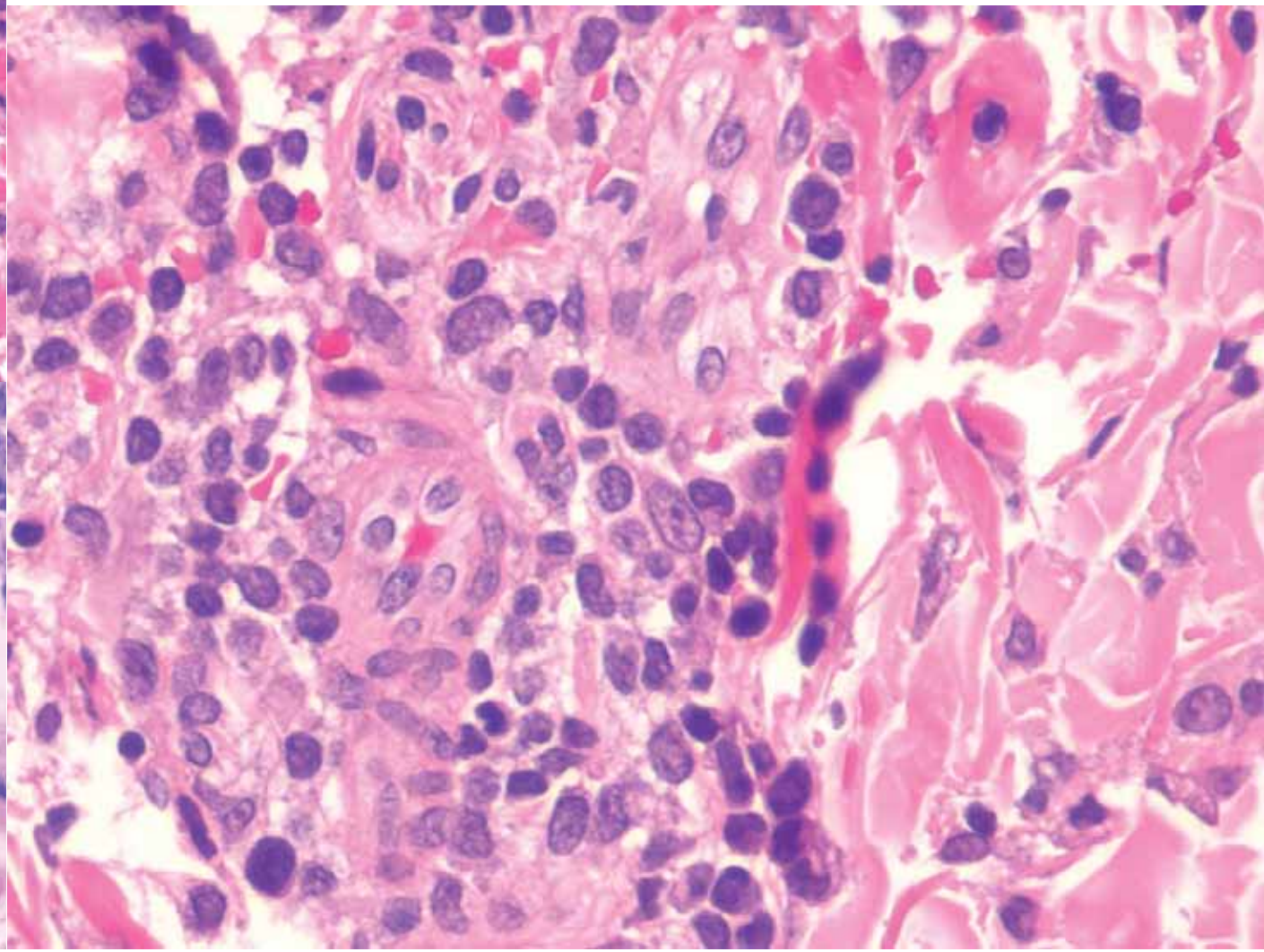


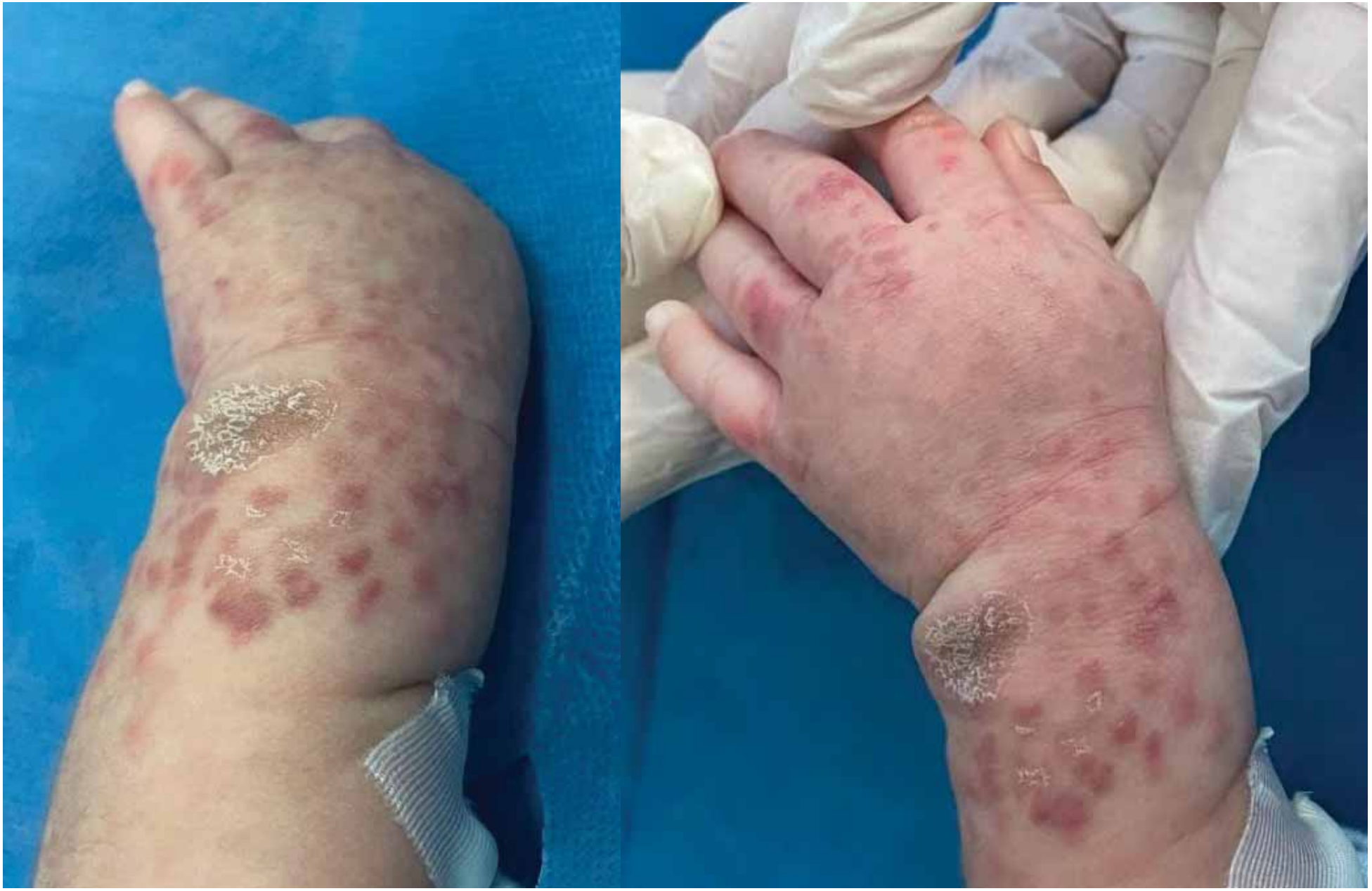












RESULT

***PSMB8*(NM_148919.4):c.224C>T (p.Thr75Met)**, missense variant, homozygous, classified as **PATHOGENIC**, associated with autosomal recessive Proteasome-associated autoinflammatory syndrome 1.

ADDITIONAL FINDINGS

No relevant additional findings in association to the reported clinical information were identified.

RESULT INTERPRETATION / RECOMMENDATIONS

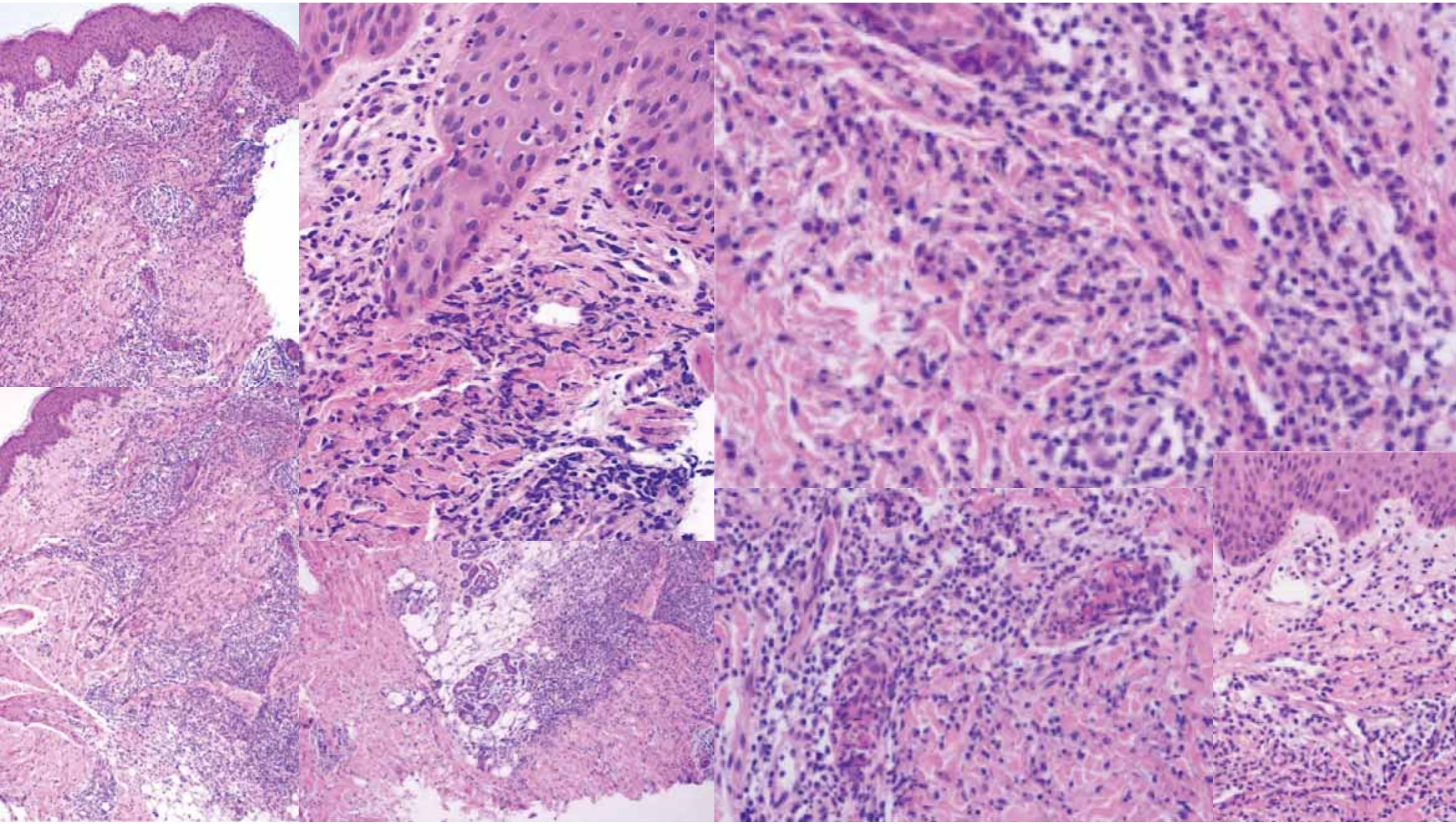
A pathogenic variant in the *PSMB8* gene has been identified in the homozygous state, associated with autosomal recessive Proteasome-associated autoinflammatory syndrome 1. It is recommended to evaluate this variant in both parents and to correlate these results with the clinical findings of the patient and/or other complementary studies since this finding could be related with the phenotype described.

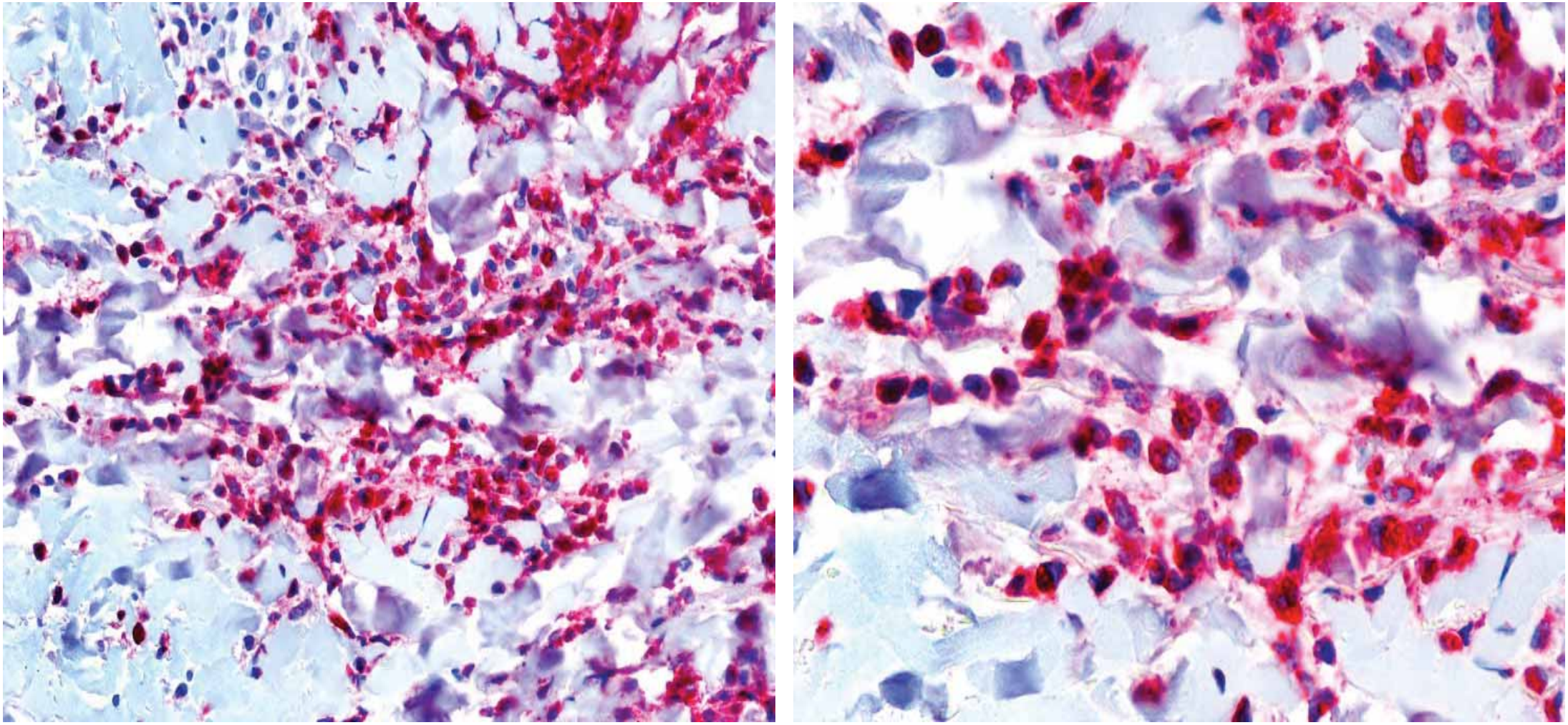
Additionally, a list of pathogenic and/or likely pathogenic variants in genes related to diseases with an autosomal recessive inheritance pattern and with a limited association to the reported clinical information are shown on the table “Pathogenic and/or likely pathogenic variants – Carrier Status”.

Moreover, a list of other variants of uncertain significance identified with limited association to the reported clinical information are shown on the table “Variants of Uncertain Significance (VUS)”.

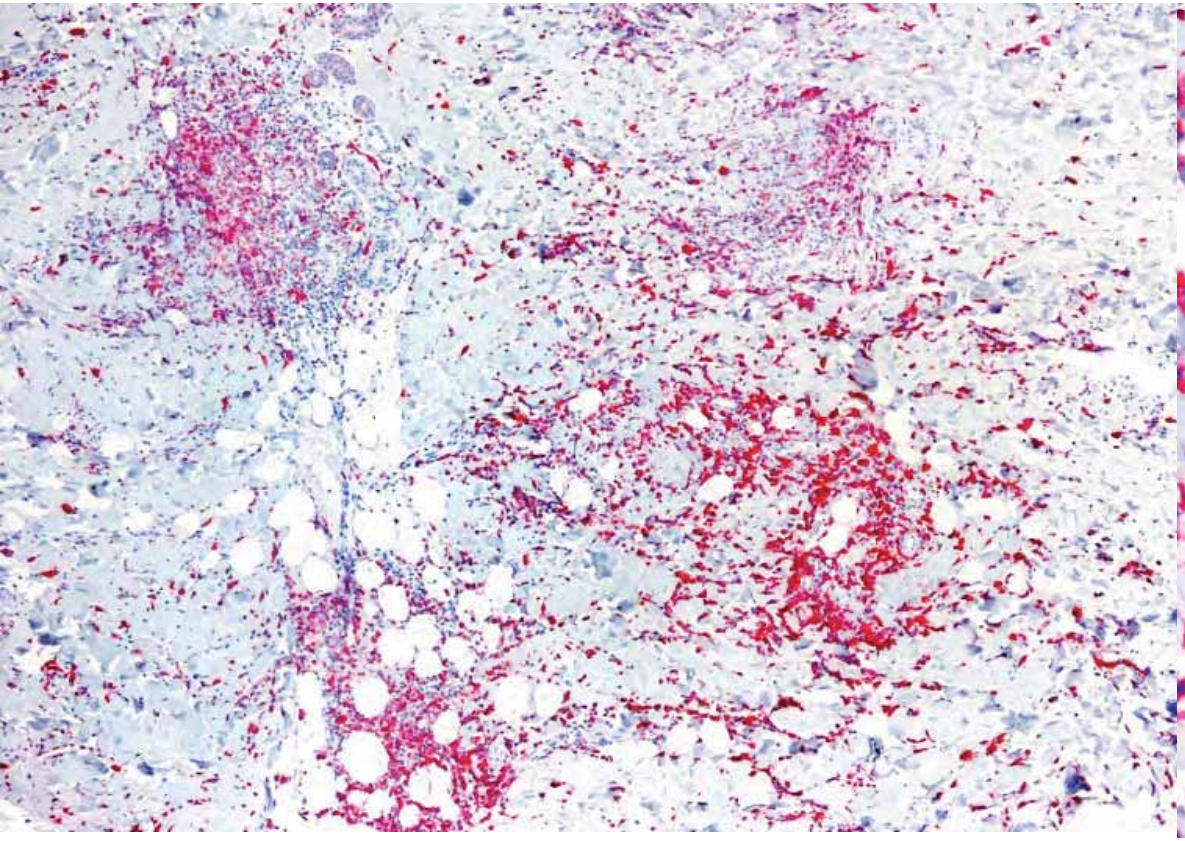
Clinical follow-up and family genetic counseling are recommended.

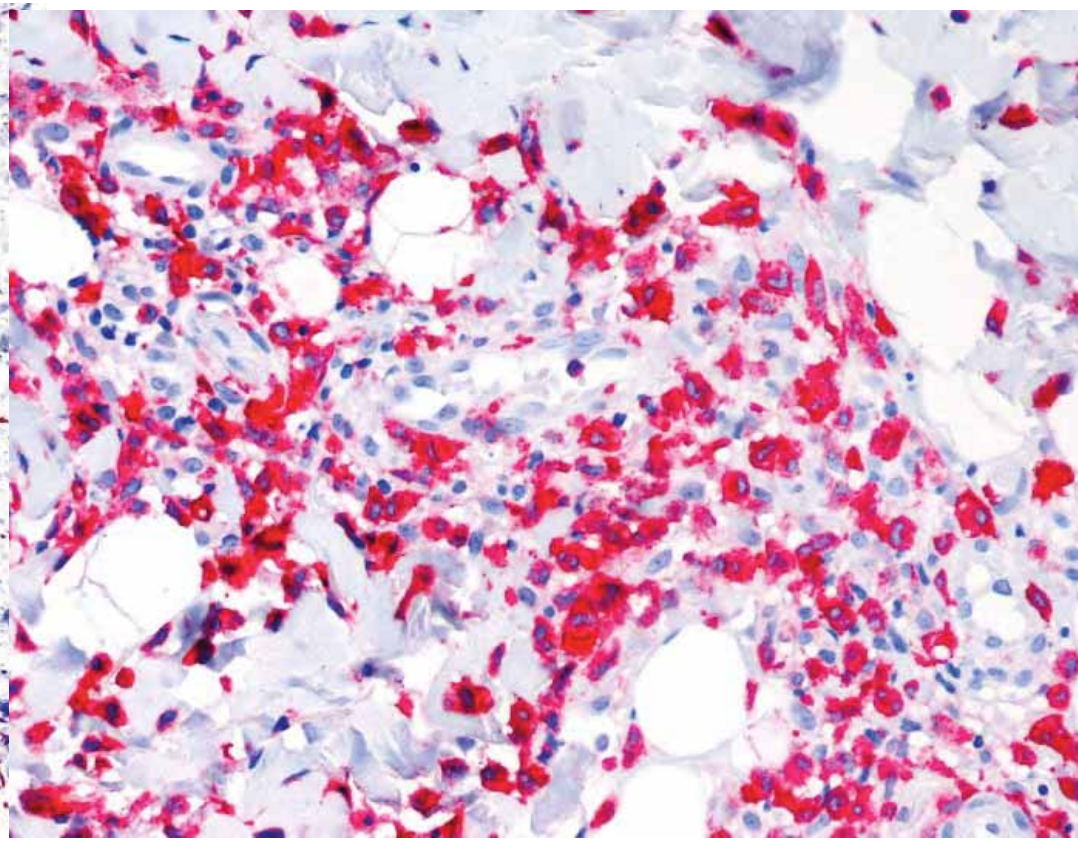
These results should be interpreted in the context of the patient's medical and family history. Consultation with a medical geneticist and / or genetic counselor is recommended to review these results.



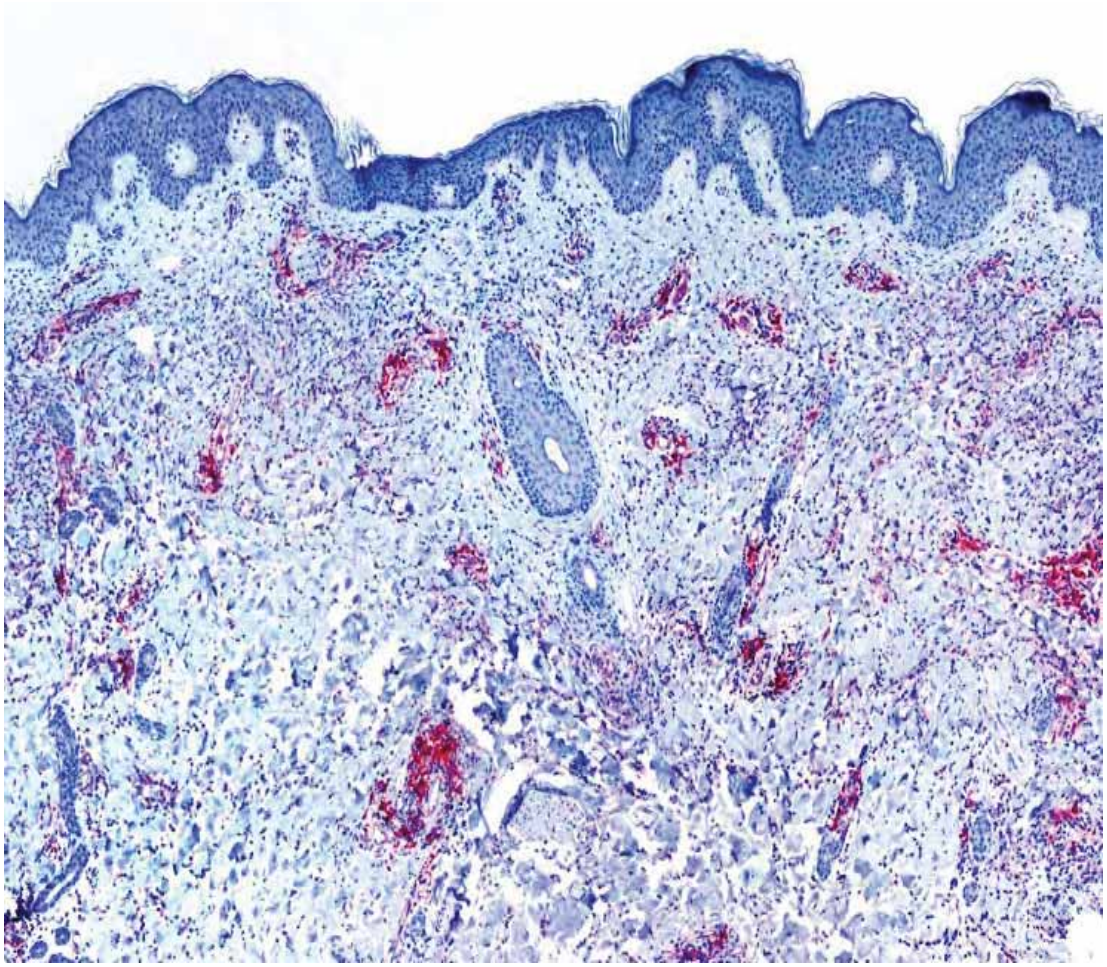


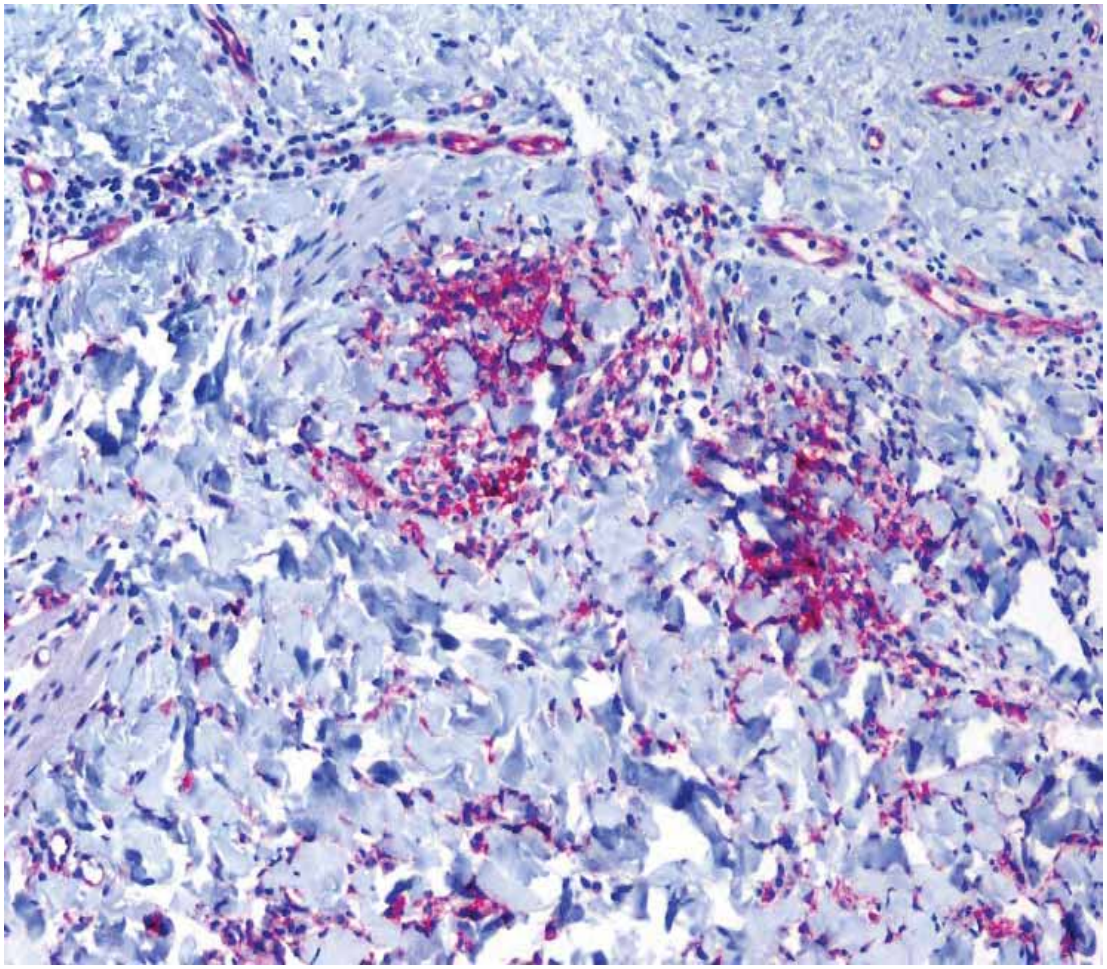
Myeloperoxidase



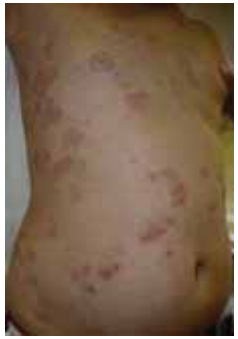


CD163





CD123



Disease course and treatment effects of a JAK inhibitor in a patient with CANDLE syndrome

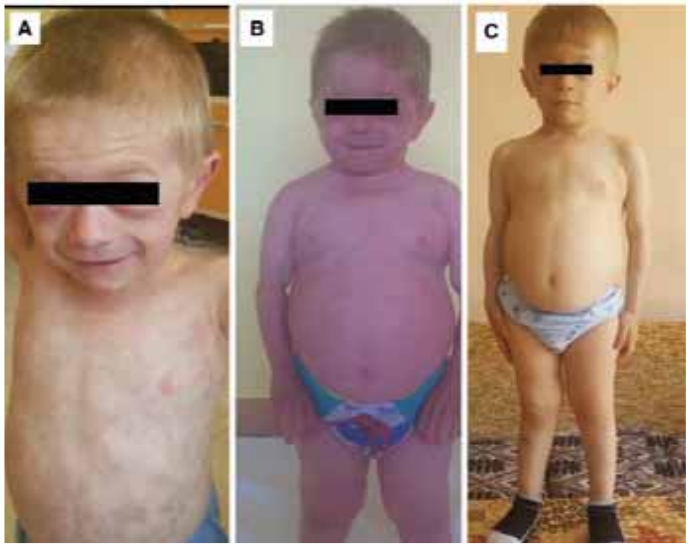
M. Boyadzhiev[1*], L. Marinov[2], V. Boyadzhiev[2], V. Iotova[1], I. Aksentijevich[3] and S. Hambleton[3]

Abstract

Background: CANDLE syndrome (an acronym for Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature) is a recently described rare autosomal recessive disorder charaterized by systemic autoinflammation. Clinical manifestations include presentation in the first year of life, episodes of fever accompanied by erythematous skin lesions, progressive lipodystrophy, violaceous periorbital swelling and failure to thrive. This syndrome is caused by loss of function mutations and malfunction of the immunoproteasome complex. Most patients have biallelic mutations in the PSMB8 gene that encodes the β5i catalytic subunit of the immunoproteasome. Examples of digenic inheritance have been also described in CANDLE. CANDLE patients have strong type I interferon gene expression signature and they are responsive to treatment with JAK inhibitors. However, possible serious side-effects remain a concern. Here, we report another patient with CANDLE whose disease activity was well controlled by the treatment with baricitinib.

Case presentation: We report a Bulgarian patient of the Turkish ancestry who carries biallelic mutations in the PSMB8 gene: p.Ala92Val and p.Lys105Gln. The pathogenic variant p.Ala92Val has not been previously described in patients with CANDLE. We also comment on the unusual feature in this patient, nephrolithiasis, that has not been described in other patients, however it might be related to the positive family history for kidney stones. We have treated the patient with the JAK inhibitor baricitinib for the past year and we observed a significant amelioration of his inflammatory episodes, skin and joint manifestations, and improvements in physical activities and growth. The treatment with glucocorticoids (GC) was completely discontinued. No side effects have been observed, however they remain in consideration for a life-long therapy of this disease.

Conclusions: CANDLE should be suspected in patients with early-onset systemic inflammatory disease and prominent skin manifestations. Molecular testing can confirm the clinical diagnosis and is very important in guiding therapies. Treatment with JAK inhibitors is highly efficacious and appears to be safe in children with CANDLE and other intereferonopathies.



The Journal of Clinical Investigation

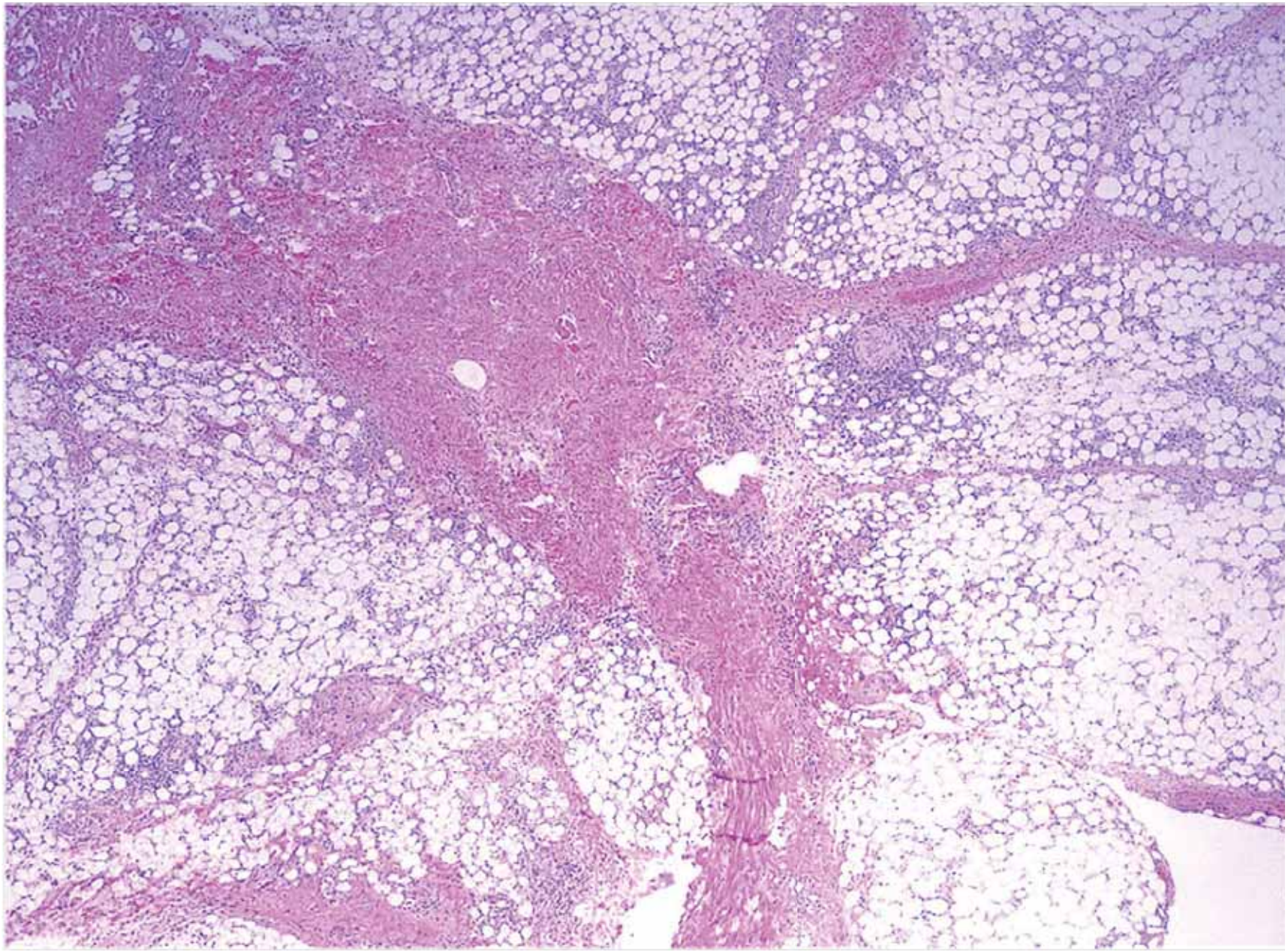
JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies

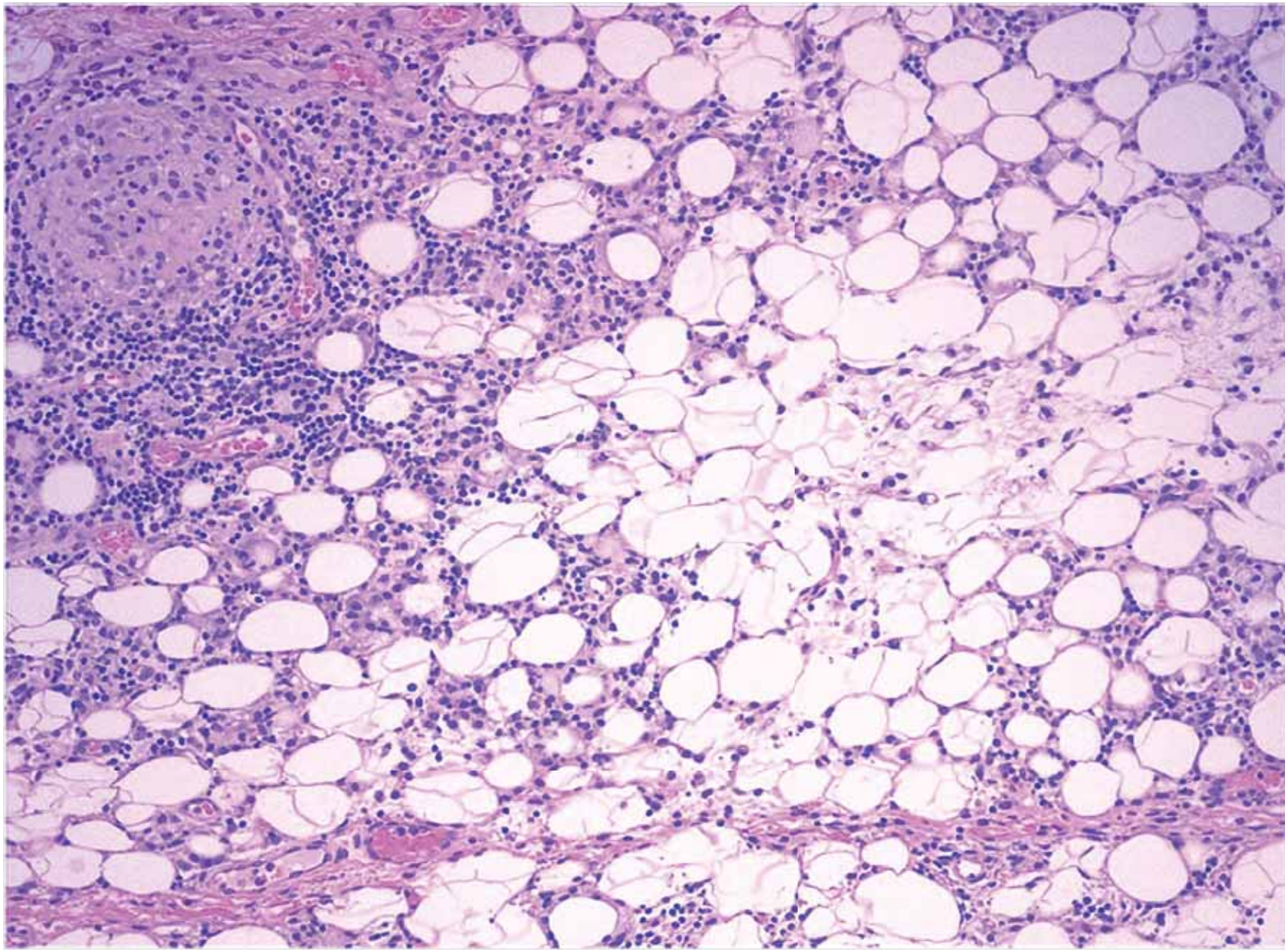
Gina A. Montealegre Sanchez,[1] Adam Reinhardt,[2] Suzanne Ramsey,[3] Helmut Wittkowski,[4] Philip J. Hashkes,[5] Yackov Berkun,[6] Susanne Schalm,[7] Sara Murias,[8] Jason A. Dare,[9] Diane Brown,[10] Deborah L. Stone,[11] Ling Gao,[9] Thomas Klausmeier,[12] Dirk Foell,[4] Adriana A. de Jesus,[1] Dawn C. Chapelle,[13] Hanna Kim,[13] Samantha Dill,[13] Robert A. Colbert,[14] Laura Failla,[1] Bahar Kost,[15] Michelle O'Brien,[13] James C. Reynolds,[16] Les R. Folio,[16] Katherine R. Calvo,[16] Scott M. Paul,[16] Nargues Weir,[13] Alessandra Brofferio,[16] Ariane Soldatos,[16] Angelique Biancotto,[13] Edward W. Cowen,[13] John J. Digiovanna,[17] Massimo Gadina,[18] Andrew J. Lipton,[19] Colleen Hadigan,[19] Steven M. Holland,[19] Joseph Fontana,[19] Ahmad S. Alawad,[20] Rebecca J. Brown,[20] Kristina I. Rother,[21] Theo Heller,[22] Kristina M. Brooks,[16] Parag Kumar,[16] Stephen R. Brooks,[23] Meryl Waldman,[23] Harsharan K. Singh,[24] Volker Nickeleit,[11] Maria Silk,[12] Apurva Prakash,[12] Jonathan M. Janes,[12] Seza Ozen,[12] Paul C. Wakim,[25] Paul A. Brogan,[26] William L. Macias,[12] and Raphaela Goldbach-Mansky[1]

Dermatopathologic clue #3

Perivascular & interstitial mononuclear & neutrophilic infiltrate

CANDLE syndrome (proteasome)

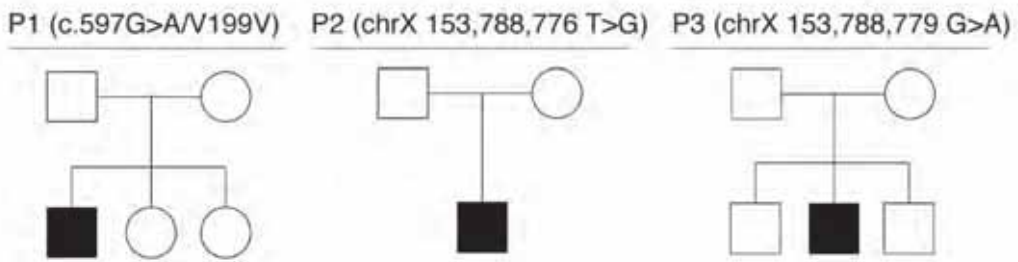




NEMO-NDAS

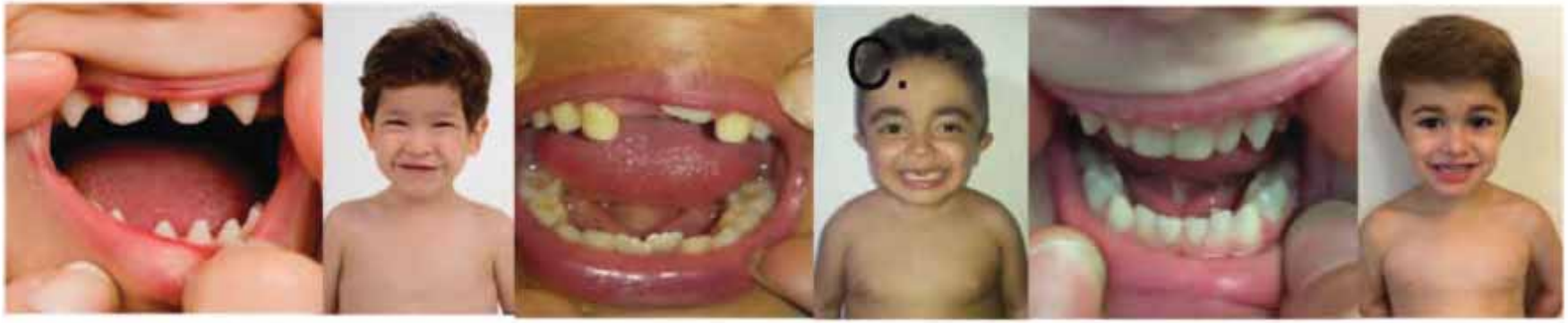
Genetically programmed alternative splicing of NEMO mediates an autoinflammatory disease phenotype

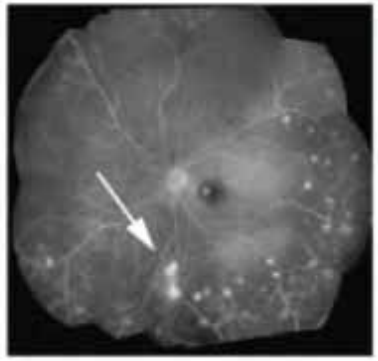
Younglang Lee,[1,2] Alex W. Wessel,[1,2] Jiazhi Xu,[3] Julia G. Reinke,[3] Eries Lee,[1,2] Somin M. Kim,[1,2] Amy P. Hsu,[4] Jevgenia Zilberman-Rudenko,[1,2] Sha Cao,[5] Clinton Enos,[1,2] Stephen R. Brooks,[6] Zuoming Deng,[6] Bin Lin,[7] Adriana A. de Jesus,[7] Daniel N. Hupalo,[8] Daniela G.P. Piotto,[9] Maria T. Terreri,[9] Victoria R. Dimitriades,[10] Clifton L. Dalgard,[8,11] Steven M. Holland,[4] Raphaela Goldbach-Mansky,[7] Richard M. Siegel,[2,12] and Eric P. Hanson[3]

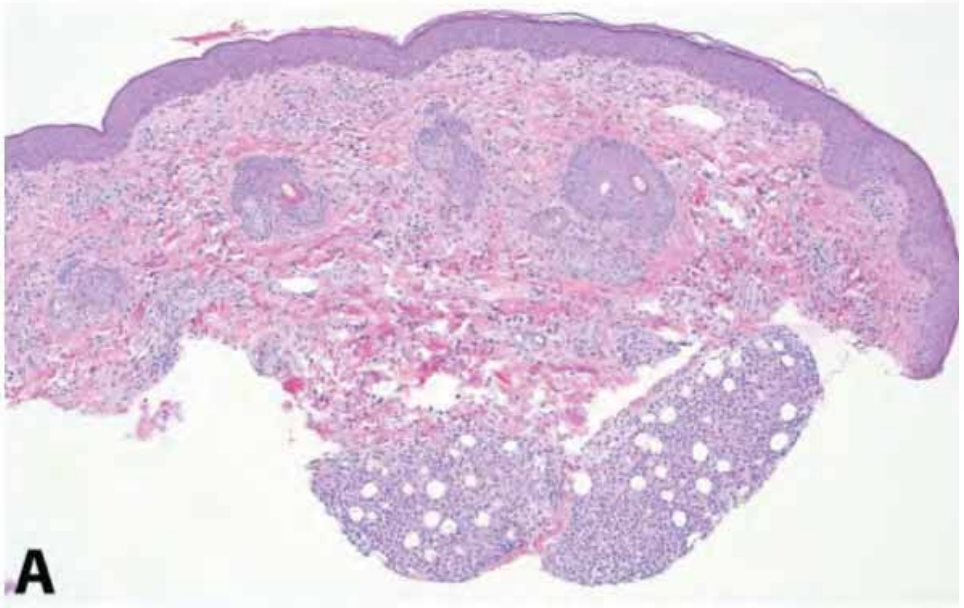


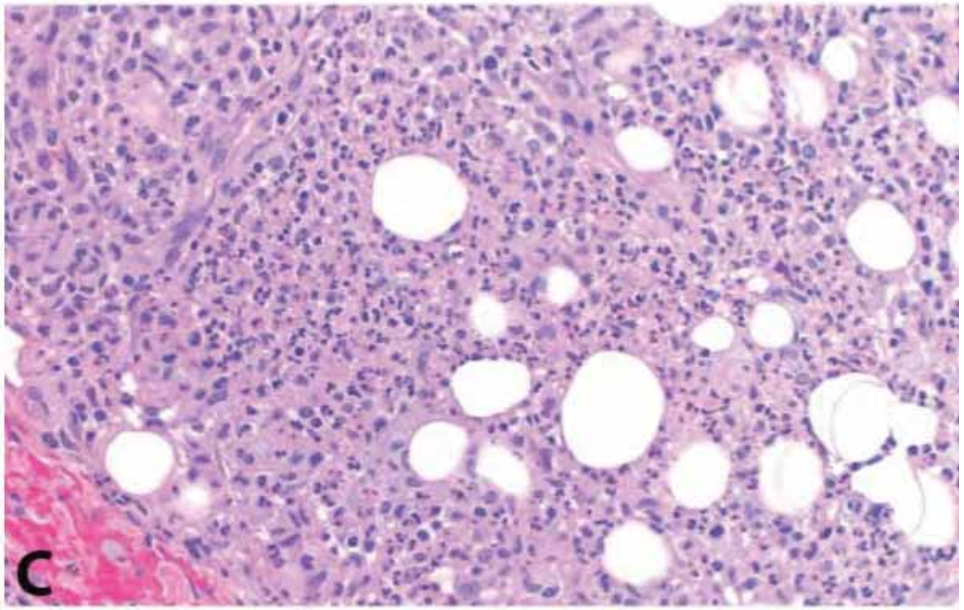
	P1	P2	P3
Genotype or NEMO protein	c.597G>A/V199V	chrX 153,788,776 T>G	chrX 153,788,779 G>A
Inflammatory disease	Sterile osteomyelitis	Systemic inflammation	Systemic inflammatio
PID/infectious disease	HG	HG, pneumonia	HG, dsDNA virus
CNS	CNS bleed, WM enhancement	CNS bleed cortical atrophy	CNS bleed, WM atroph
EYE	Optic neuritis, panuveitis, chorioretinitis	None	Anterior uveitis
SKIN	Granulomatous panniculitis	Lymphohistiocytic panniculitis	Lymphohistiocytic panniculitis with poorl formed granuloma
EDA	Conical teeth	None	None
BLOOD	HSM	HSM, anemia, G6PD deficiency, thrombocytopenia	HSM, lymphopenia
GI	None	None	None

HG, hypogammaglobulinemia; NTM, nontuberculous mycobacteria; EDA, gastrointestinal; IBD, inflammatory bowel disease; PID, primary immune







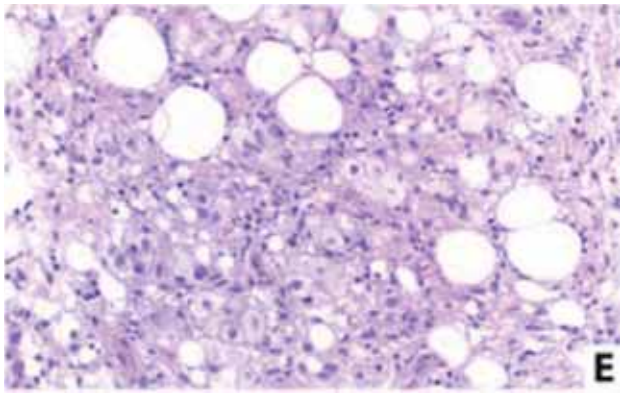


EXTRAORDINARY CASE REPORT

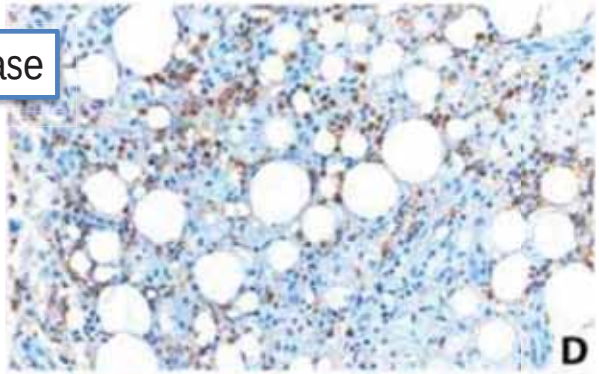
NEMO-NDAS: A Panniculitis in the Young Representing an Autoinflammatory Disorder in Disguise

Shaymaa Hegazy, MD, Mariana C. Marques, MD,† Scott W. Canna, MD,‡ Raphaela Goldbach-Mansky, MD, MHS,§ Adriana A. de Jesus, MD, PhD,§ Miguel Reyes-Múgica, MD,* and Claudia M. Salgado, MD, PhD**

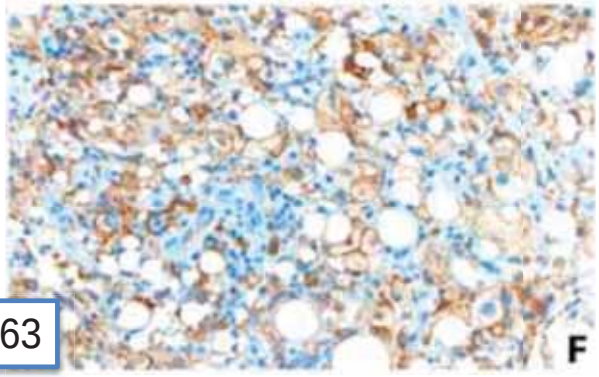
(*Am J Dermatopathol* 2022;00:1–3)

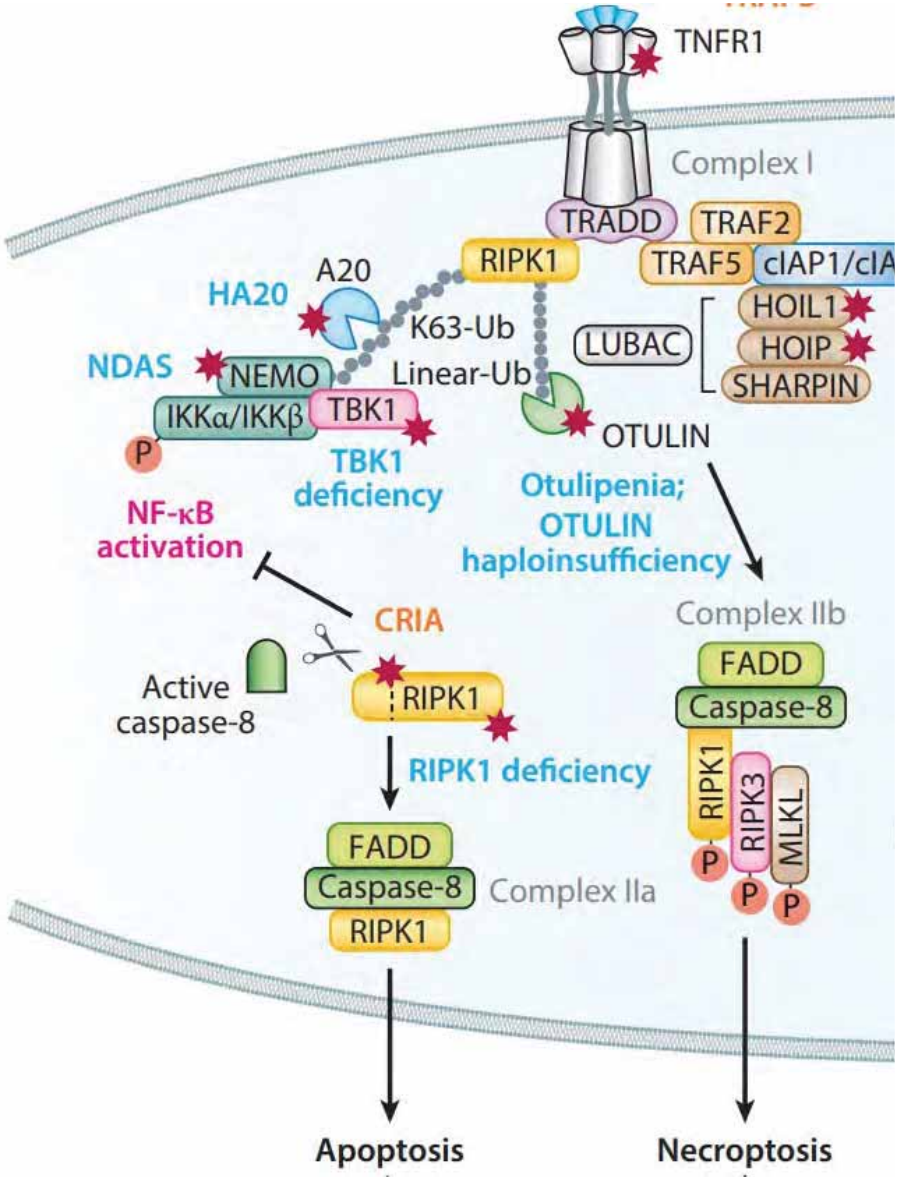


Myeloperoxidase



CD163





Total number of patients (n)		40
Sex (%)	Females	60.0
	Males	40.0
	Total patients	40
Pooled mean age of disease onset (weeks)		7.1
	Total patients	5
Country (%)	United States	50.0
	Turkey	33.3
	Brazil	16.7
	Total studies	6

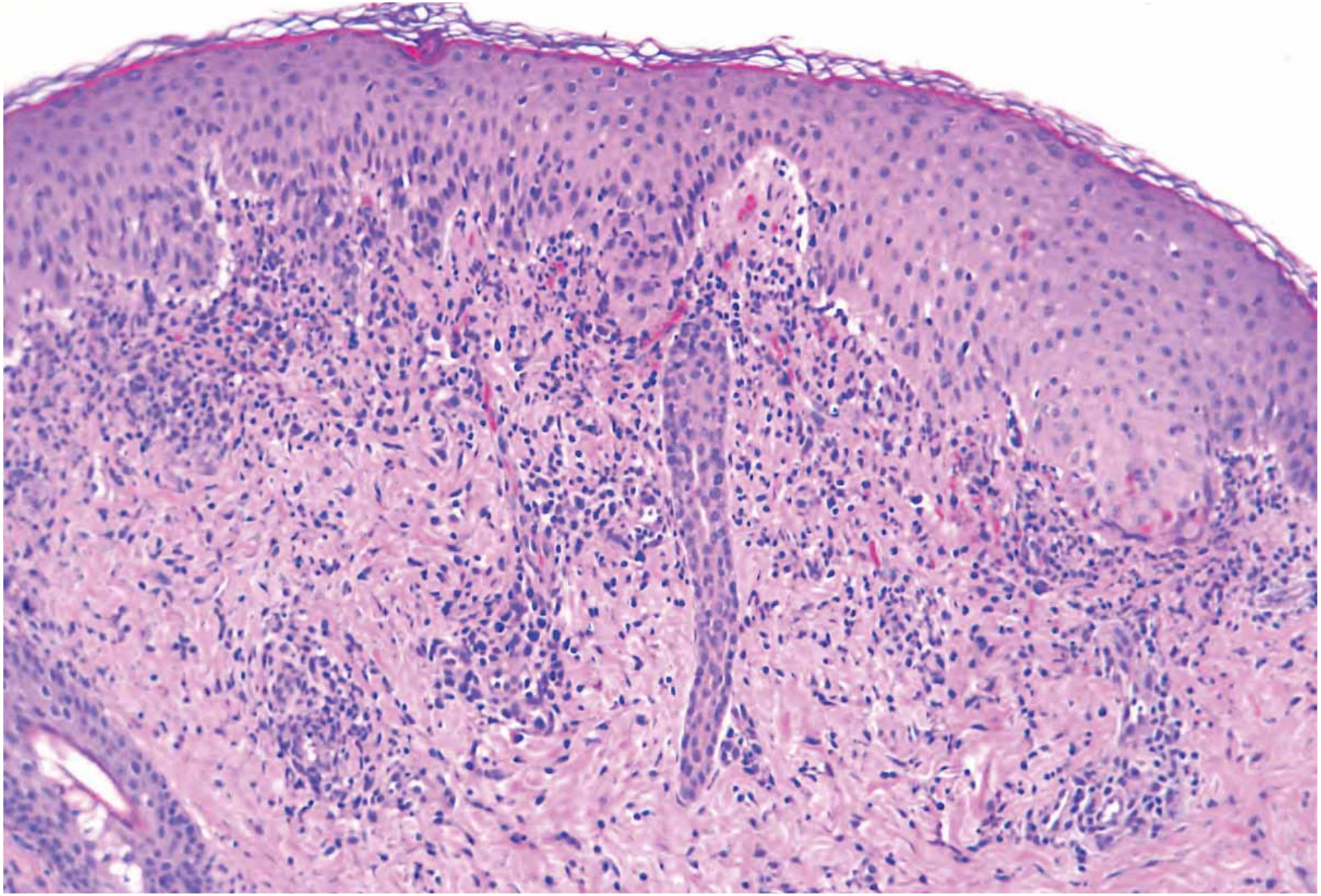
Cutaneous features	n	%
Panniculitis	37	92.5
Ectodermal dysplasia	25	62.5
Dyskeratosis	7	17.5
Lipoatrophy/lipodystrophy	4	10.0
Rash NYD	3	7.5
Subcutaneous nodules	2	5.0
Conical teeth	2	5.0
Neutrophilic dermatitis	1	2.5
Erythema nodosum	1	2.5

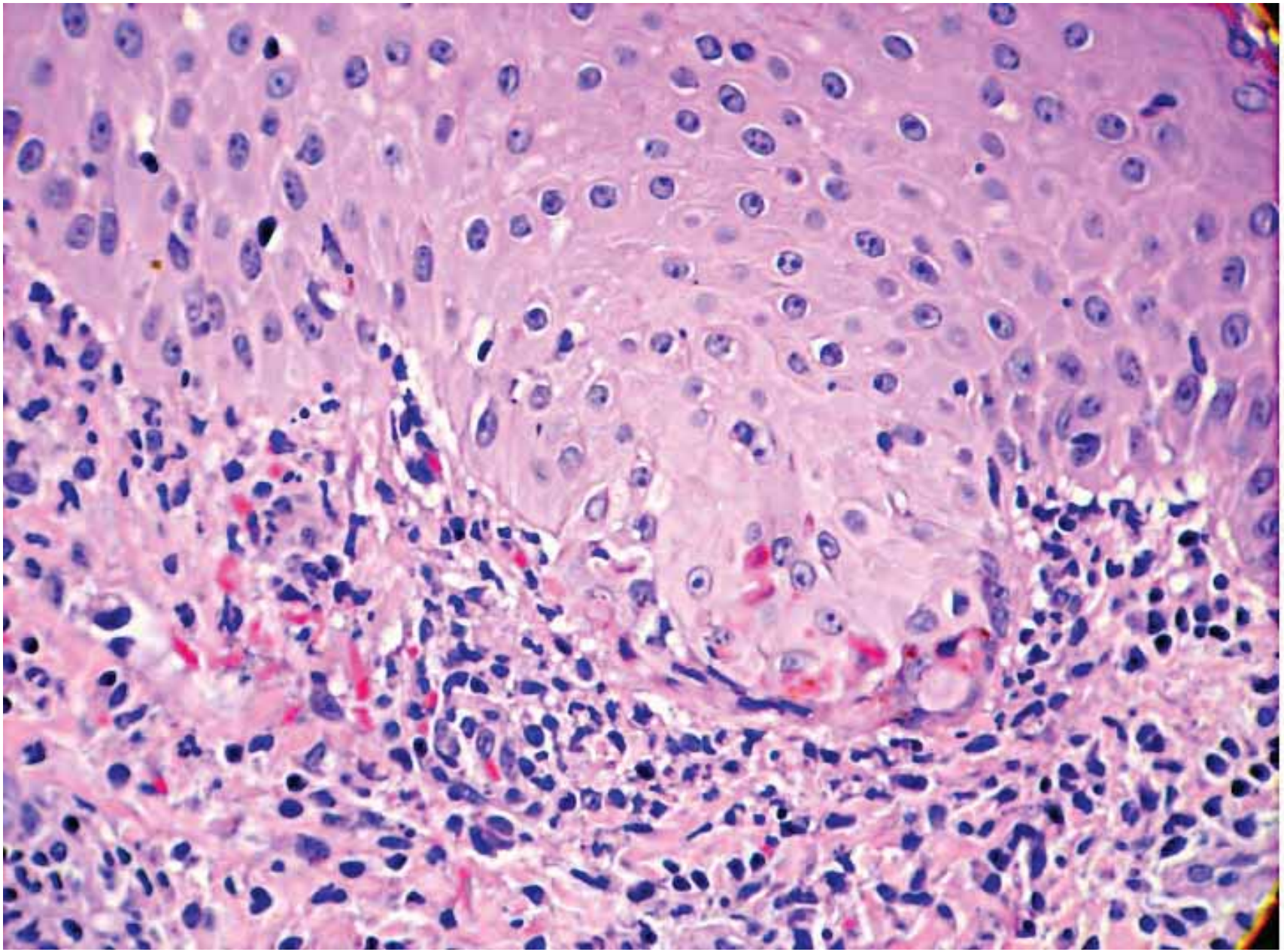
Systemic inflammatory features		
Systemic inflammation	35	87.5
Hepatosplenomegaly	31	77.5
Lymphopenia	29	72.5
Hypogammaglobulinemia	6	15.0
Fevers	5	12.5
Granulomatous hepatitis	4	10.0
Anemia	3	7.5
CNS Bleed	3	7.5
Subdural Hemorrhage	3	7.5
Thrombocytopenia	2	5.0
Hypertension	2	5.0
Pneumonia	2	5.0
Chorioretinitis	2	5.0
Anterior uveitis	2	5.0

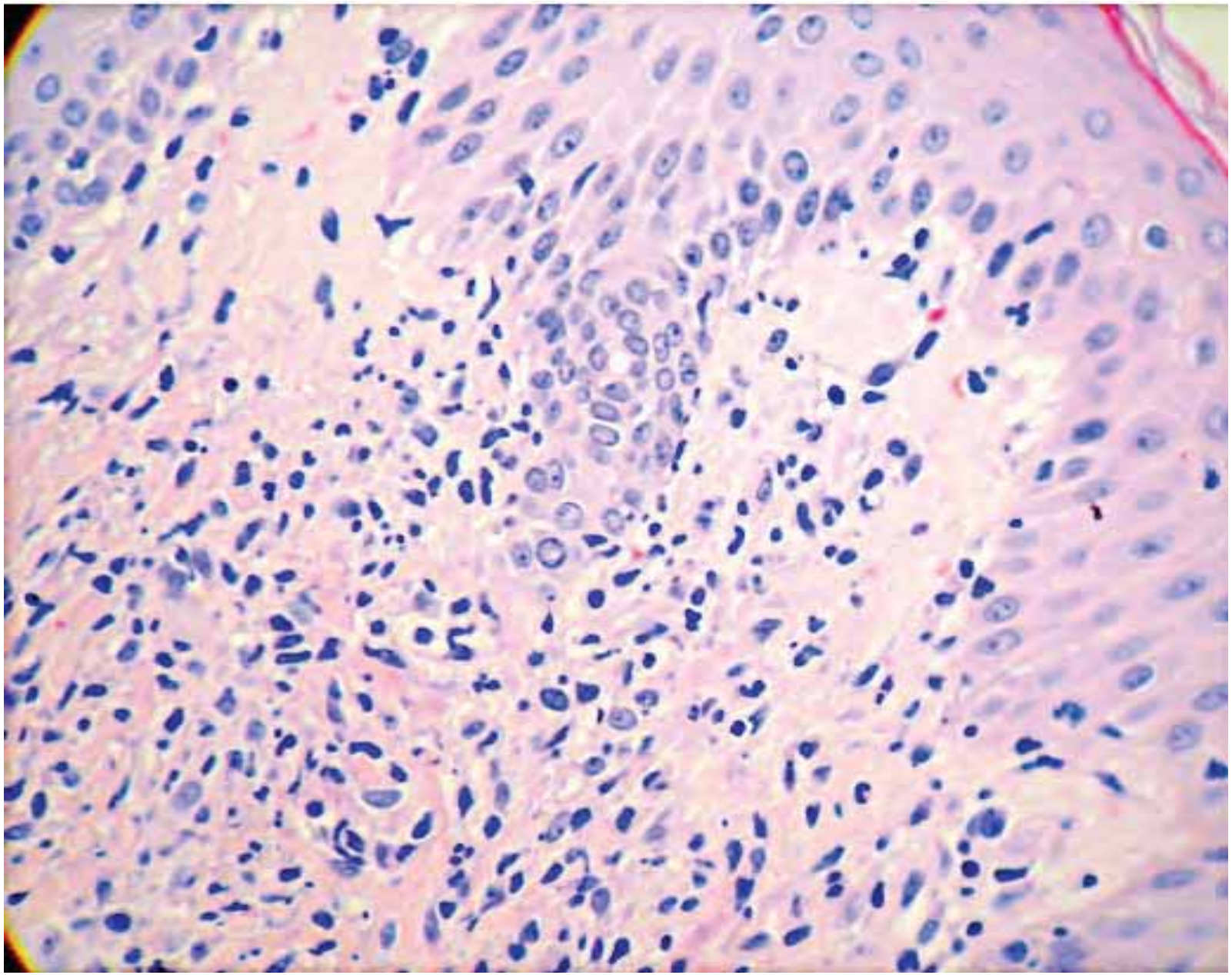
Dermatopathologic clue #4

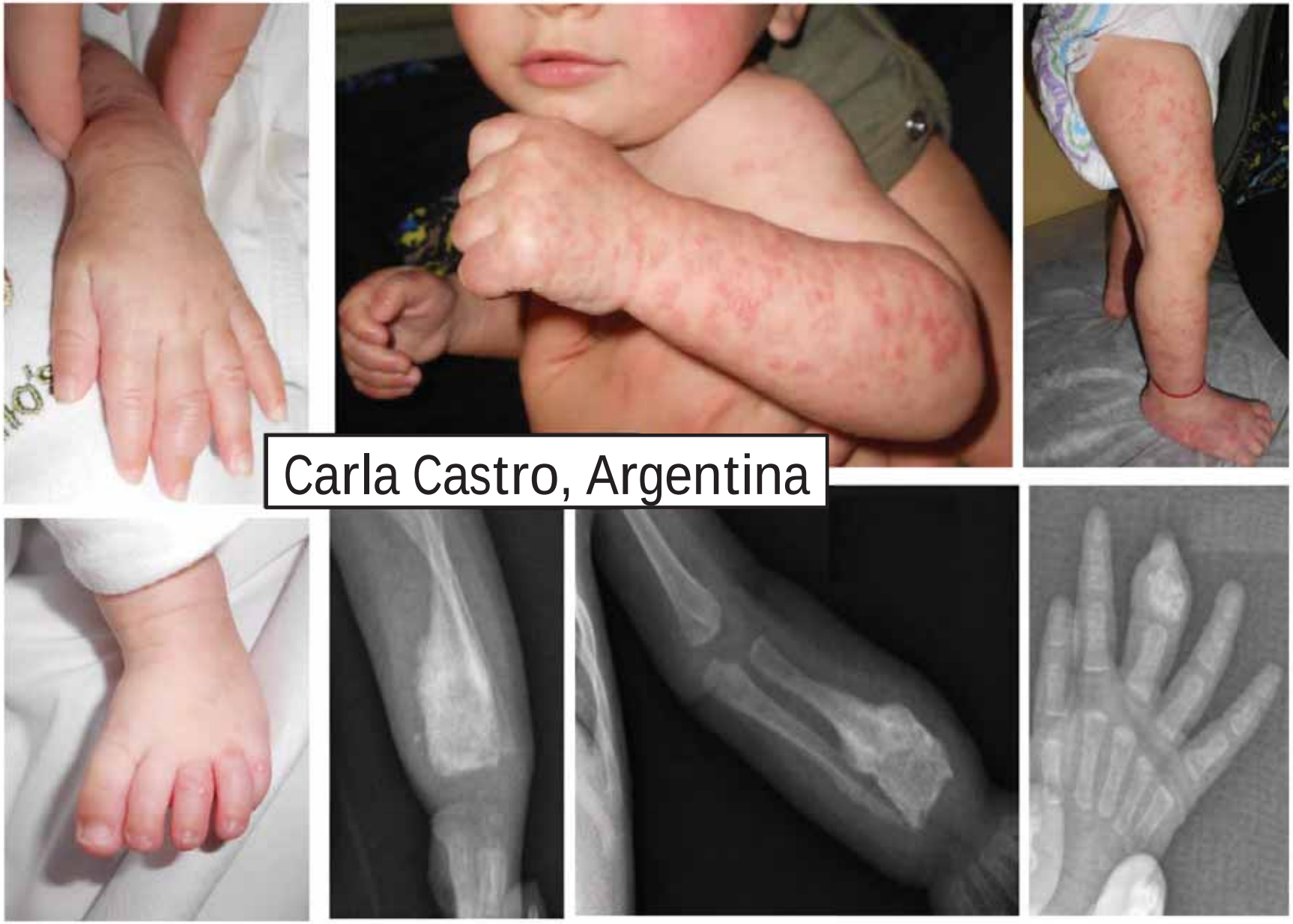
Lobar panniculitis neutrophils & macrophages & granulomas

NEMO-NDAS (NEMO exon 5 deleted auto inflammatory syndrome)







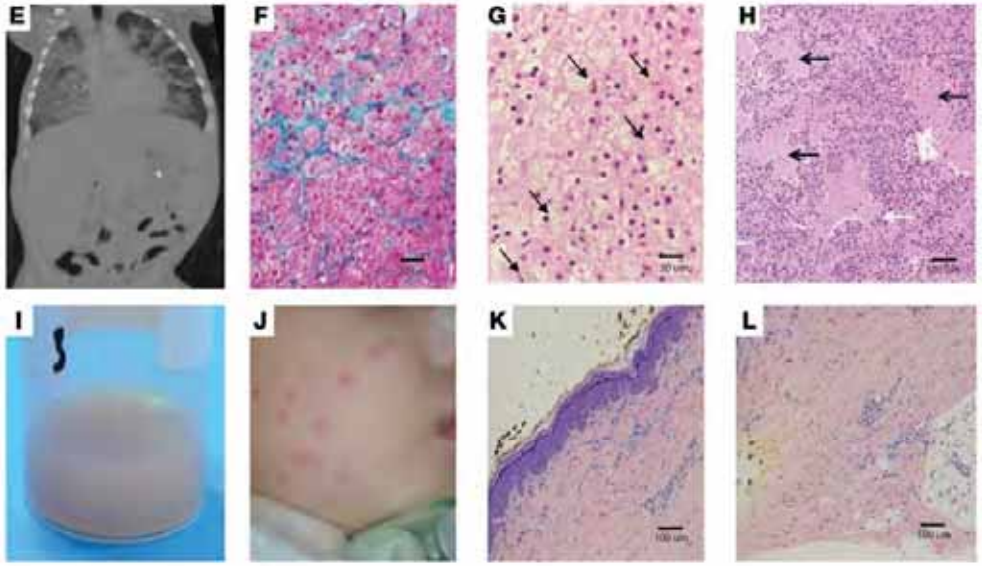

Carla Castro, Argentina

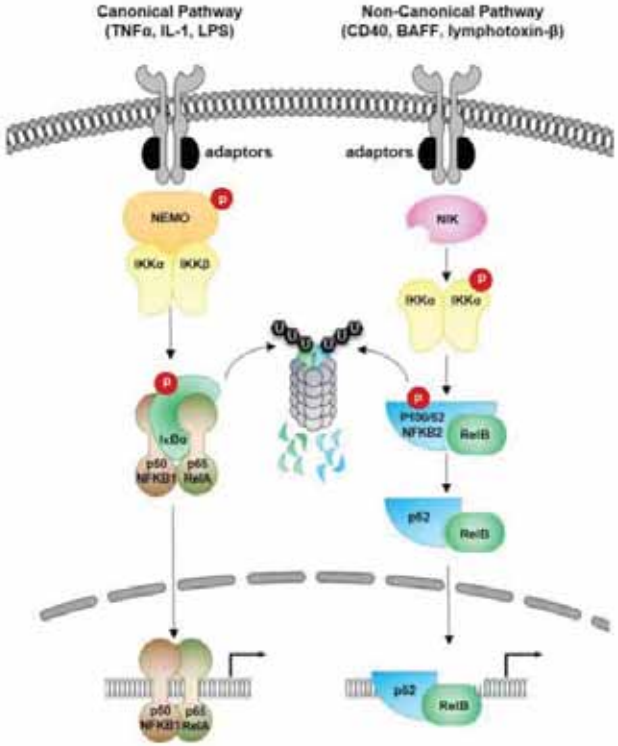
The Journal of Clinical Investigation

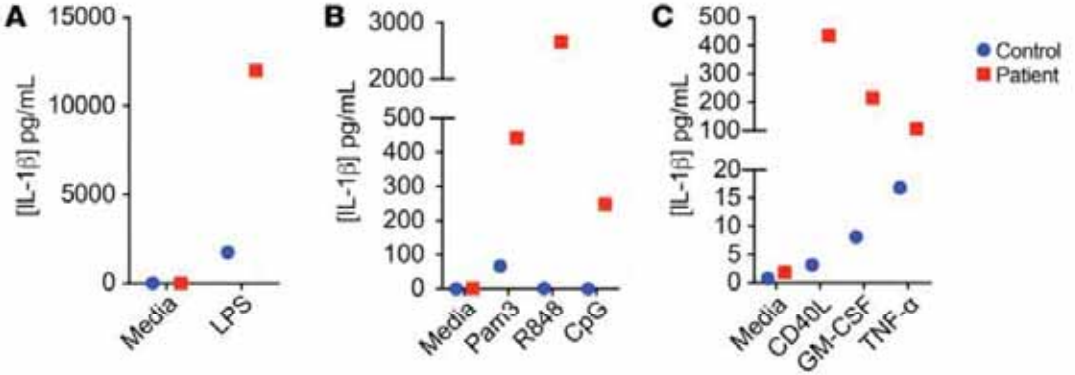
RESEARCH ARTICLE

Dominant-negative NFKBIA mutation promotes IL-1β production causing hepatic disease with severe immunodeficiency

Enrica E.K. Tan,[1,2] Richard A. Hopkins,[3] Chrissie K. Lim,[3] Saumya S. Jamuar,[1,2] Christina Ong,[2,4] Koh C. Thoon,[2,4] Mark J.A. Koh,[2,5] Eun Mong Shin,[6,7,8] Derrick W.Q. Lian,[1,2,9] Madhushanee Weerasooriya,[10,11] Christopher Z.W. Lee,[12] Andreas Alvin Pumomo Soetedjo,[6] Chang Siang Lim,[6] Veonice B. Au,[3] Edmond Chua,[3] Hui Yin Lee,[6] Leigh Ann Jones,[3] Sharmy S. James,[10,11] Nivashini Kaliaperumal,[3] Jeffery Kwok,[3] Ee Shien Tan,[2,4] Biju Thomas,[2,4] Lynn Xue Wu,[3] Lena Ho,[6] Anna Marie Fairhurst,[6] Florent Ginhoux,[12] Adrian K.K. Teo,[6] Yong Liang Zhang,[10,11] Kok Huar Ong,[6] Weimiao Yu,[6] Byrappa Venkatesh,[6] Vinay Tergaonkar,[9,13,14,15] Bruno Reversade,[6,16,17,18] Keh Chuang Chin,[3,19] Ah Moy Tan,[12] Woei Kang Liew,[2,4] and John E. Connolly[3,4,20,21]

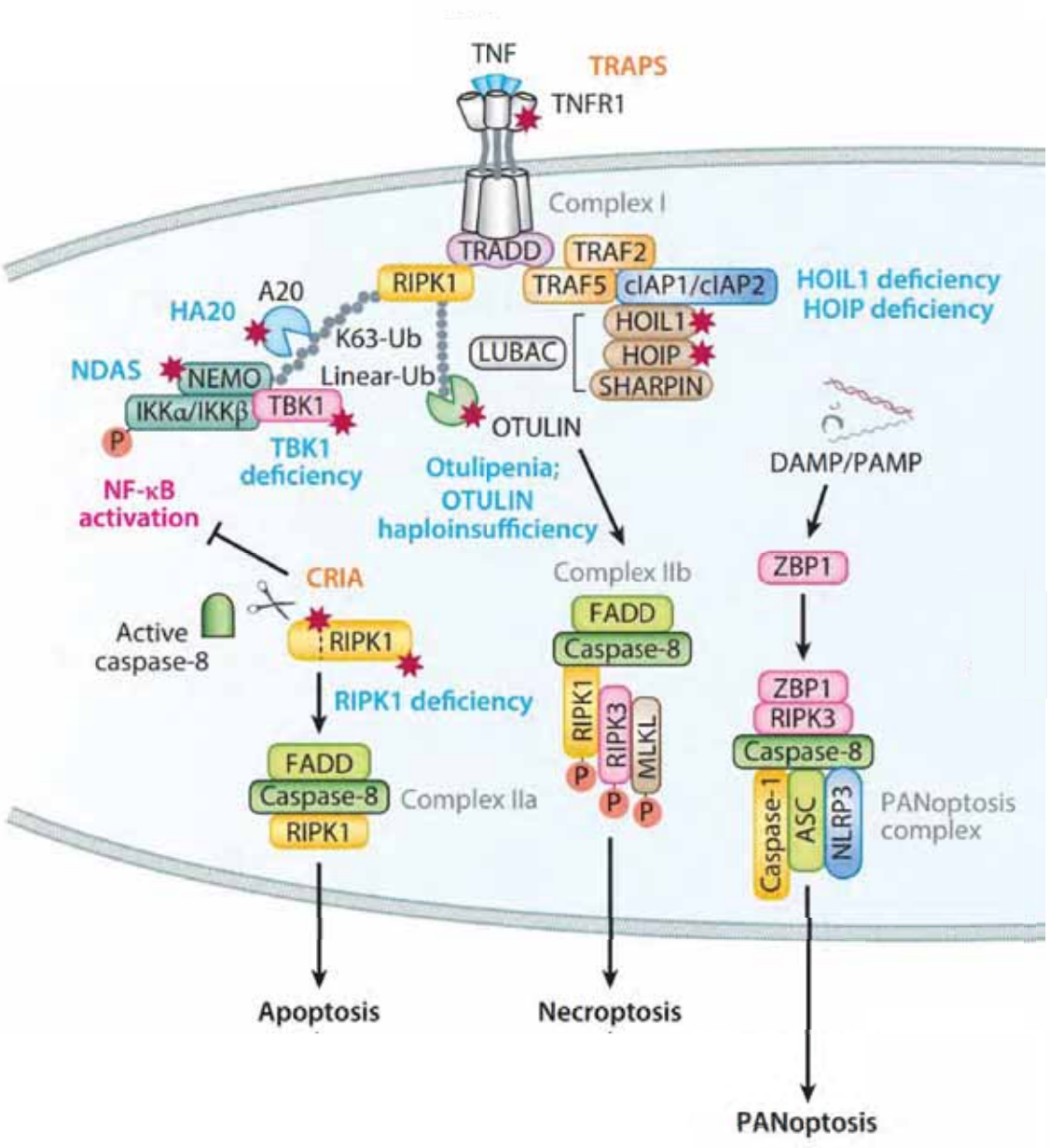


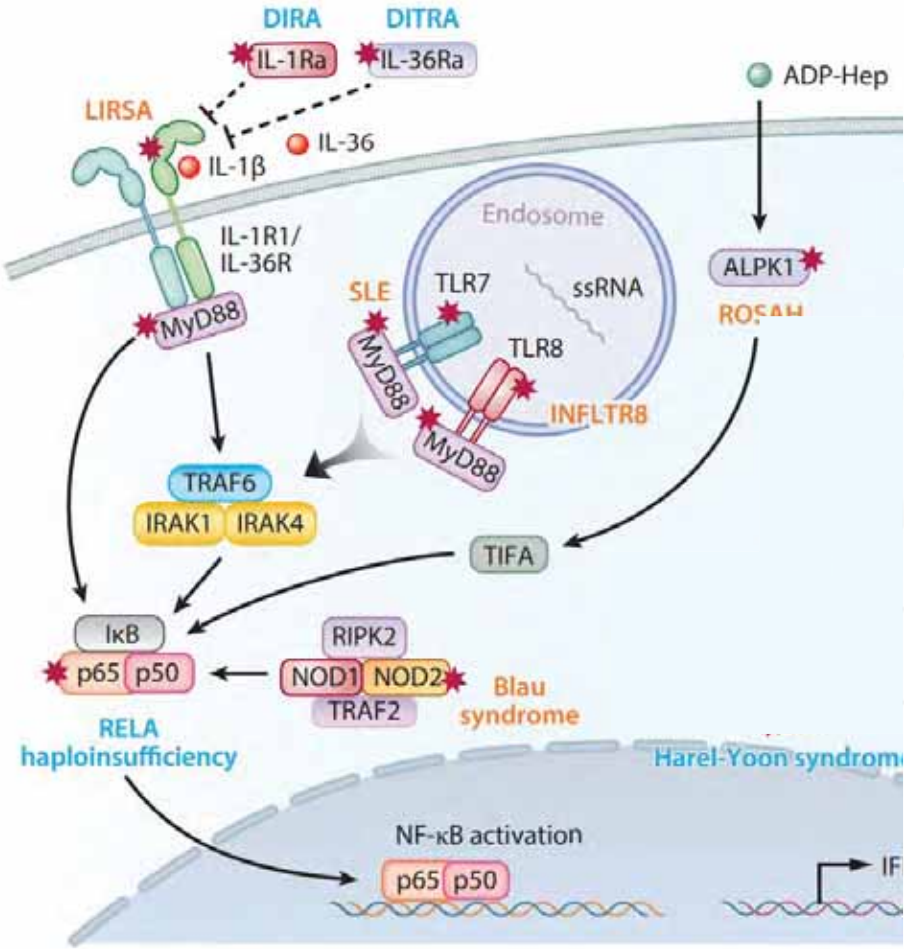




Death cell associated AIDs

Complex and varied immune mechanisms
Mostly activation of NF-kB

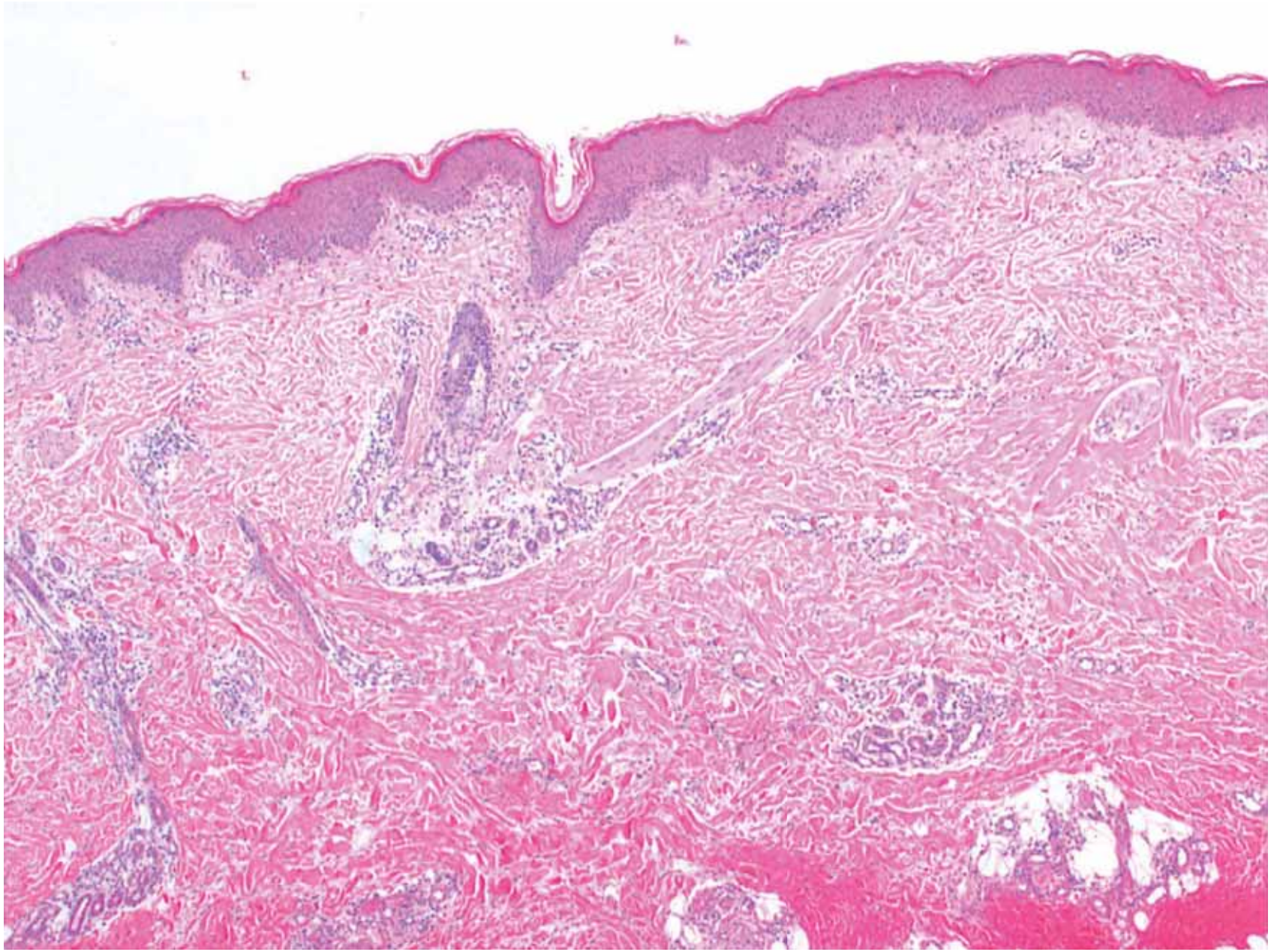


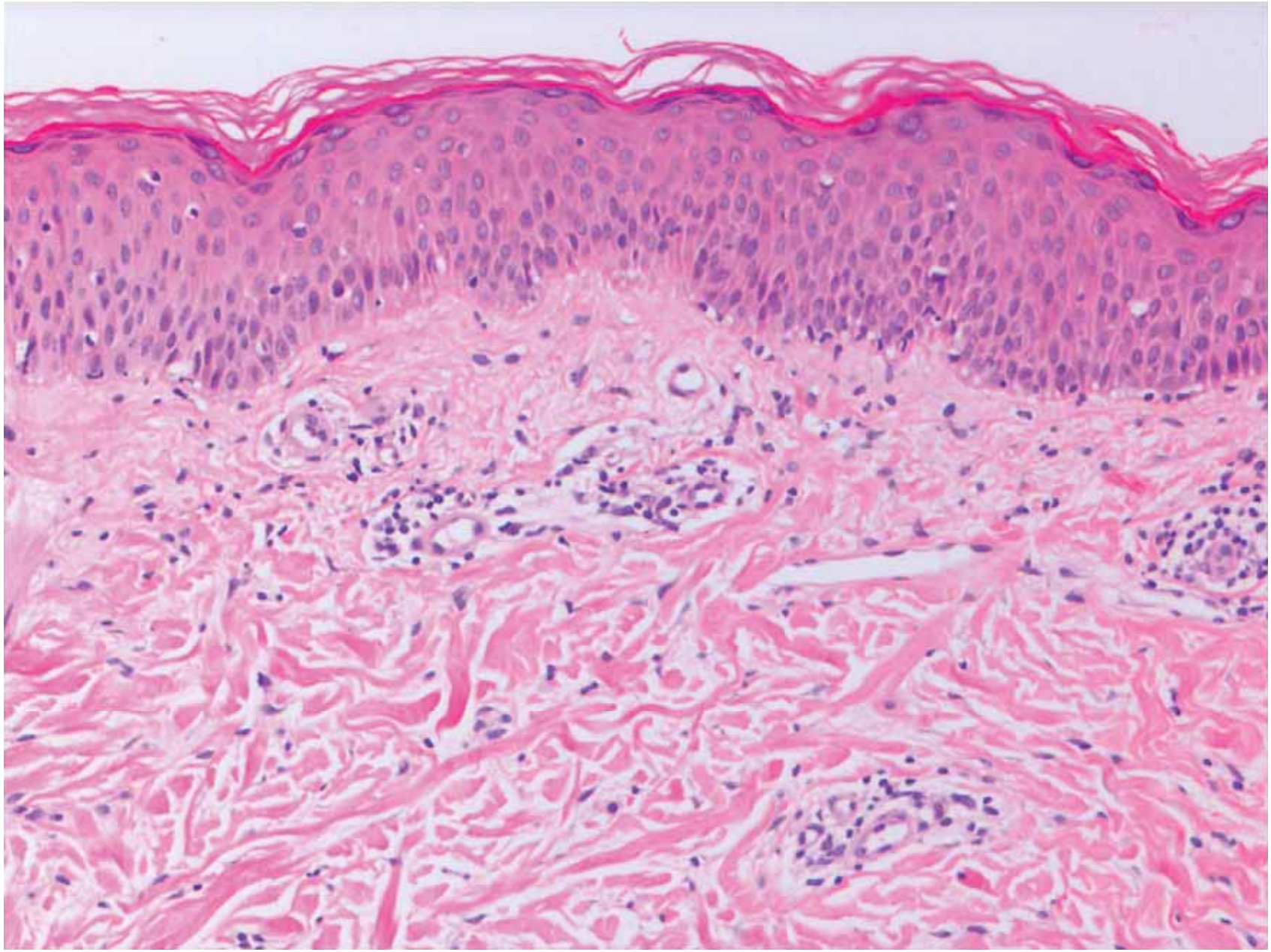


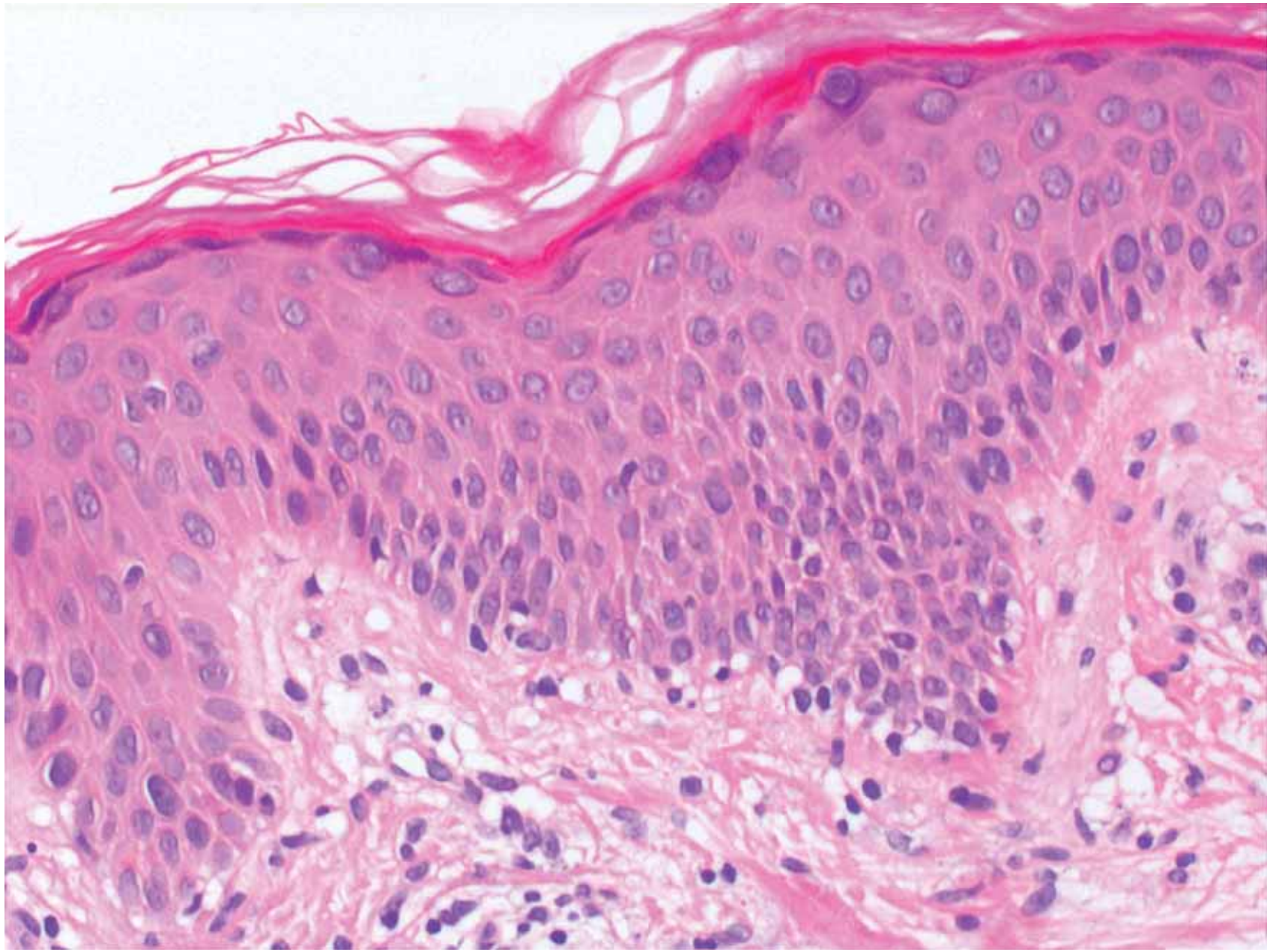
Dermatopathologic clue #5

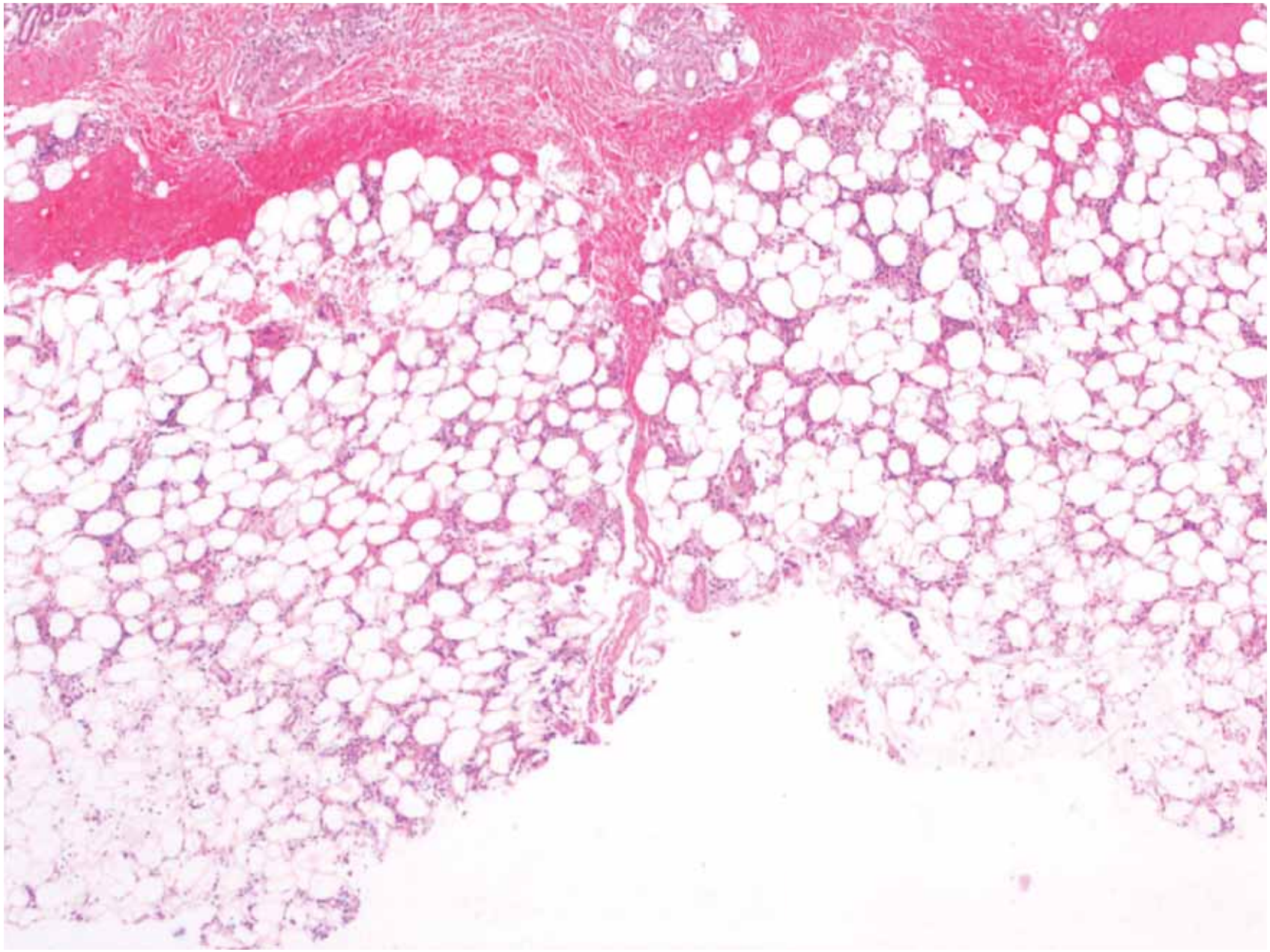
Interface vacuolar dermatitis
neutrophils & lymphocytes

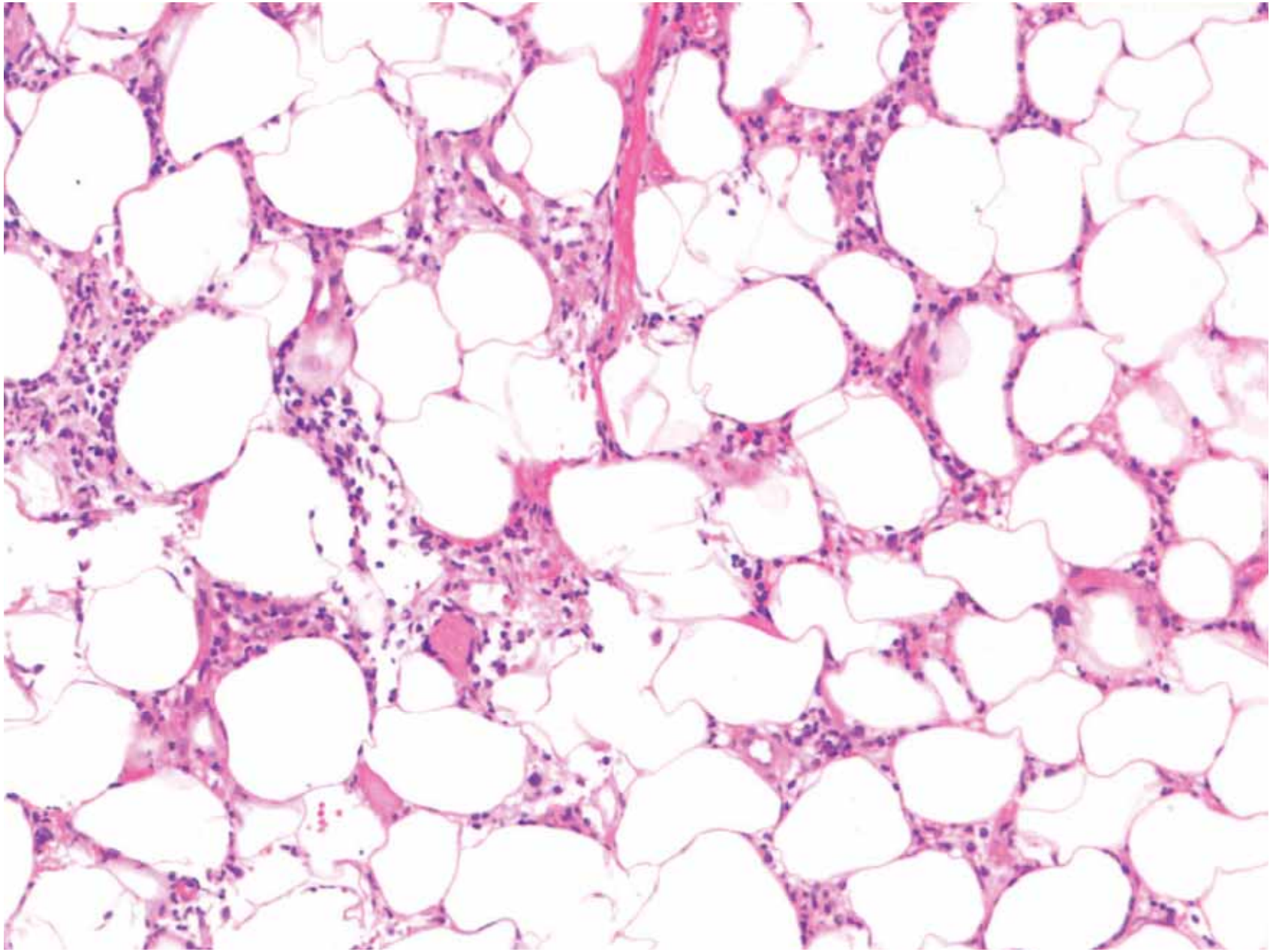
NFKBIA deficiency

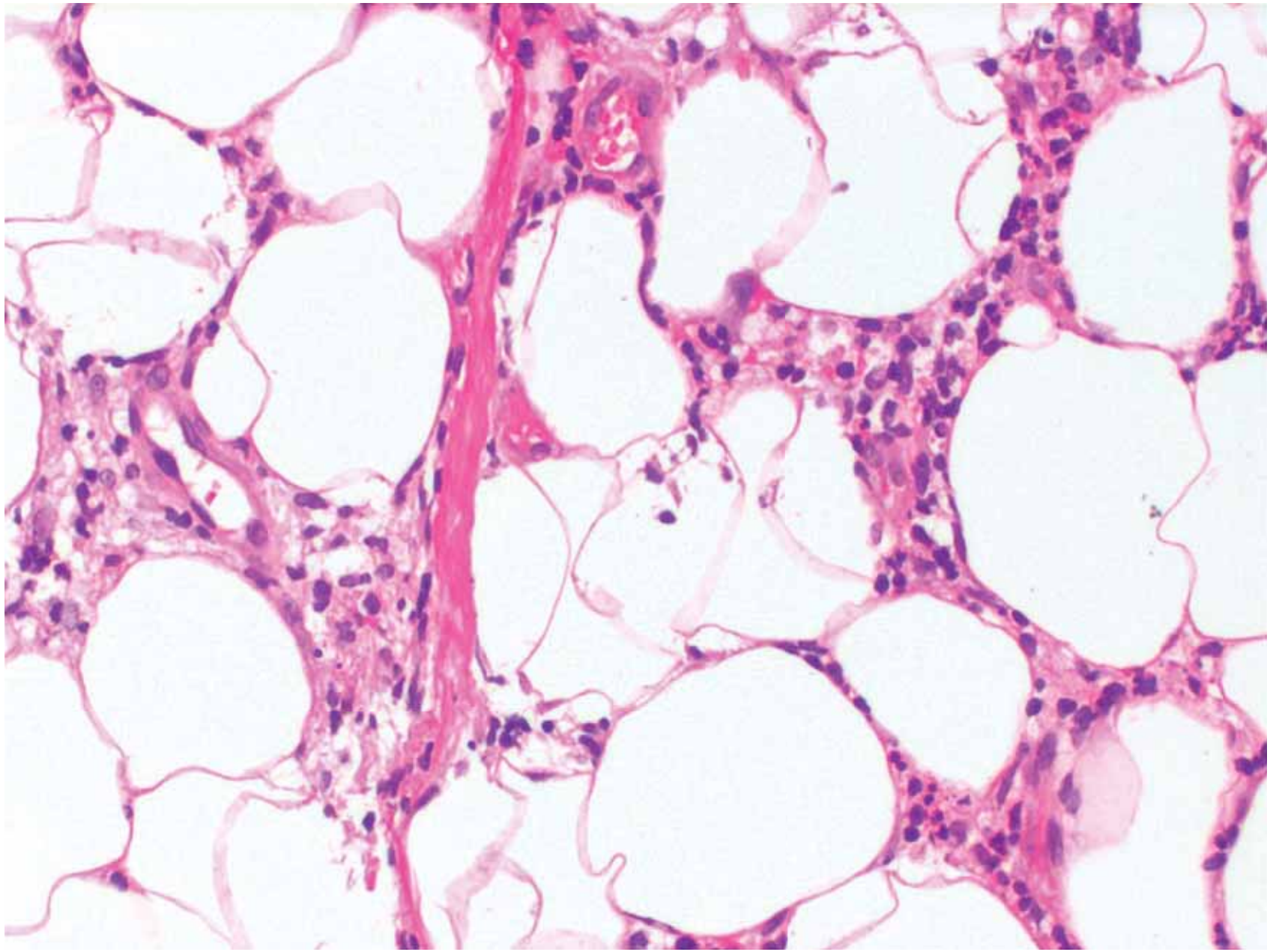


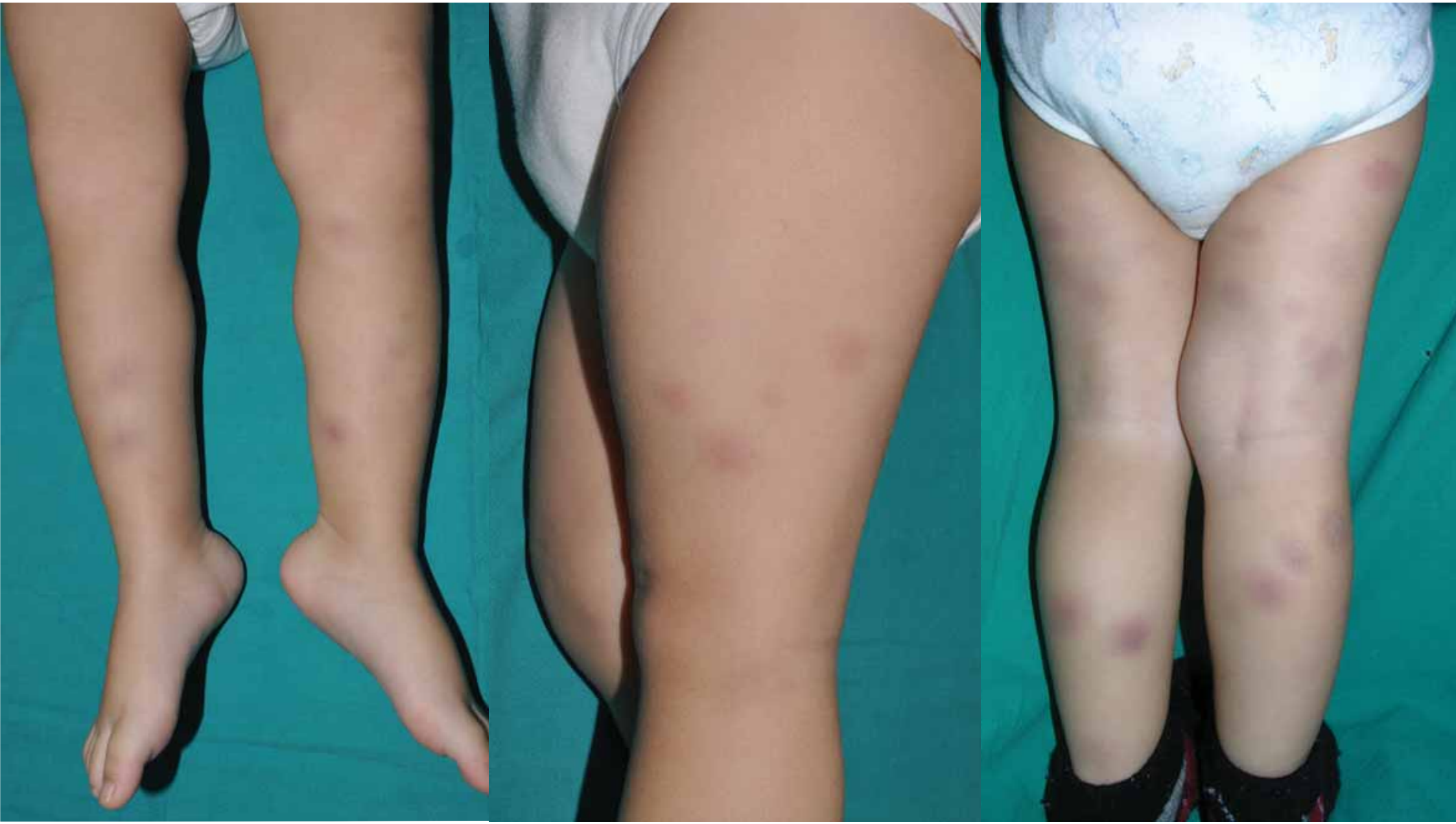


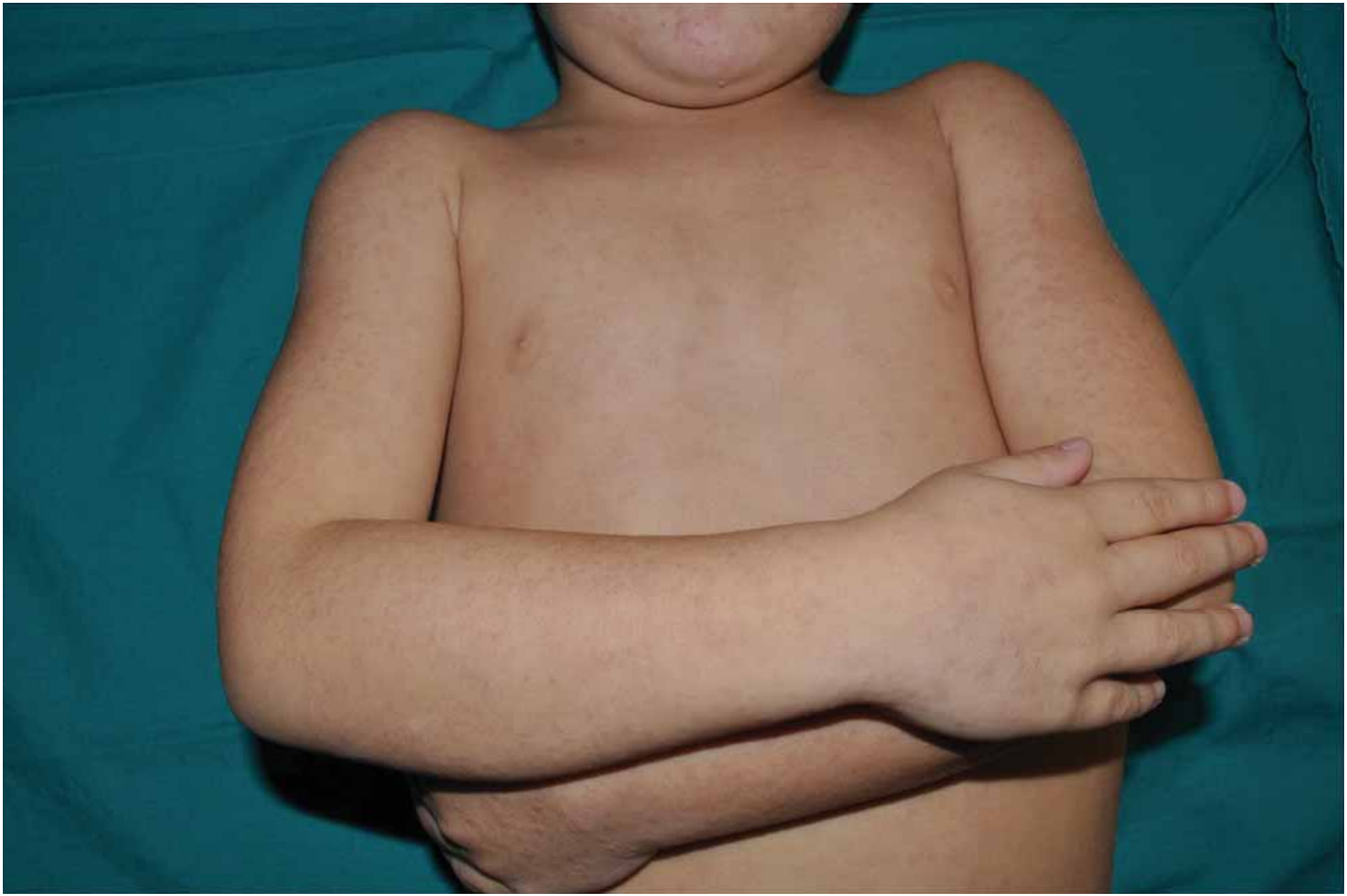


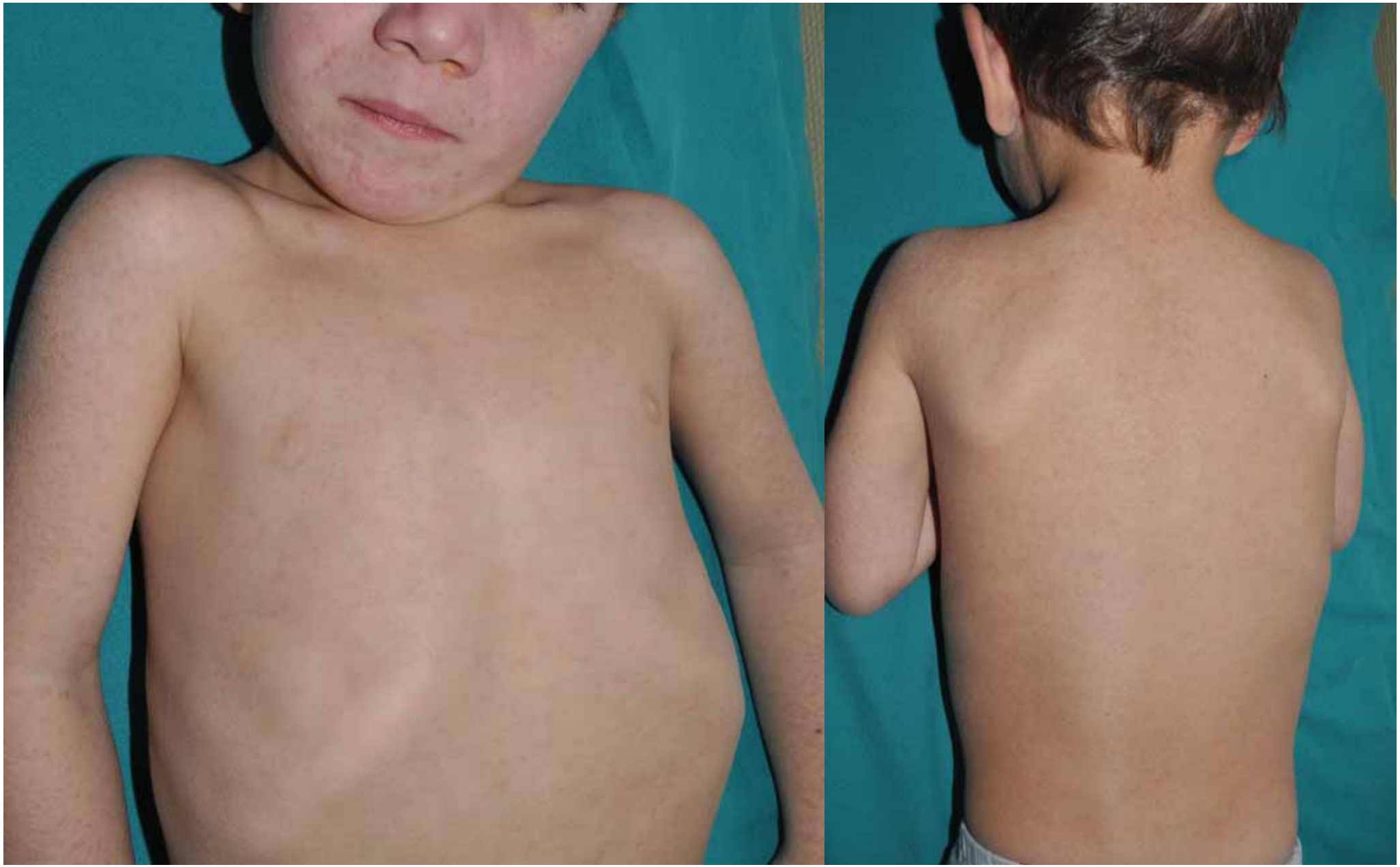


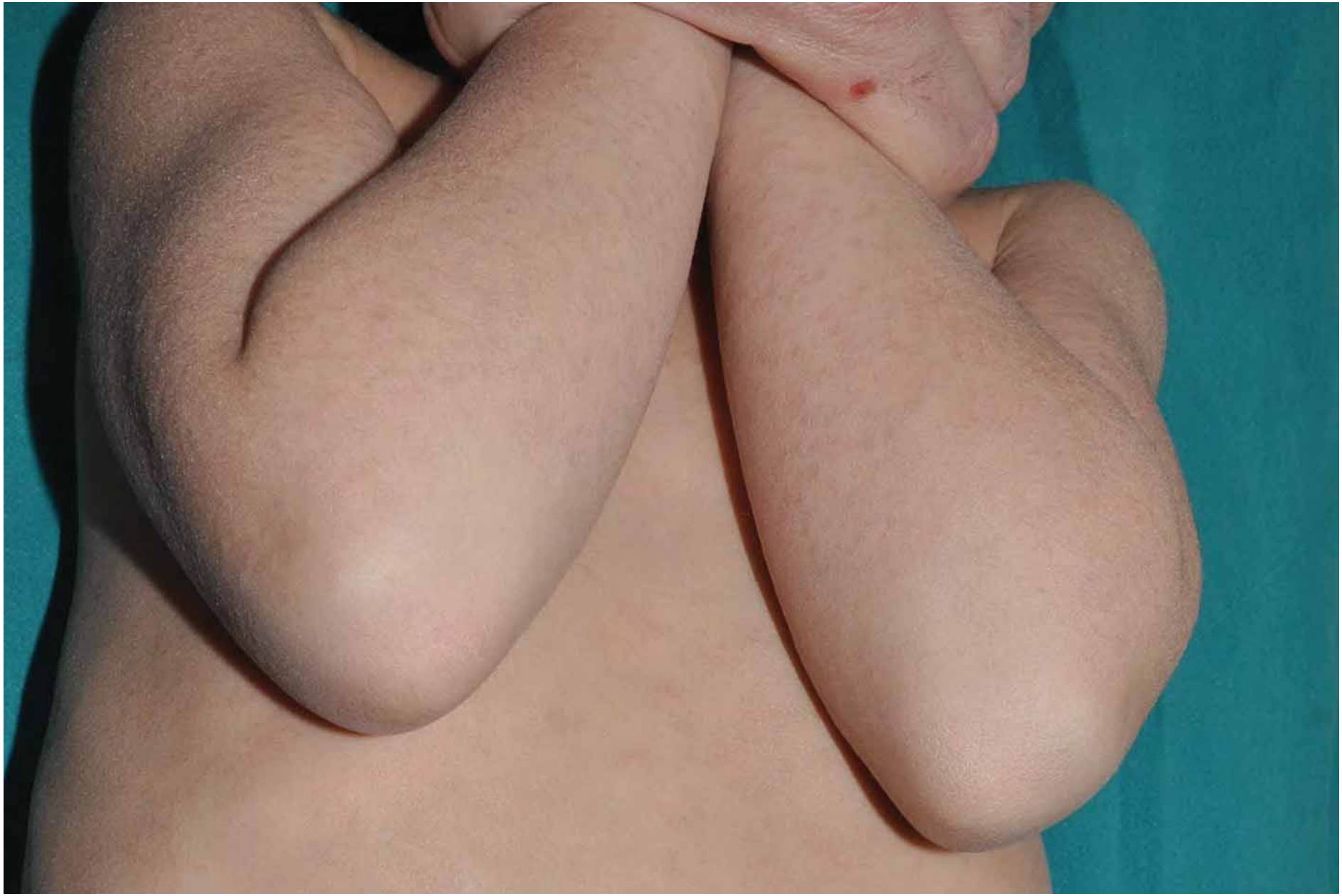


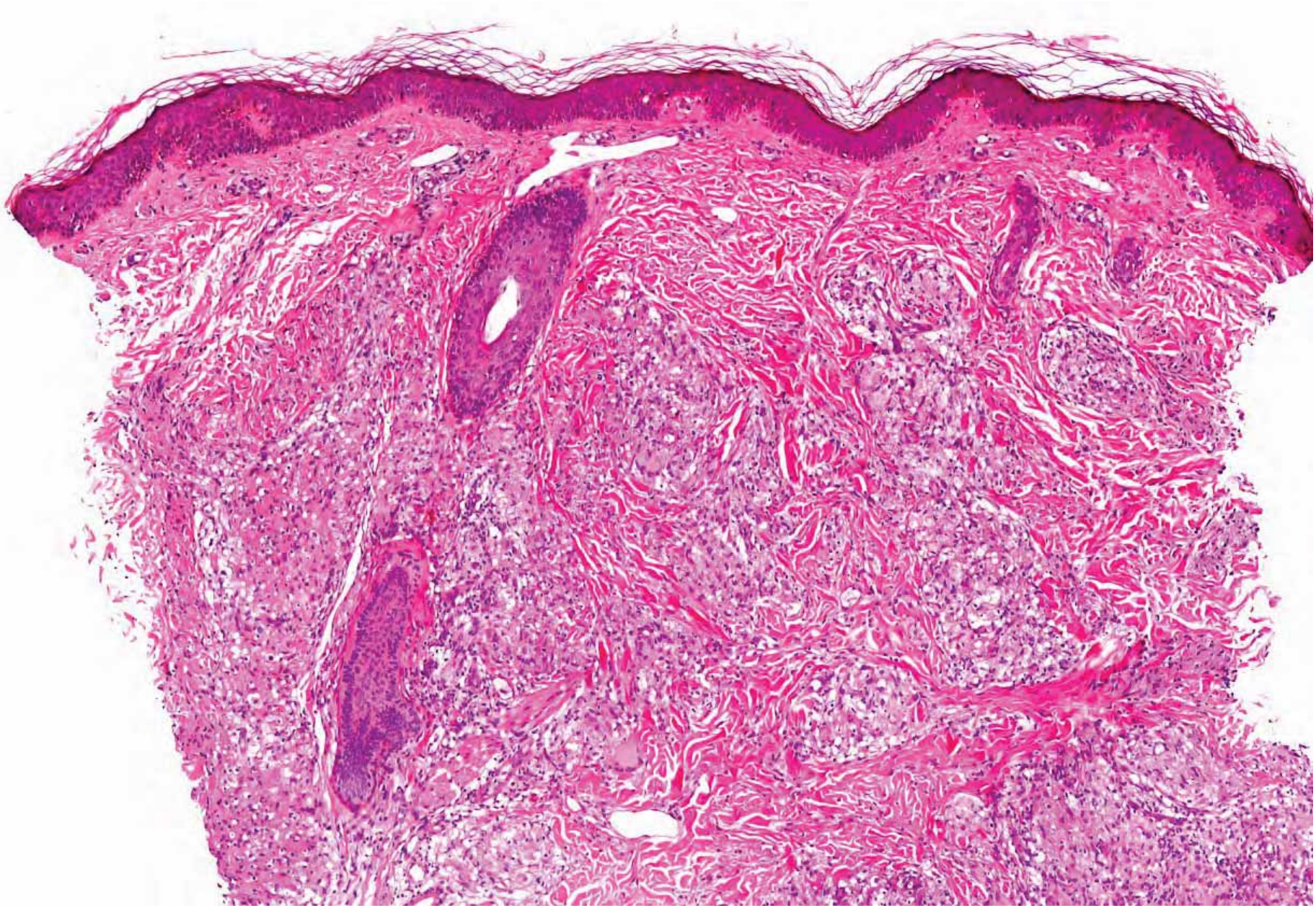


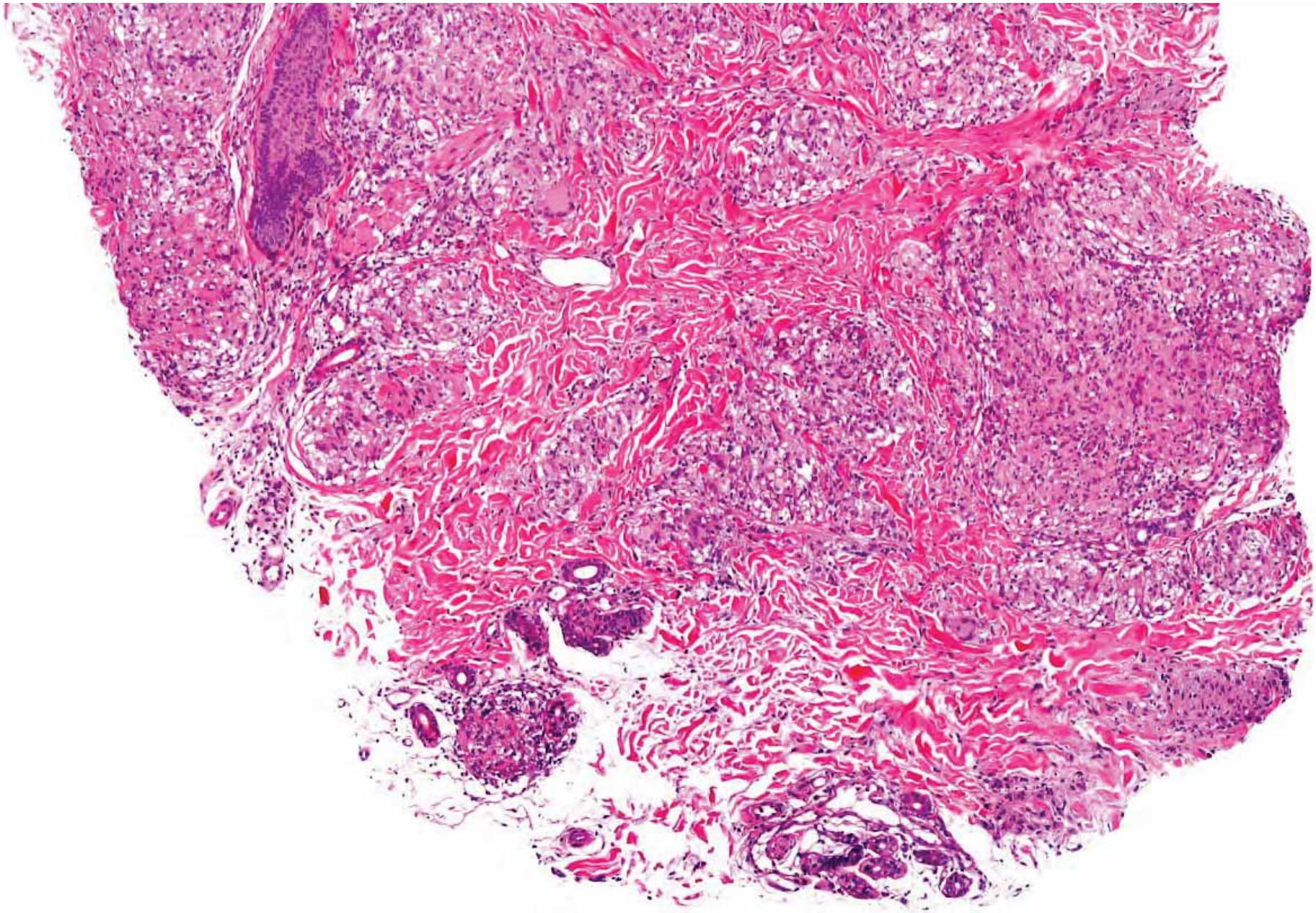


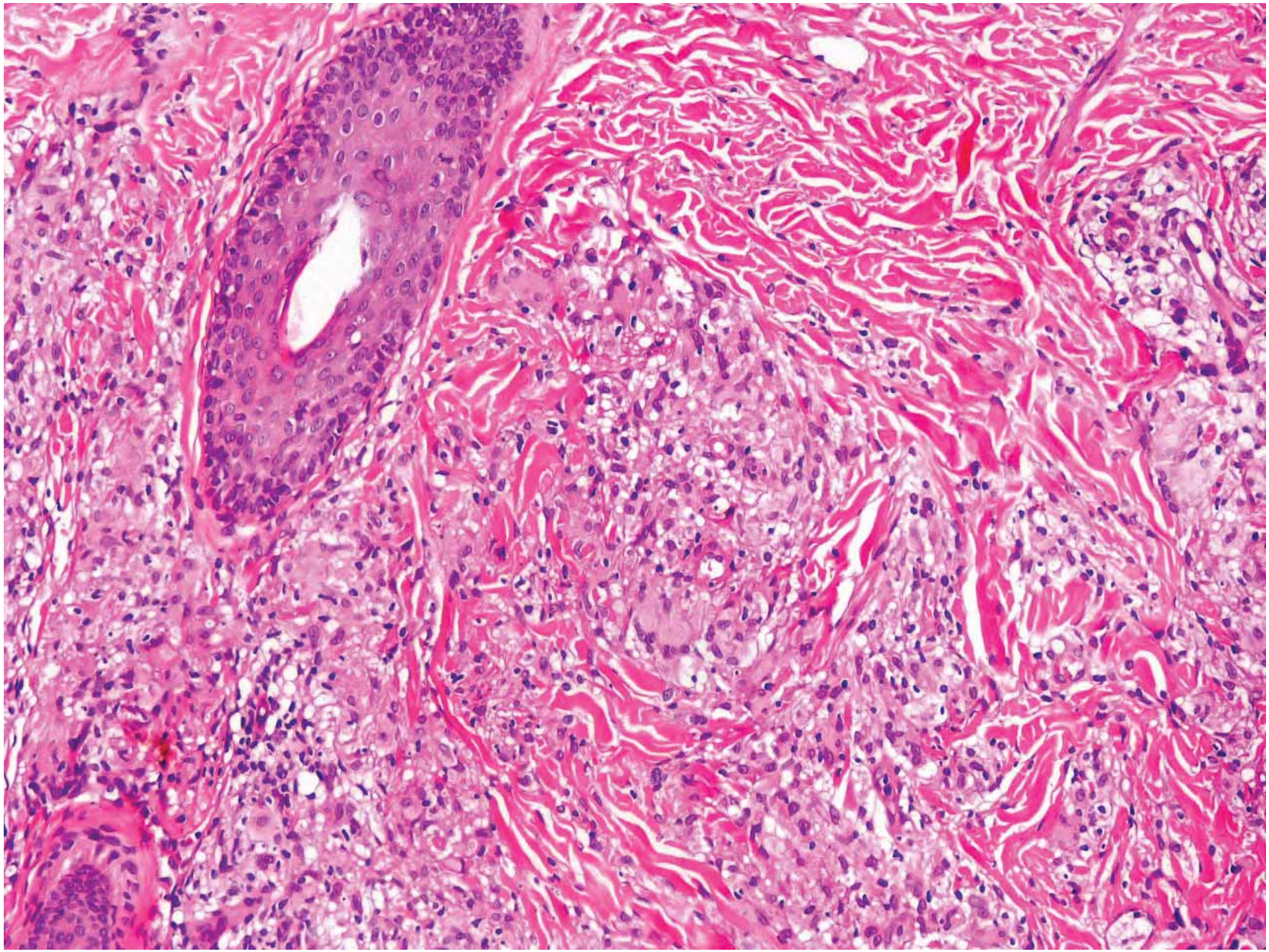


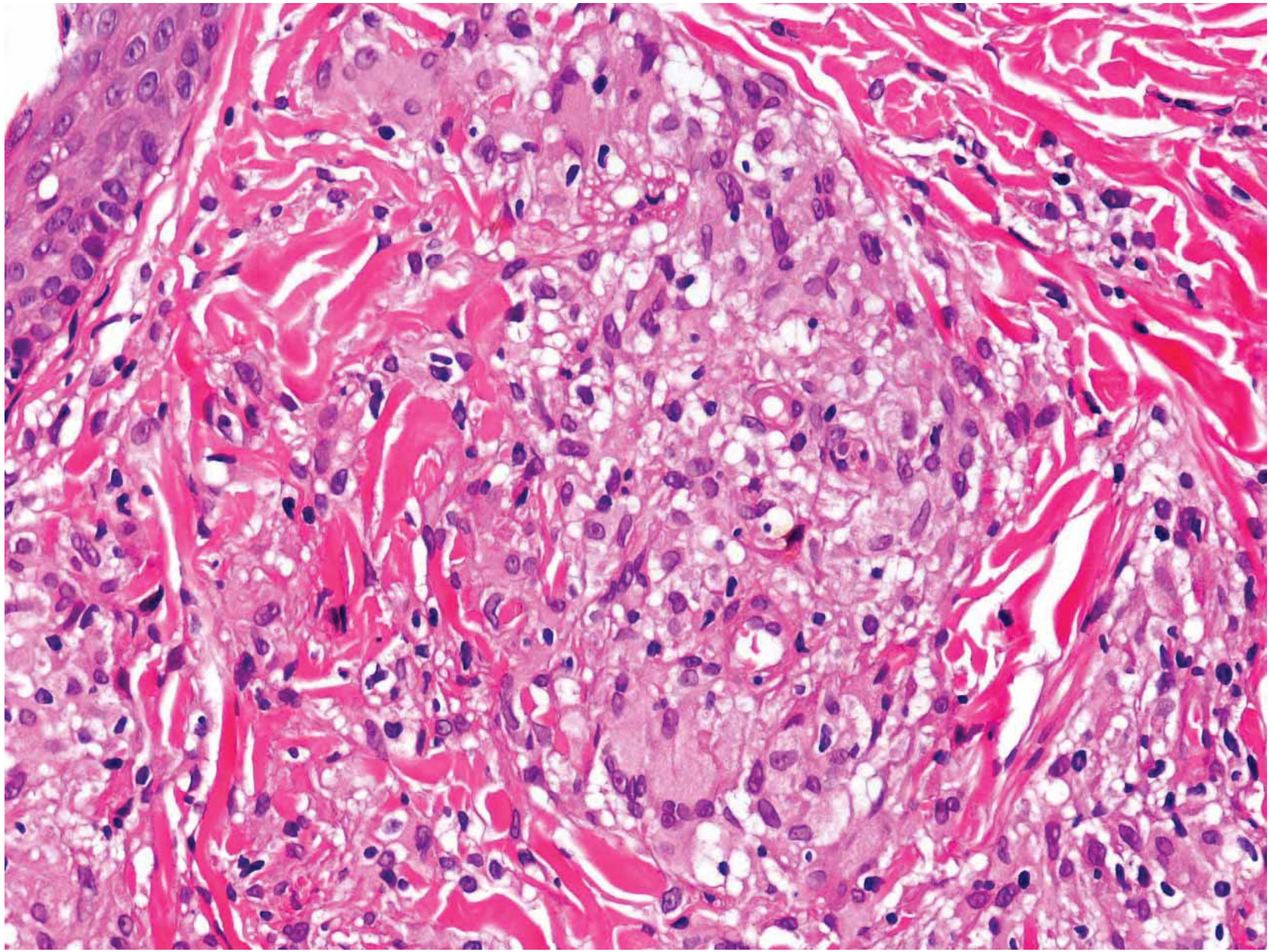


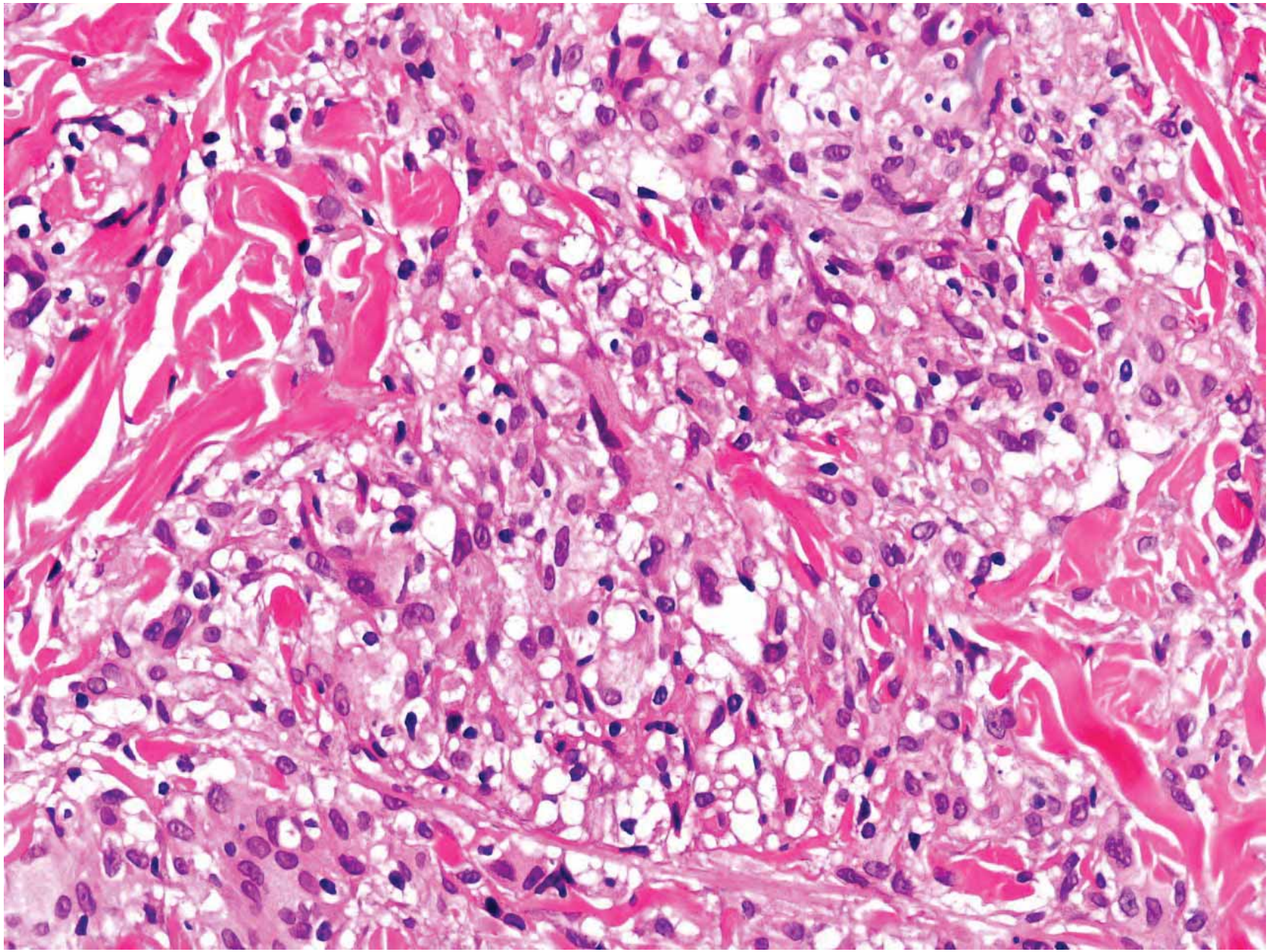


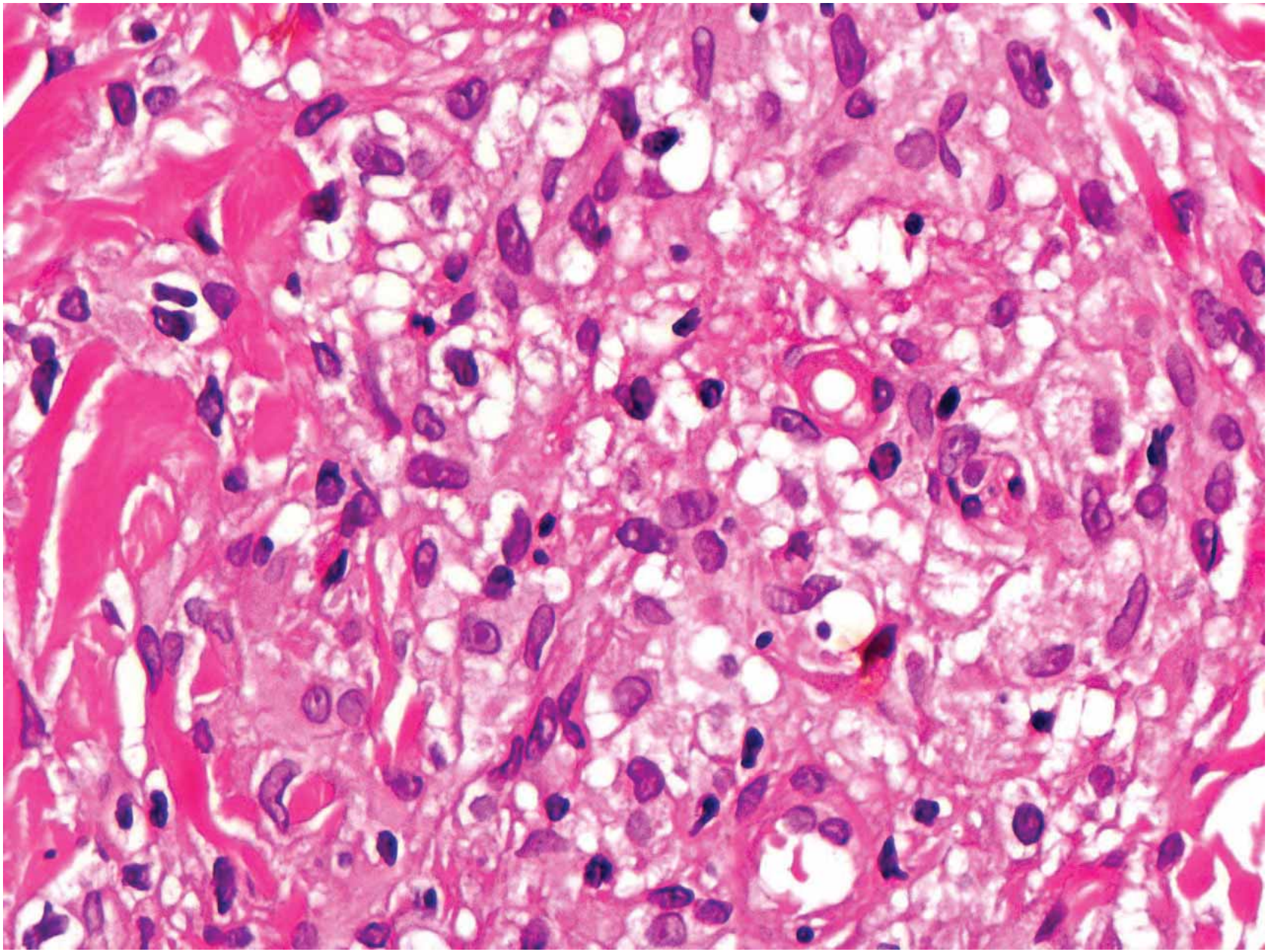


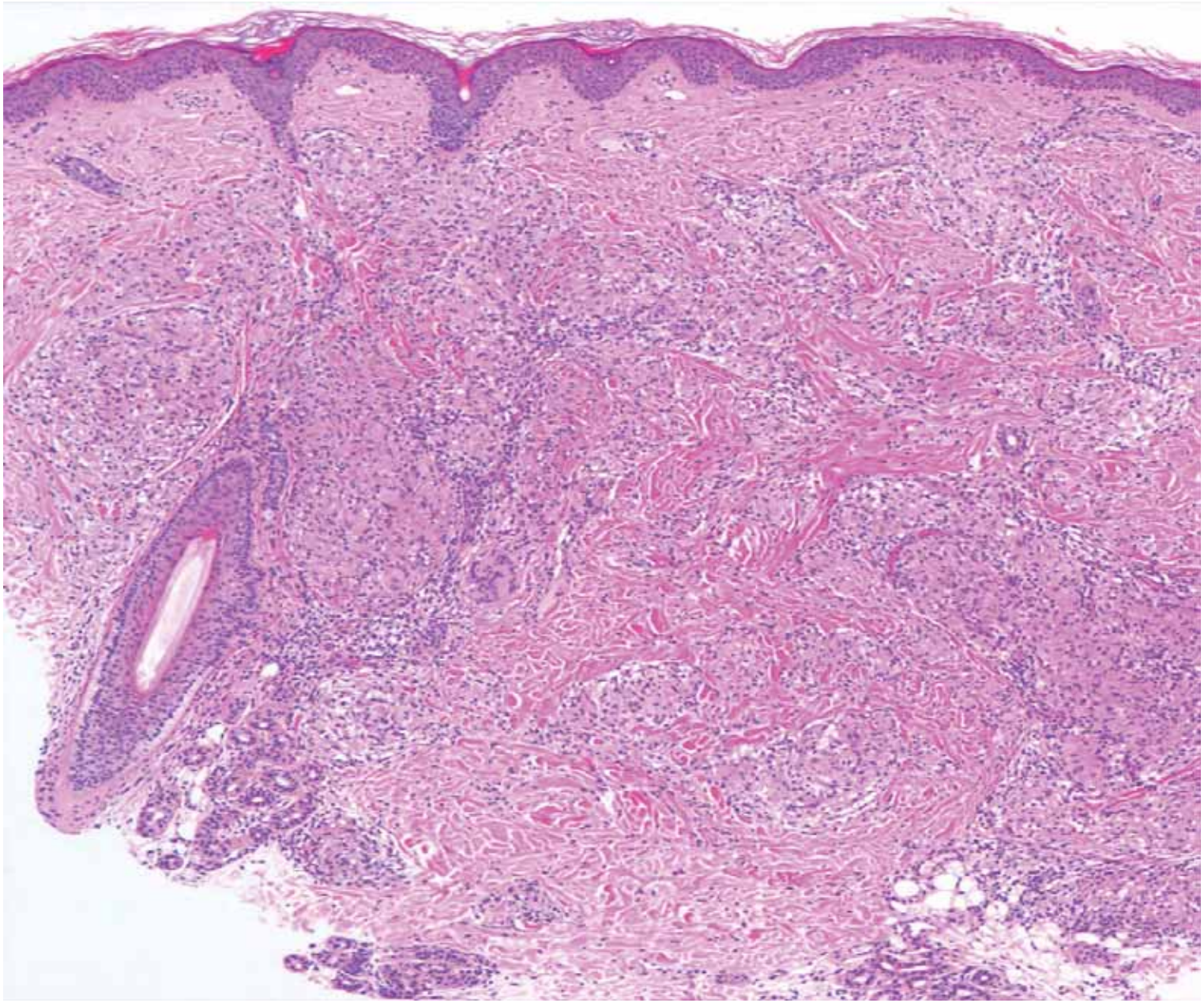


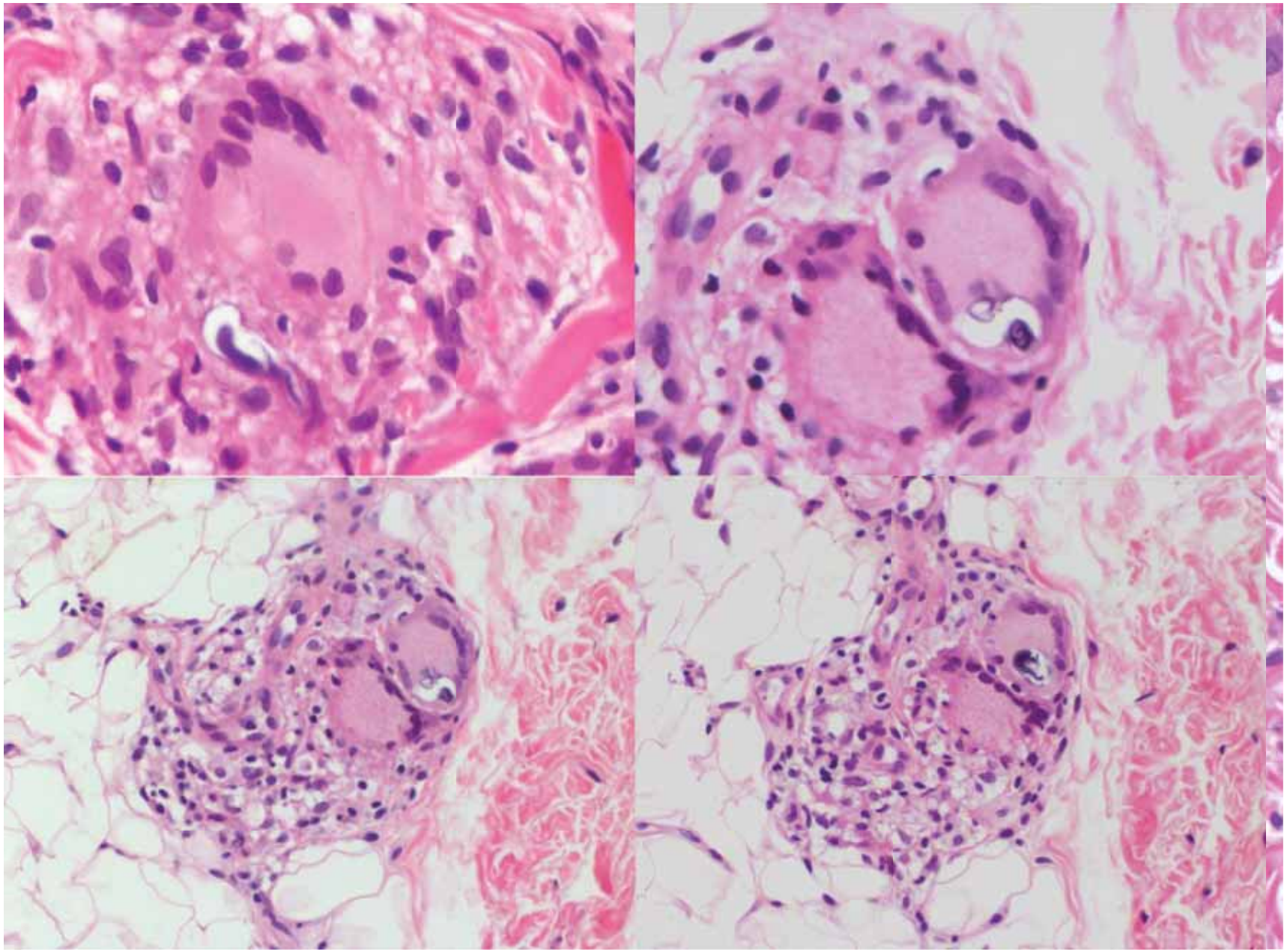


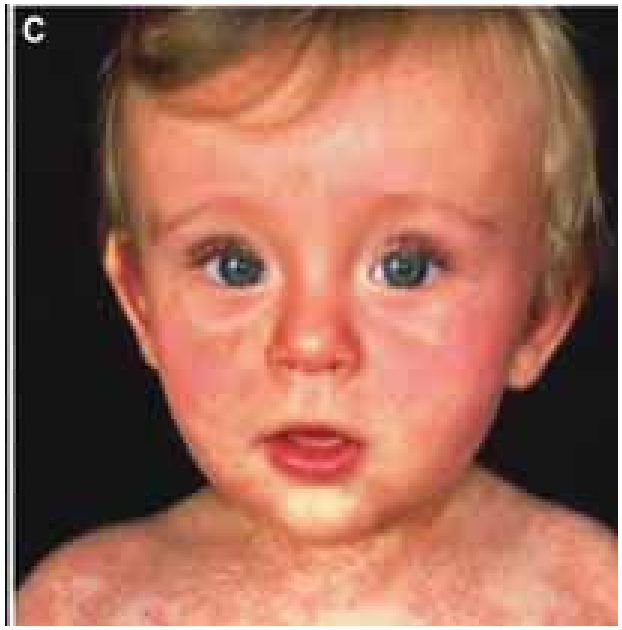


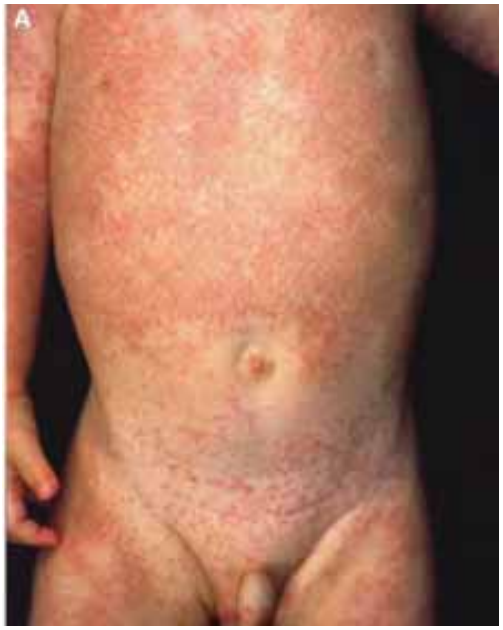












Pediatric Dermatology Vol. 27 No. 1 69–73, 2010

Sporadic Blau Syndrome With Onset of Widespread Granulomatous Dermatitis in the Newborn Period

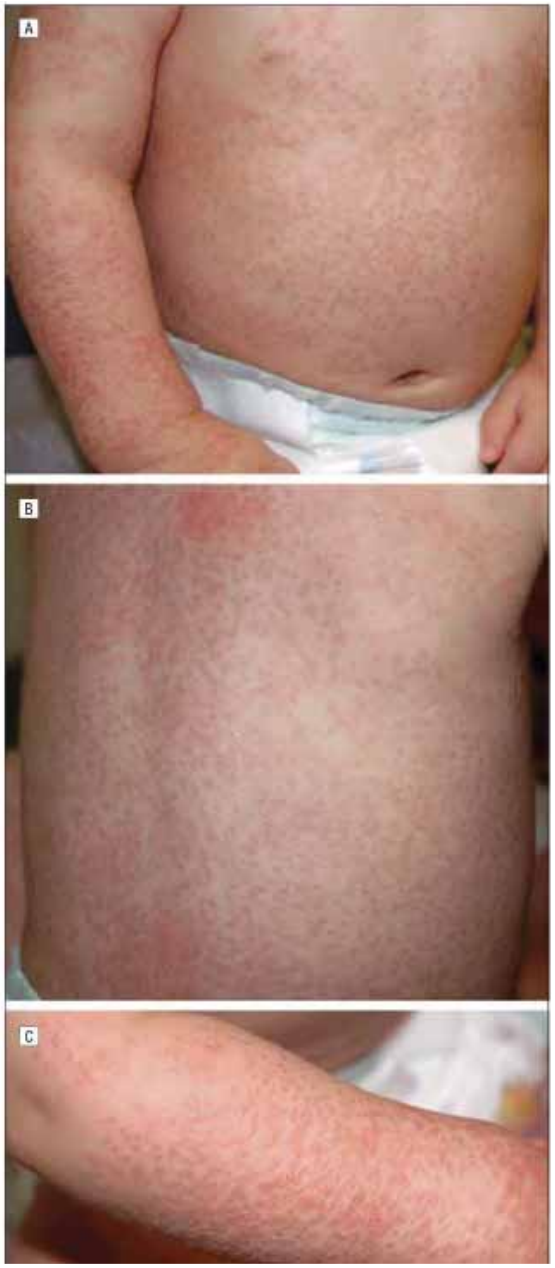
Johanna Stoevesandt, M.D.,* Henner Morbach, M.D.,† Tammy M. Martin, Ph.D.,‡ Manfred Zierhut, M.D.,§ Hermann Girschick, M.D.,† and Henning Hamm, M.D.*

Widespread Granulomatous Dermatitis of Infancy

An Early Sign of Blau Syndrome

Julie V. Schaffer, MD; Pranil Chandra, DO; Brian R. Keegan, MD, PhD; Patricia Heller, MD; Helen T. Shin, MD

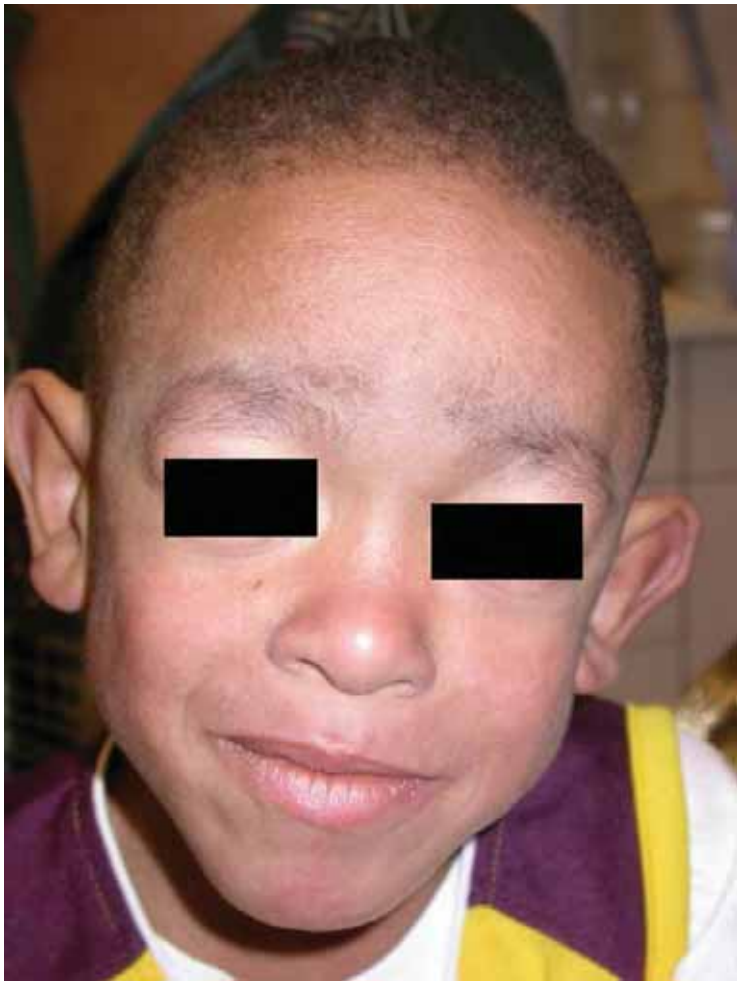
Arch Dermatol. 2007;143:386-391

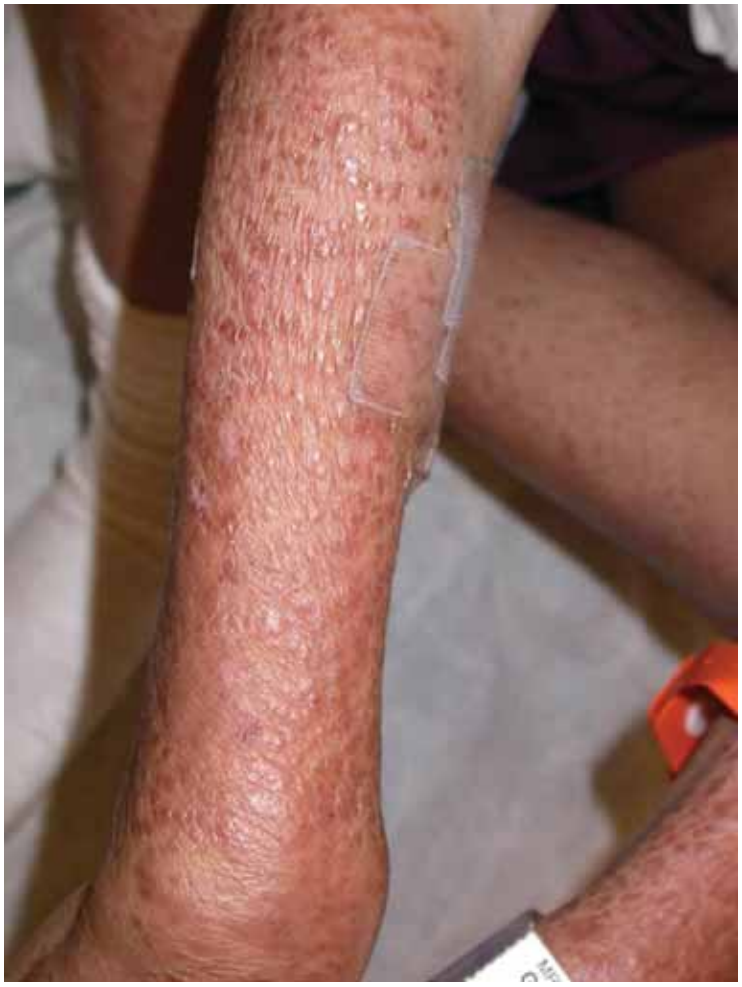


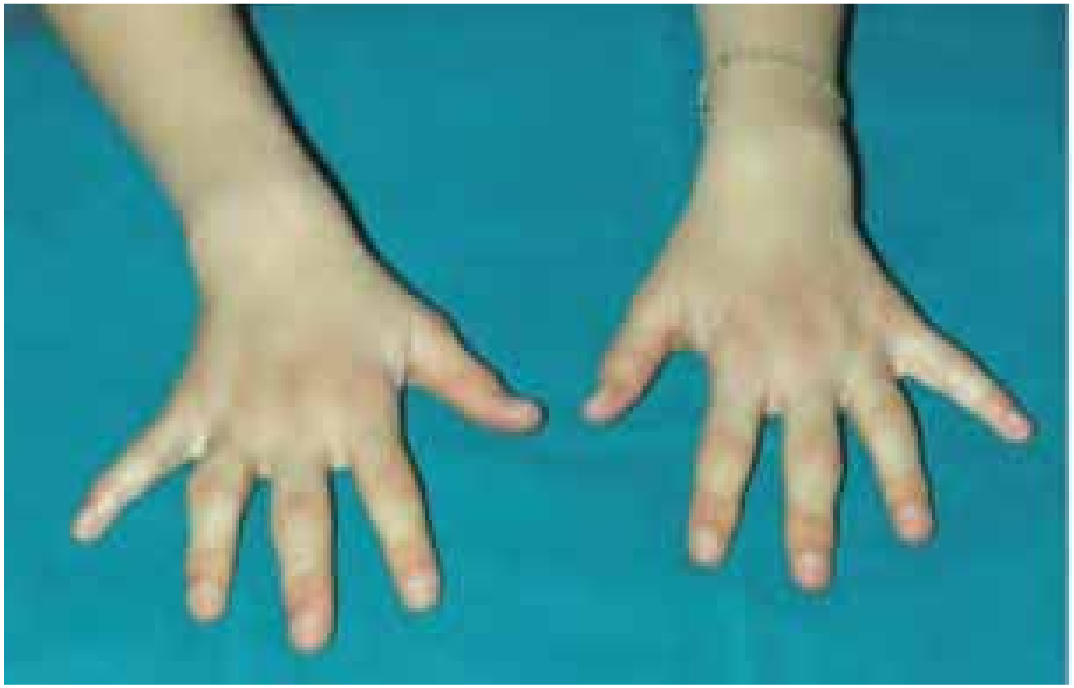
Two pediatric cases of Blau syndrome

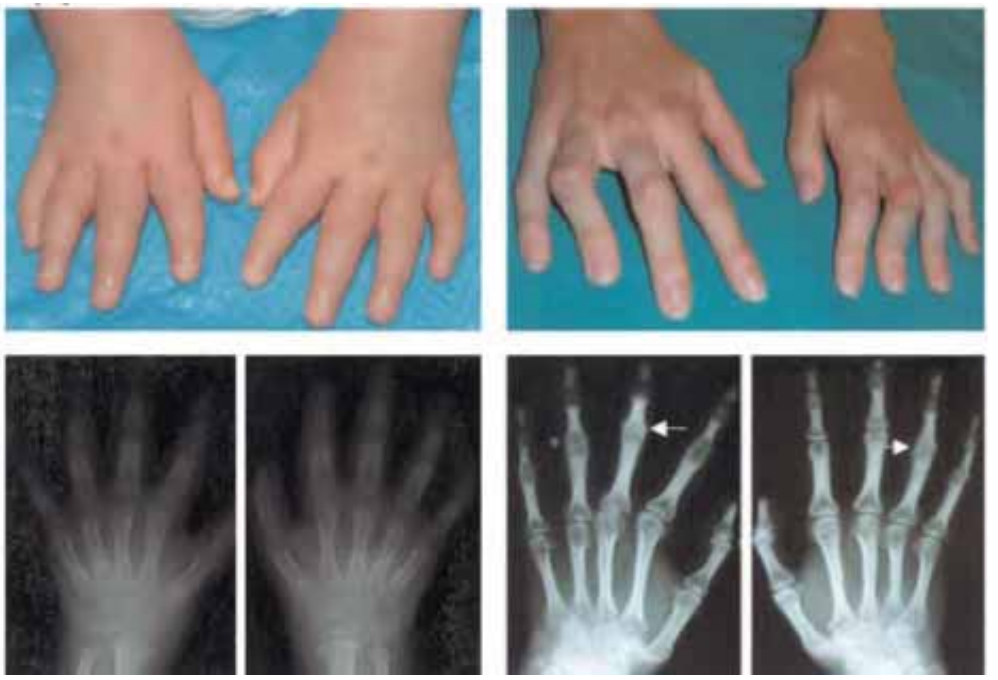
Donald A Glass II MD, PhD[1], Jennifer Maender MD[1], Denise Metry MD[1,2]

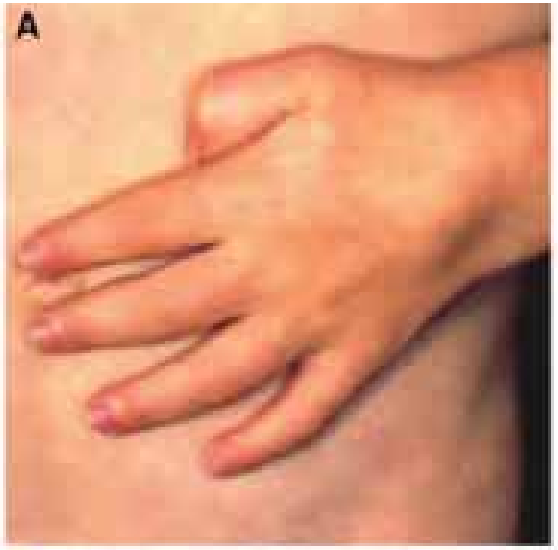
Dermatology Online Journal 15 (12): 5

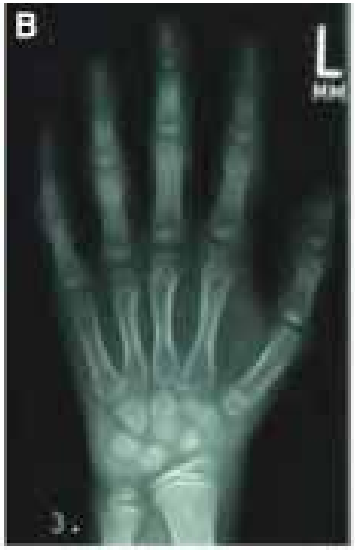


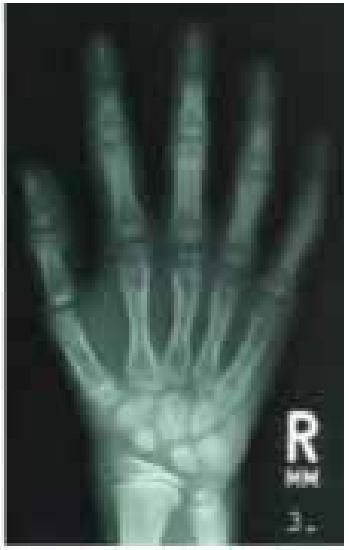










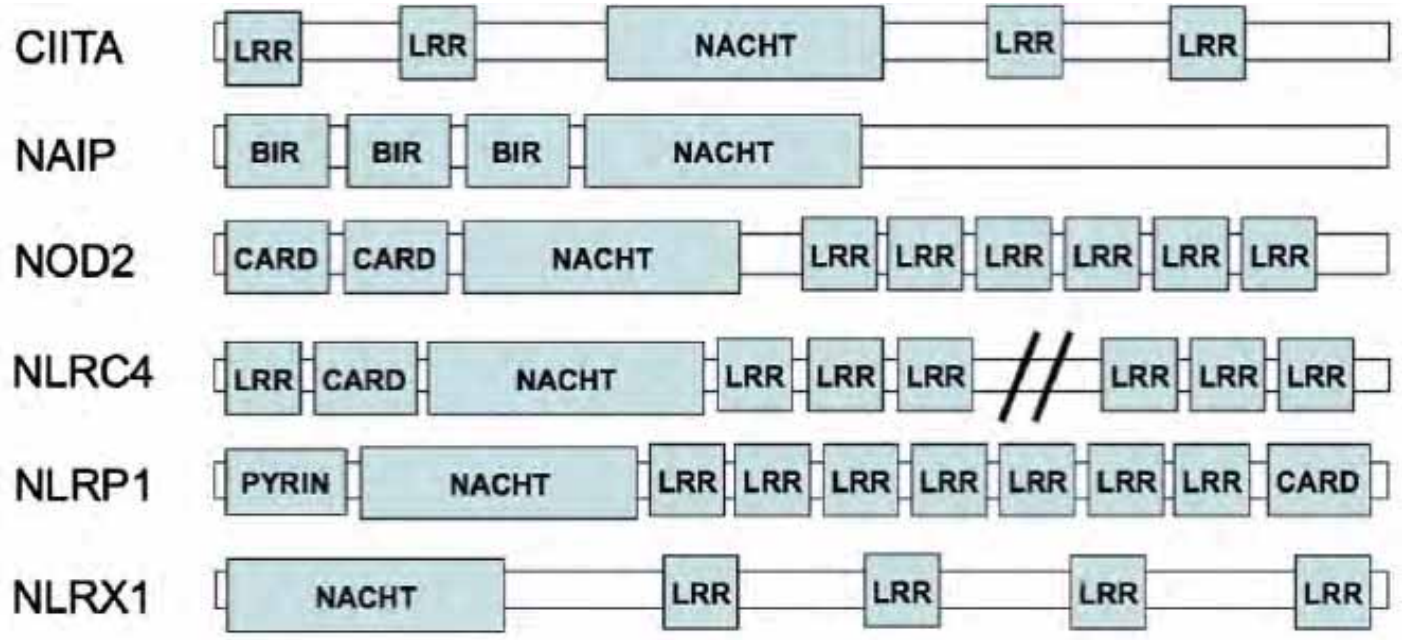


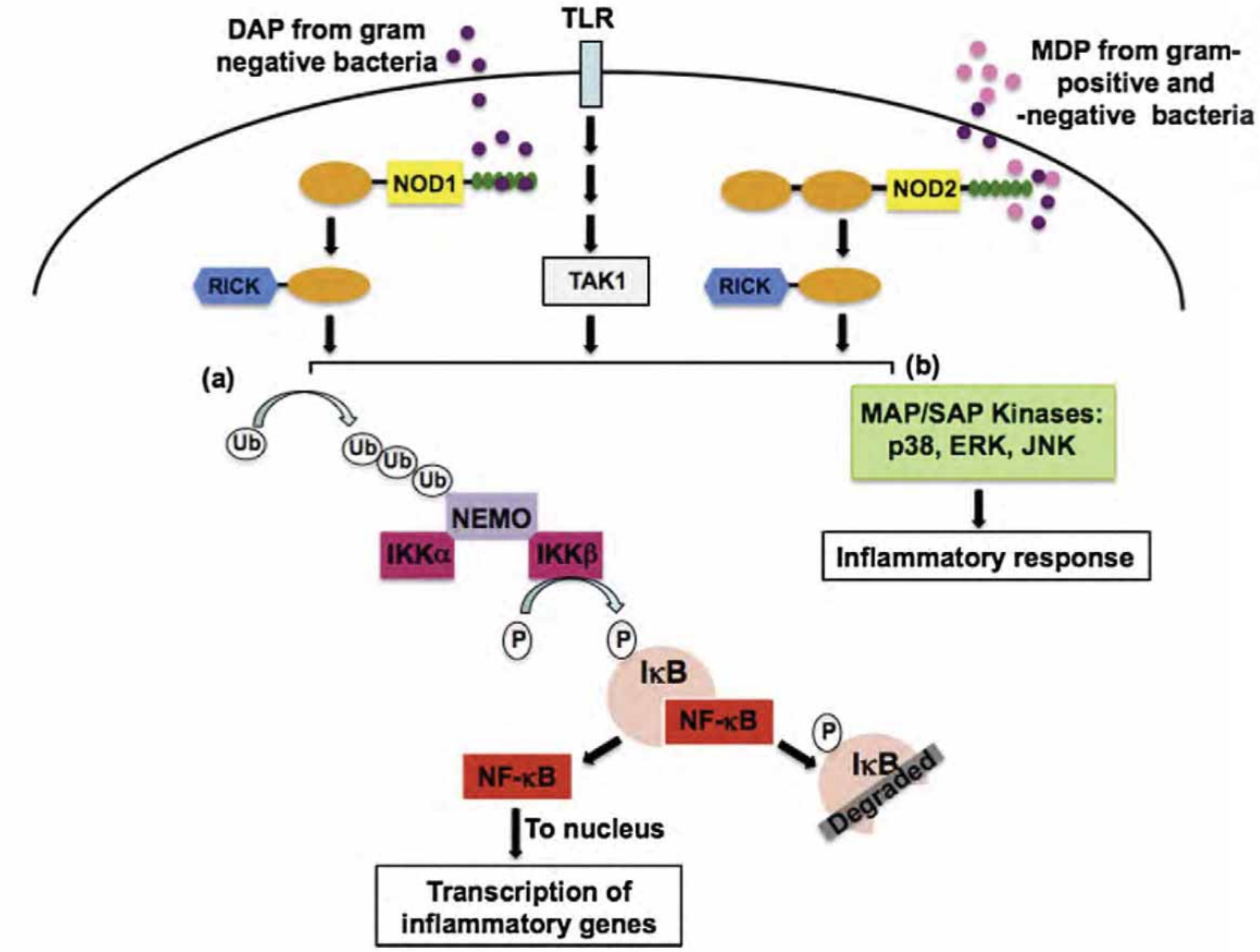
- Symmteric chronic polyarthritis
- Tenosynovitis, synovial thickenings
- Deformities, luxation

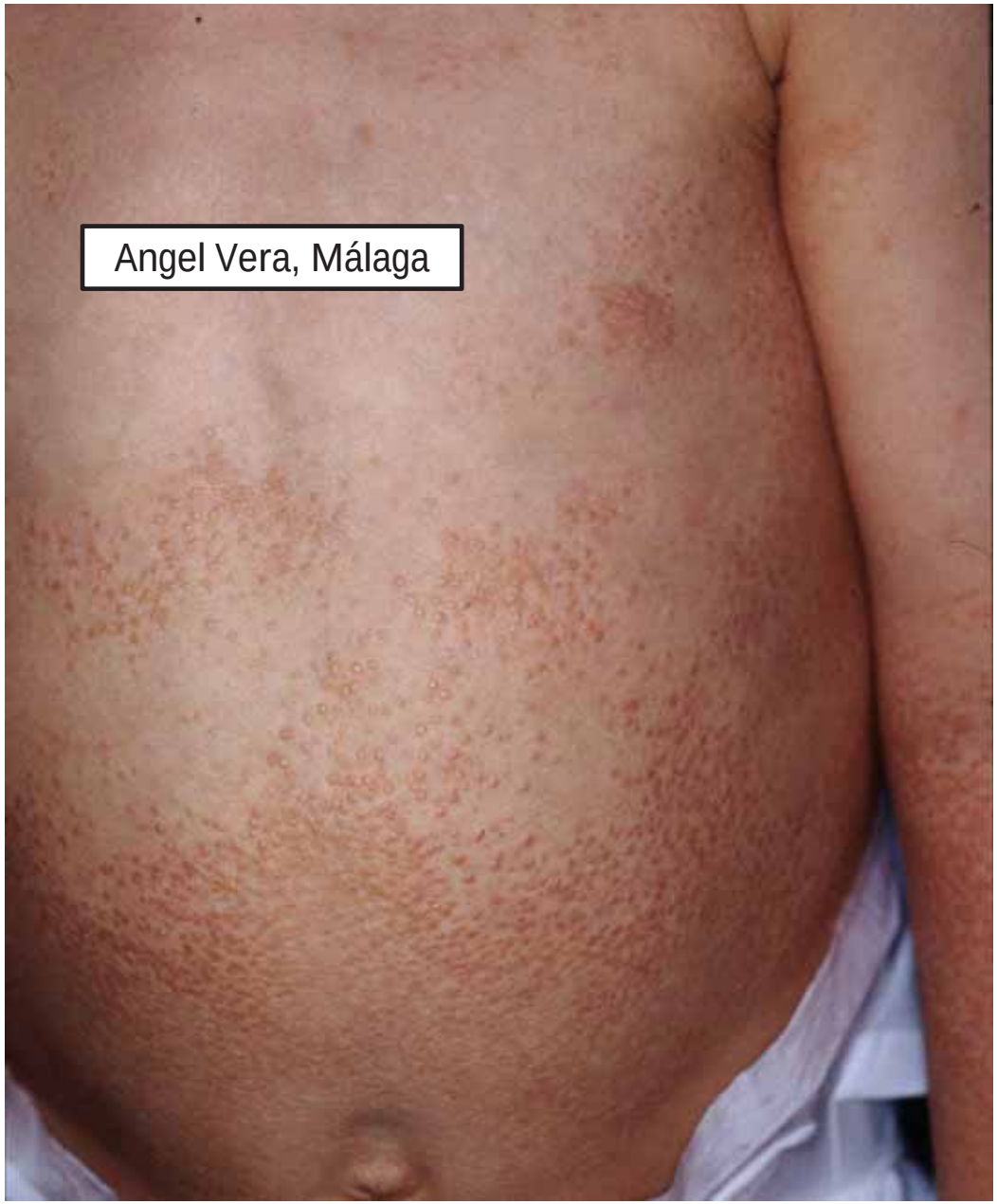
UVEITIS

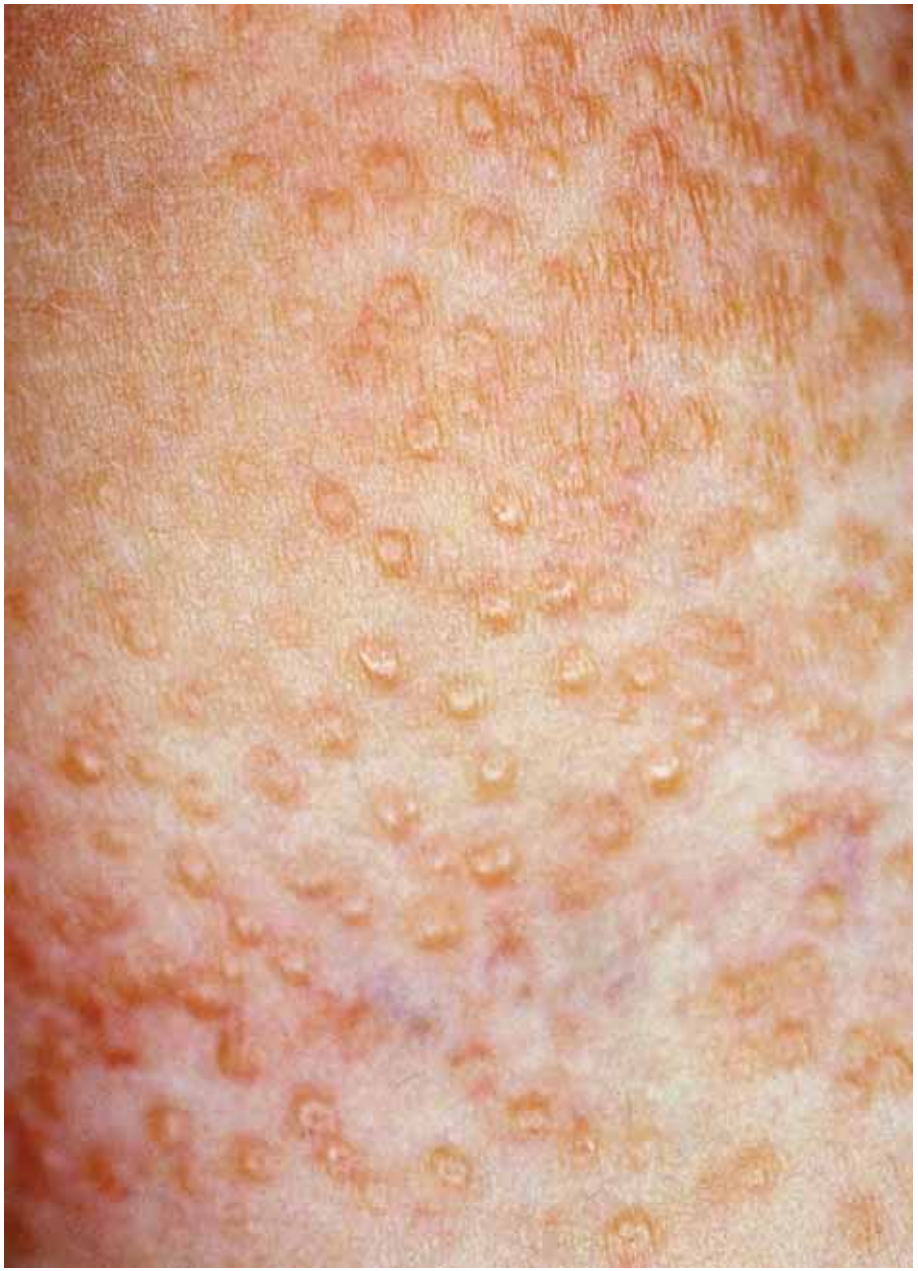
Table 1 Members and subfamilies of the NOD-like receptor (NLR) family of proteins.

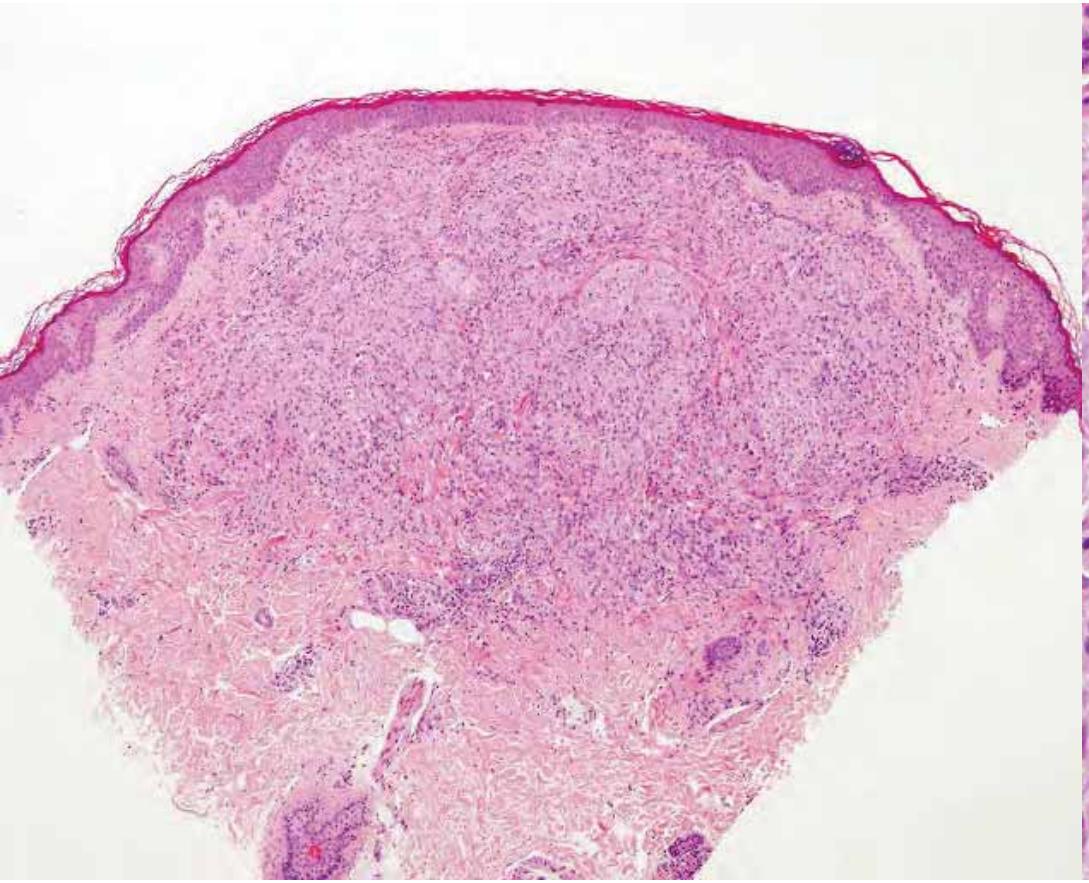
Name	Family	Gene	Chromosome
MHC class II (C-II) transactivator	NLR	*CIITA*	16p13
Neuronal apoptosis inhibitory protein	NLRB	*NAIP*	5q13
Nucleotide-binding oligomerization domain (NOD) 1 and 2	NLRC	*NOD1,2*	7p15, 16q12
NOD-like receptor caspase recruitment domain containing proteins 3–5	NLRC	*NLRC3–5*	16p13, 2p22, 16q13
NACHT, LRR, and PRD containing proteins 1–14	NLRP	*NLRP1*	17p13
		NLRP2, 4, 5, 7–9, 11–13	19q13
		NLRP3	1q44
		NLRP6, 10, 14	11p15
NOD-like receptor with "unknown" domain	NLRX	*NLRX1*	11q23

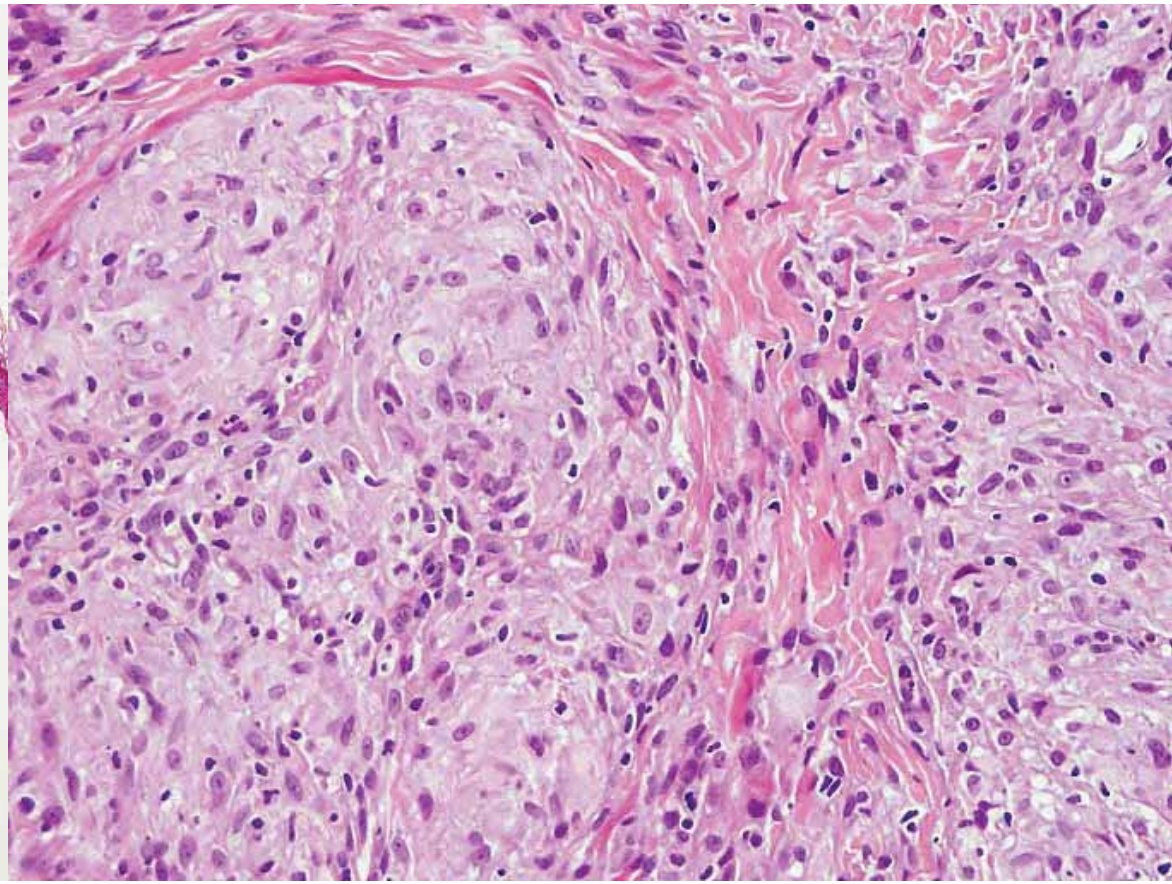



DAP from gram negative bacteria
TLR
MDP from gram-positive and -negative bacteria
NOD1
NOD2
RICK
TAK1
RICK
(a)
(b)
Ub
Ub
Ub
Ub
NEMO
IKKα
IKKβ
MAP/SAP Kinases: p38, ERK, JNK
Inflammatory response
P
P
IκB
NF-κB
P
IκB
Degraded
NF-κB
To nucleus
Transcription of inflammatory genes


Angel Vera, Málaga



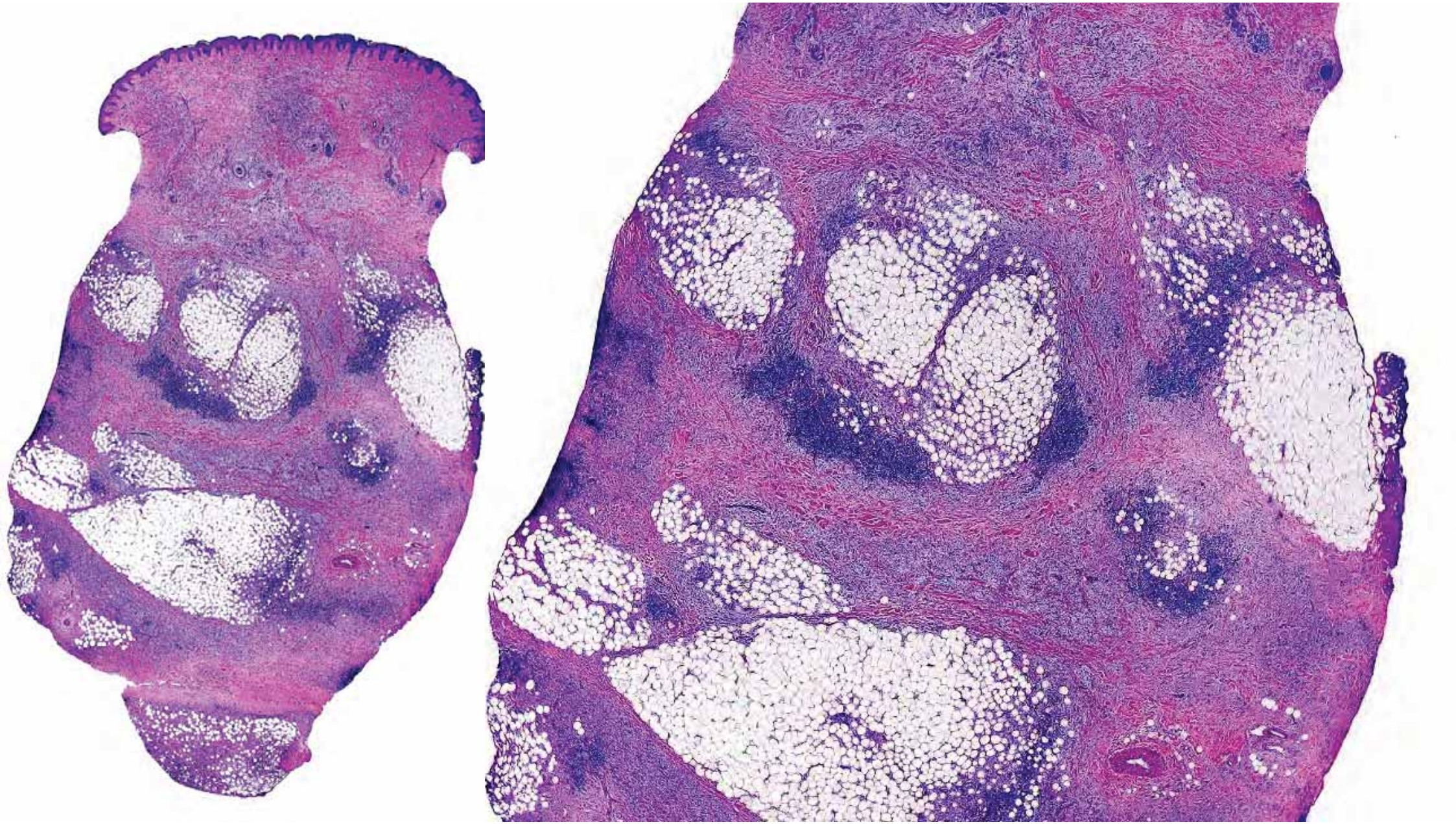


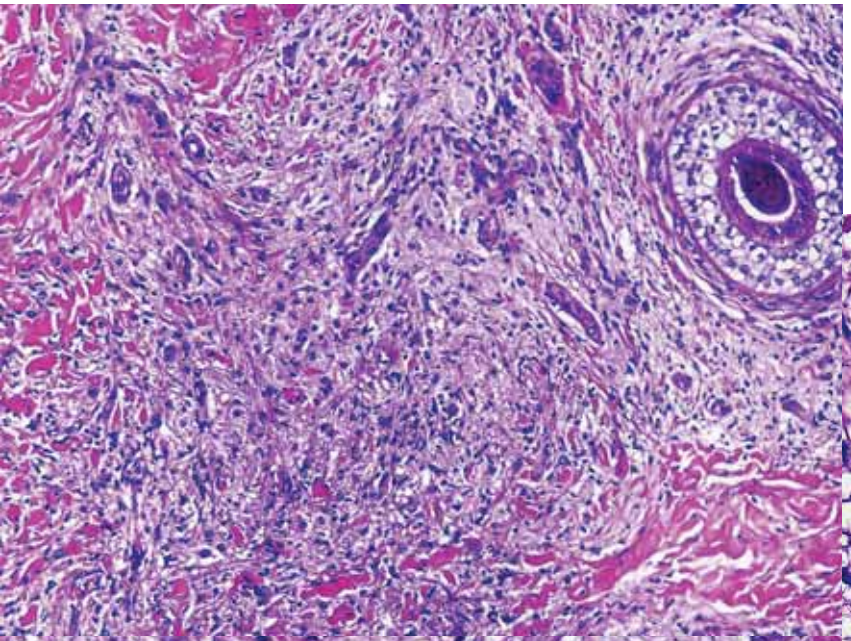


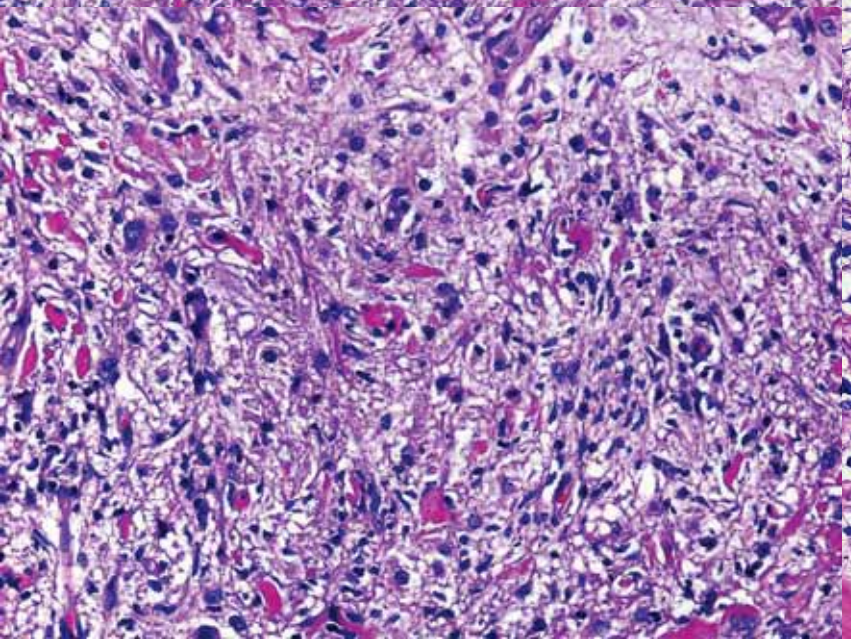
Dermatopathologic clue #6

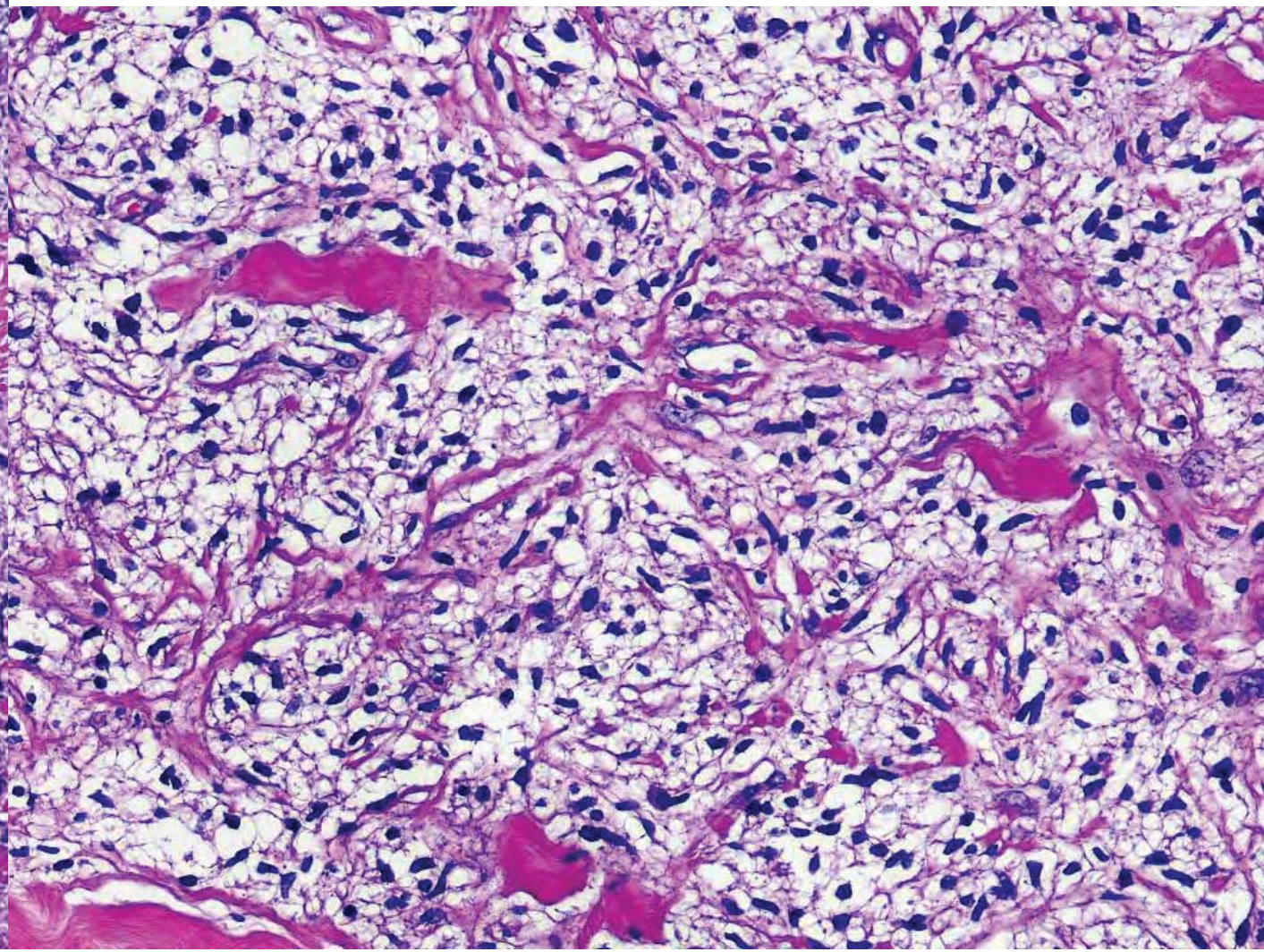
Panniculitis & sarcoid granulomas < 4 years

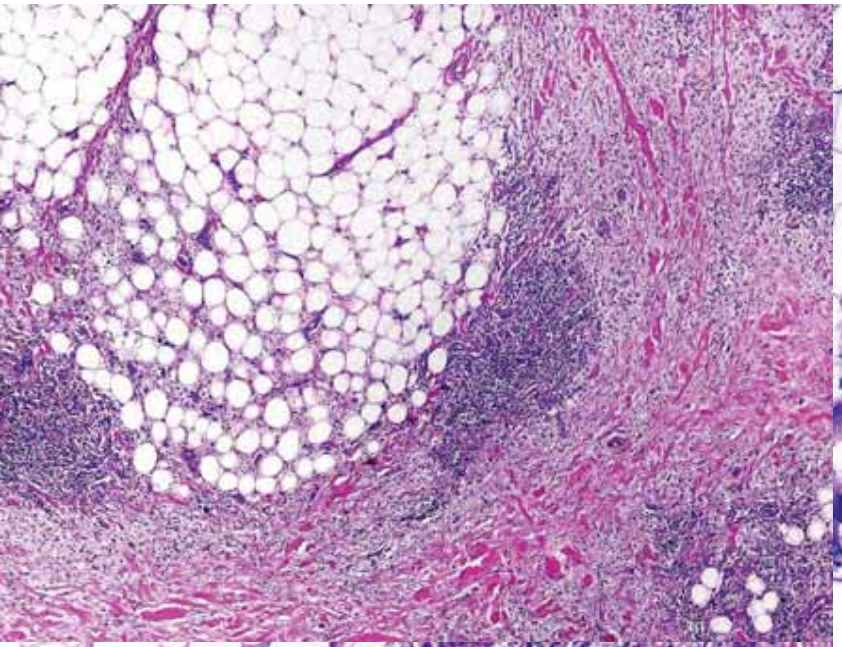
Blau syndrome (NOD2 – CARD15)

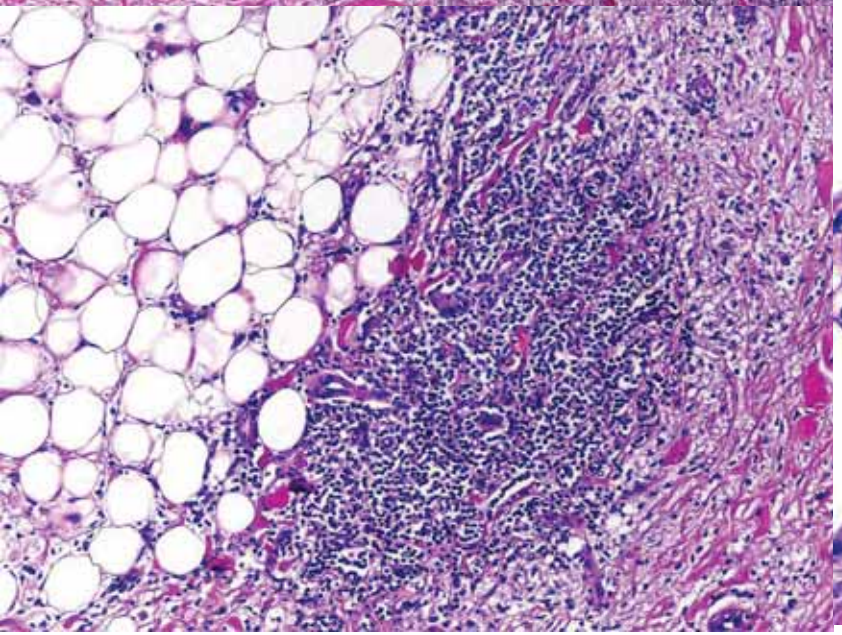


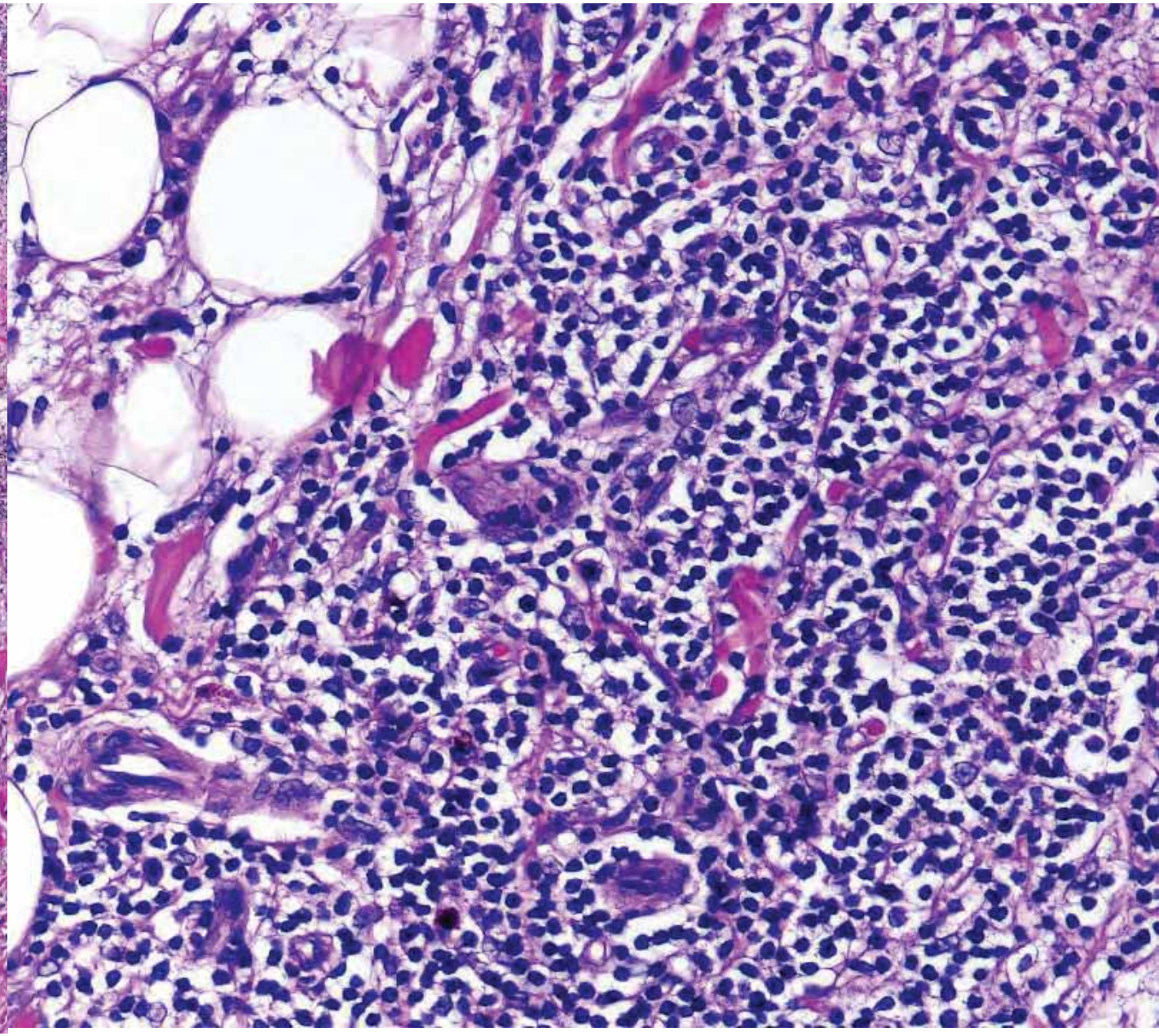


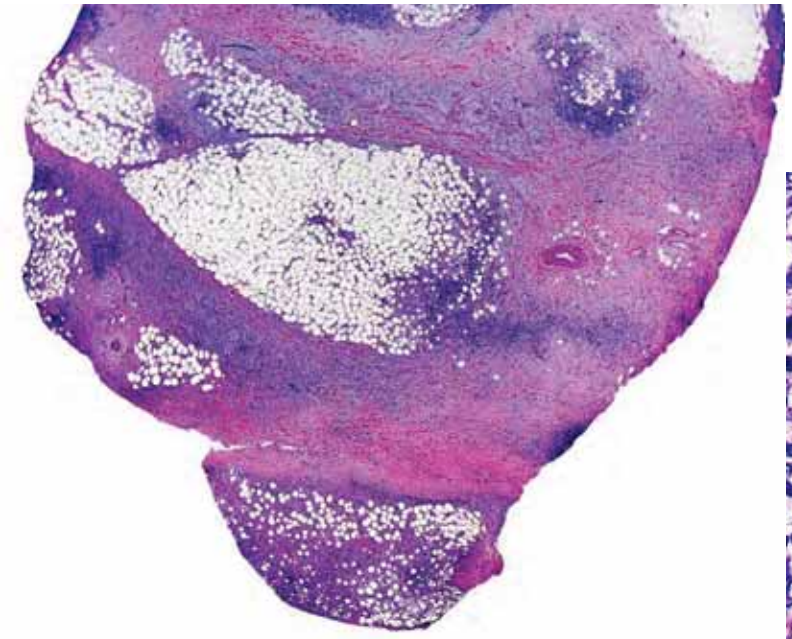


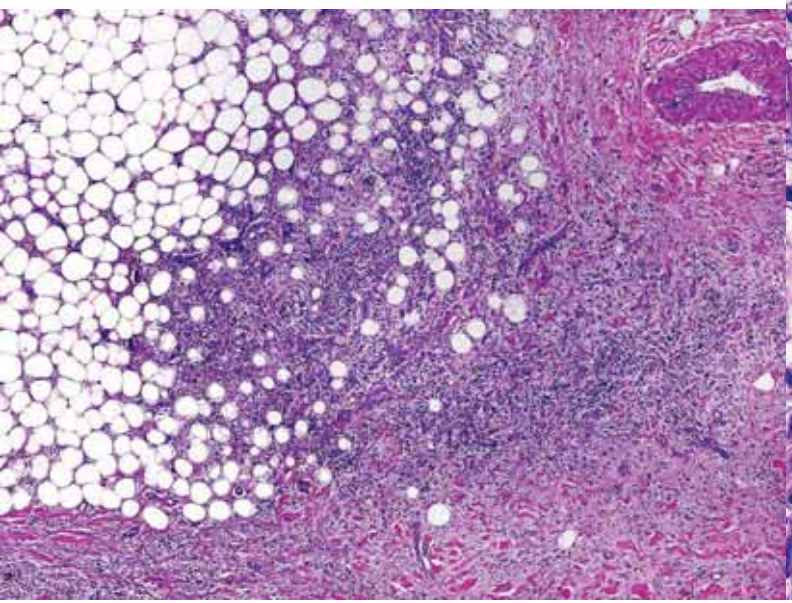


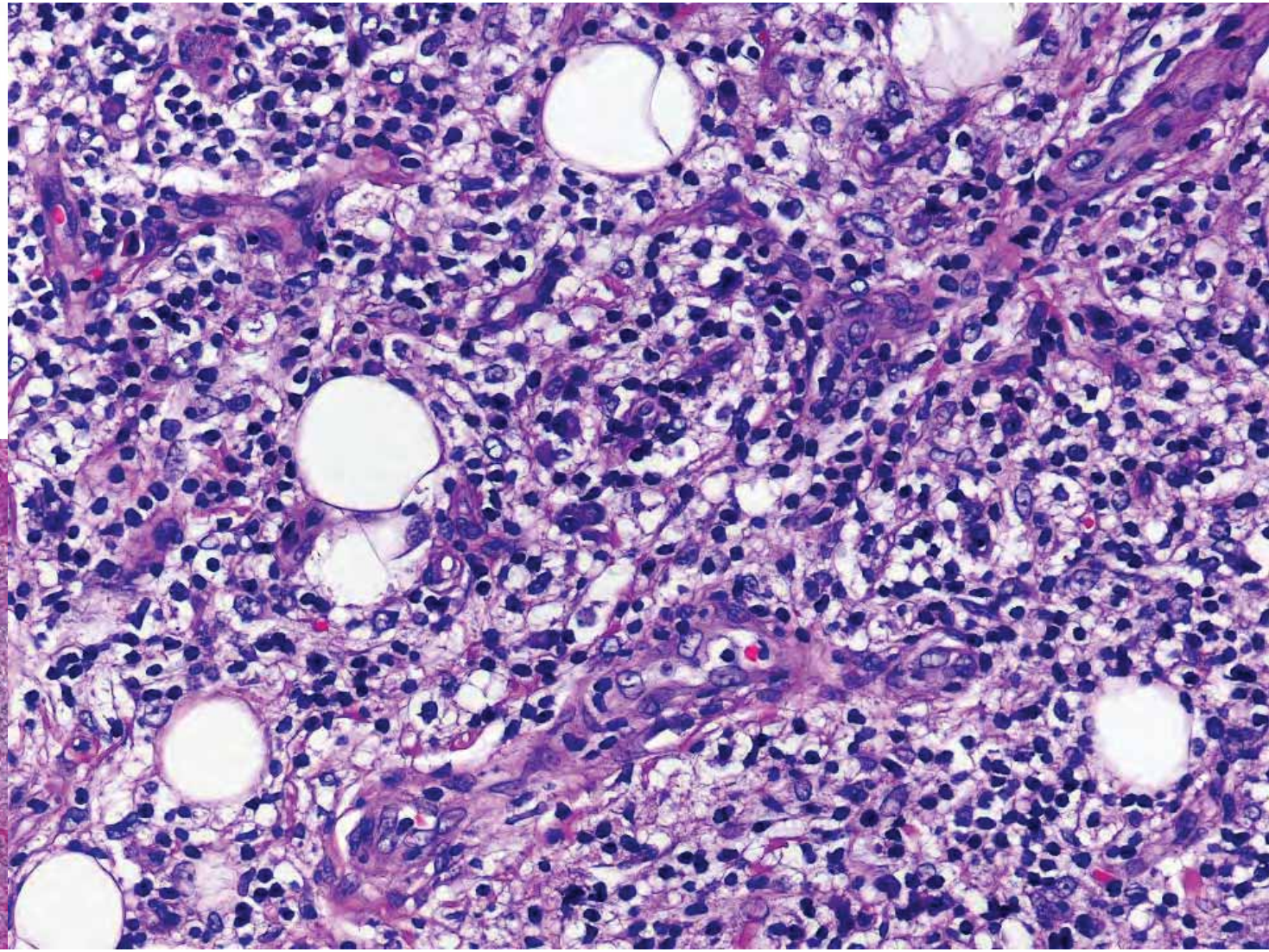


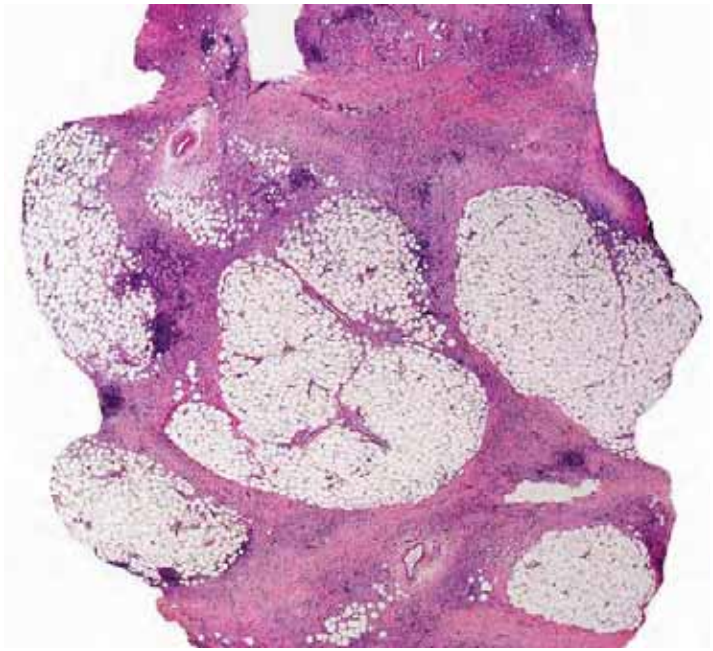


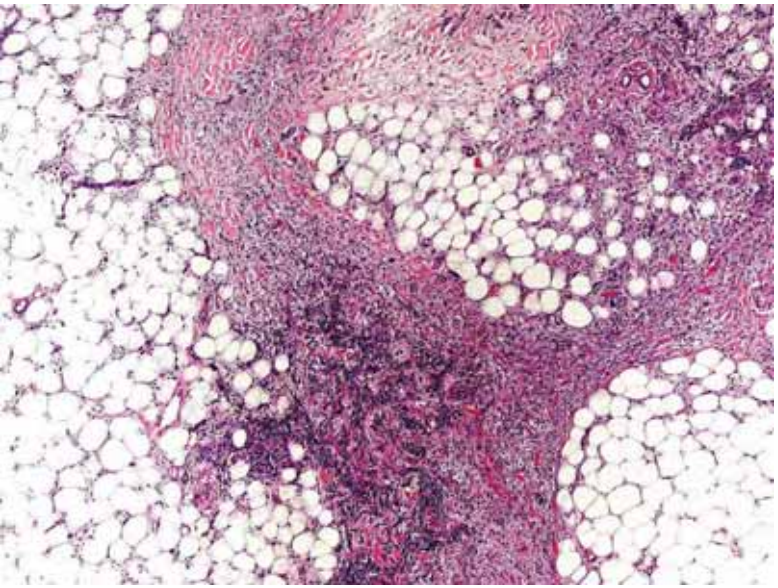


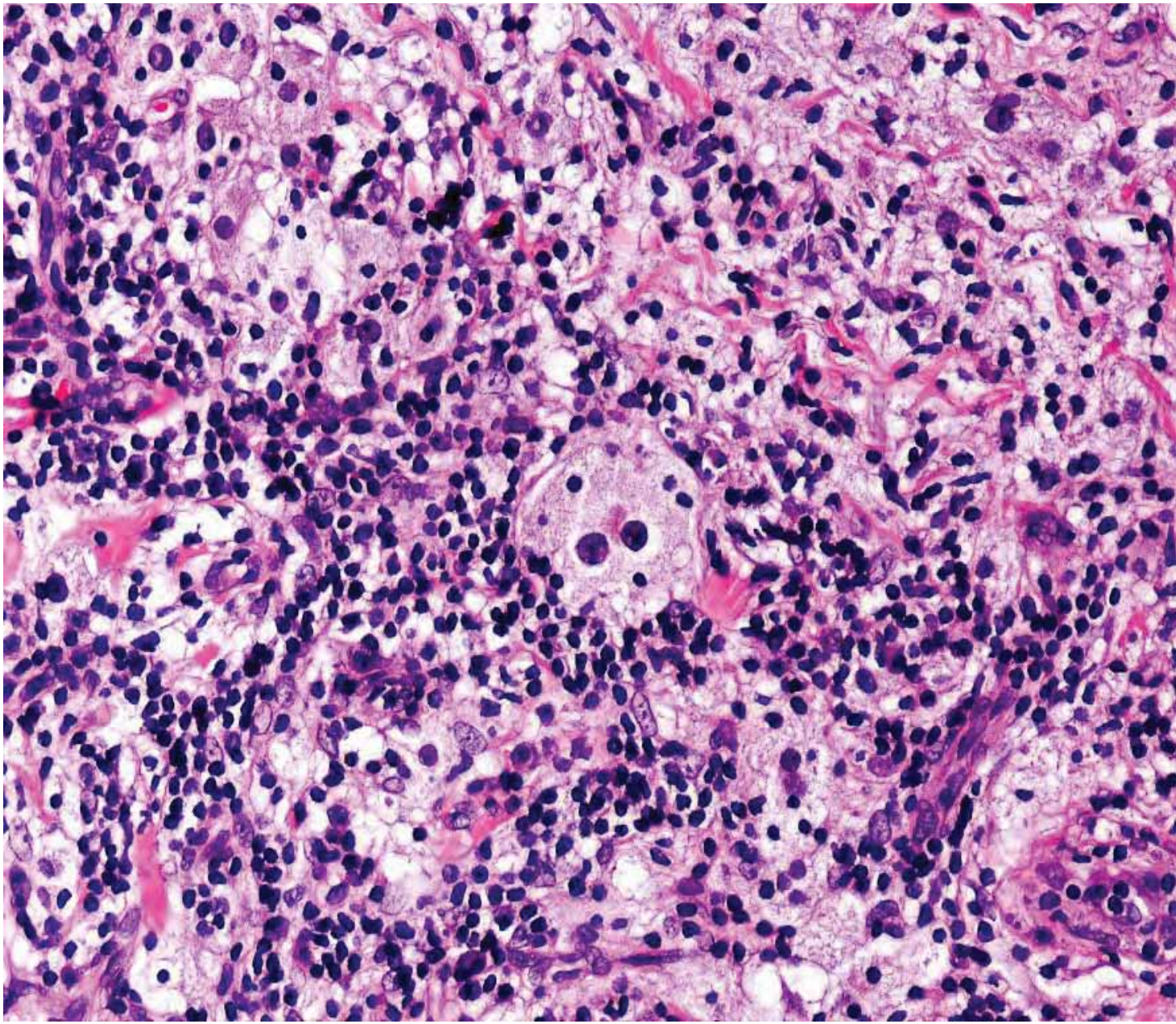


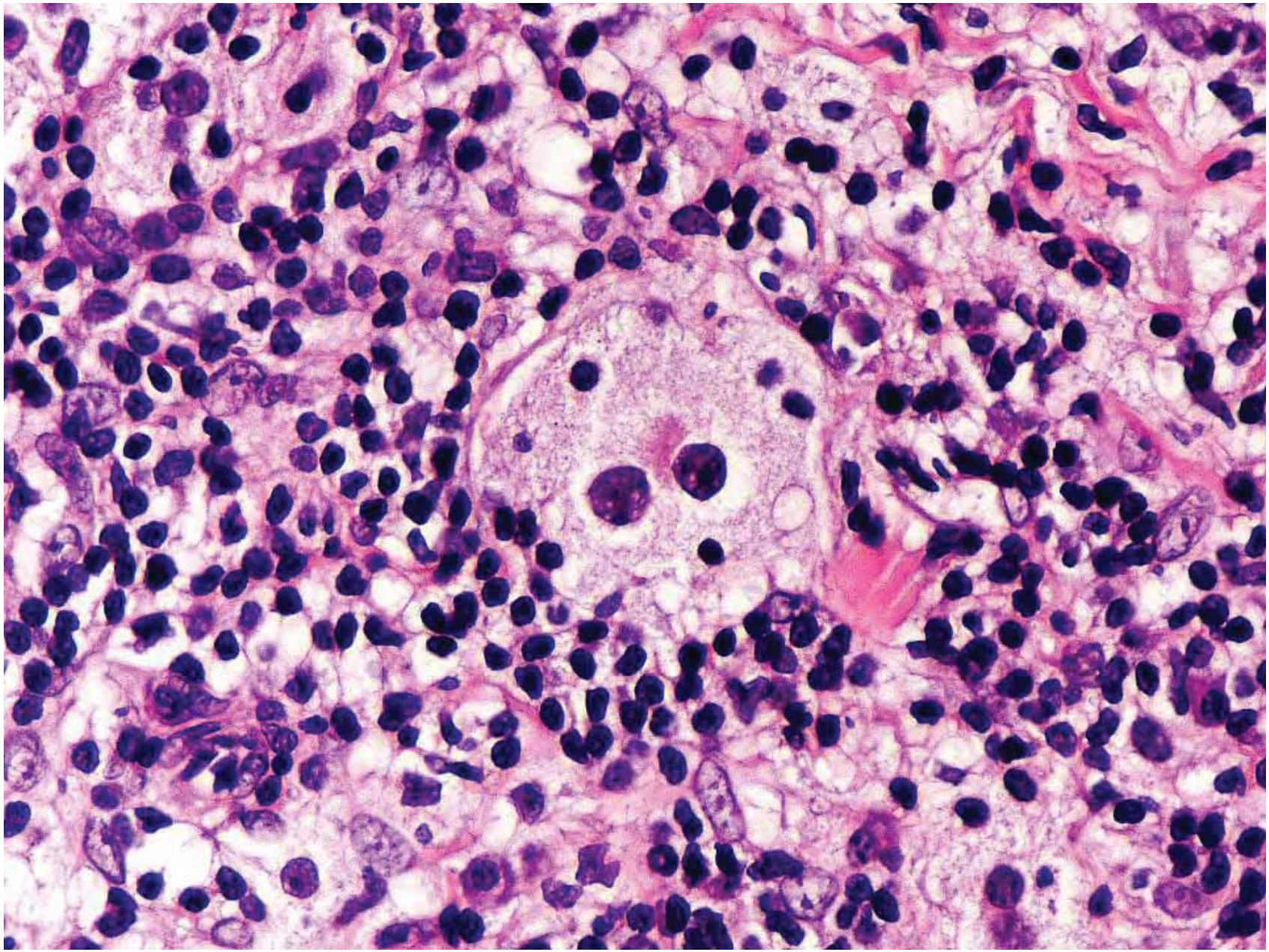


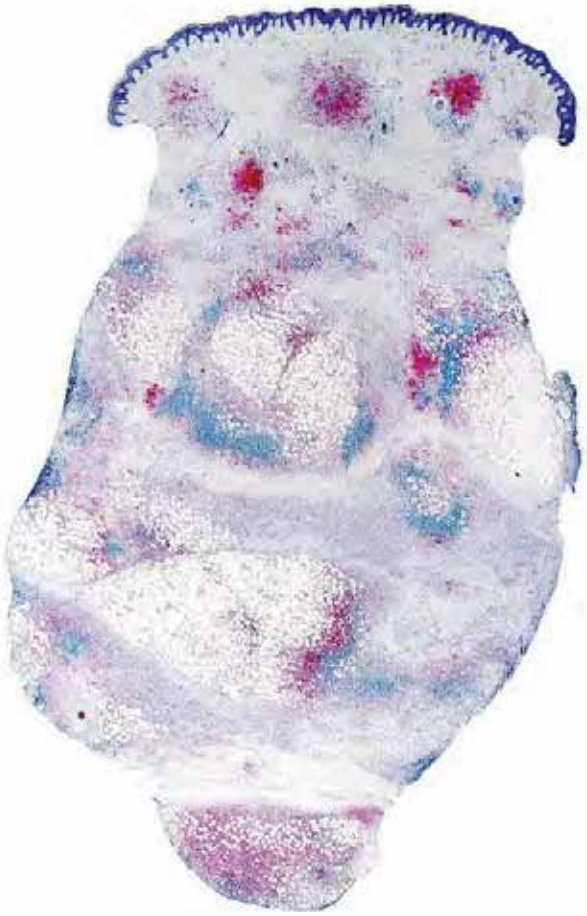


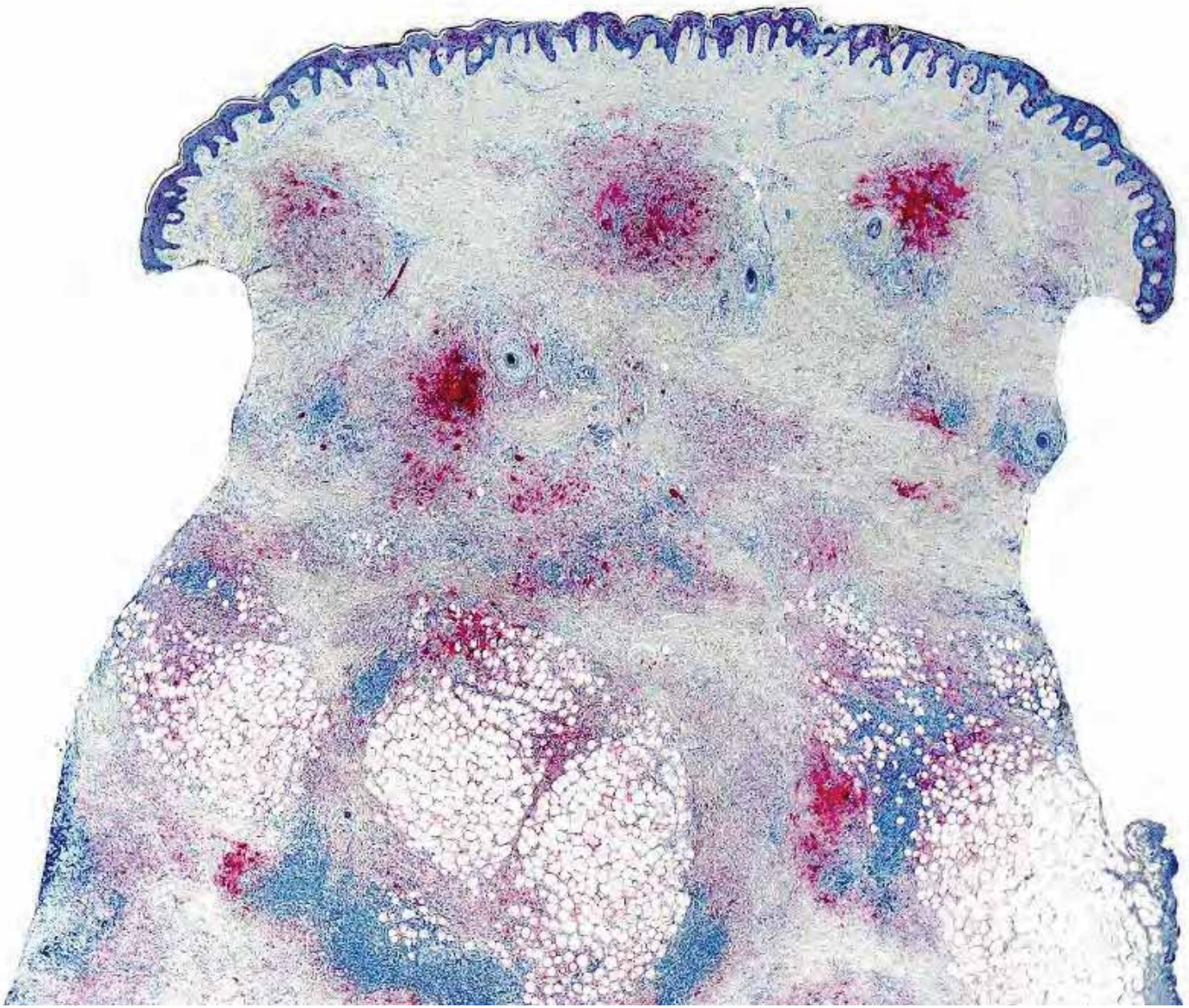


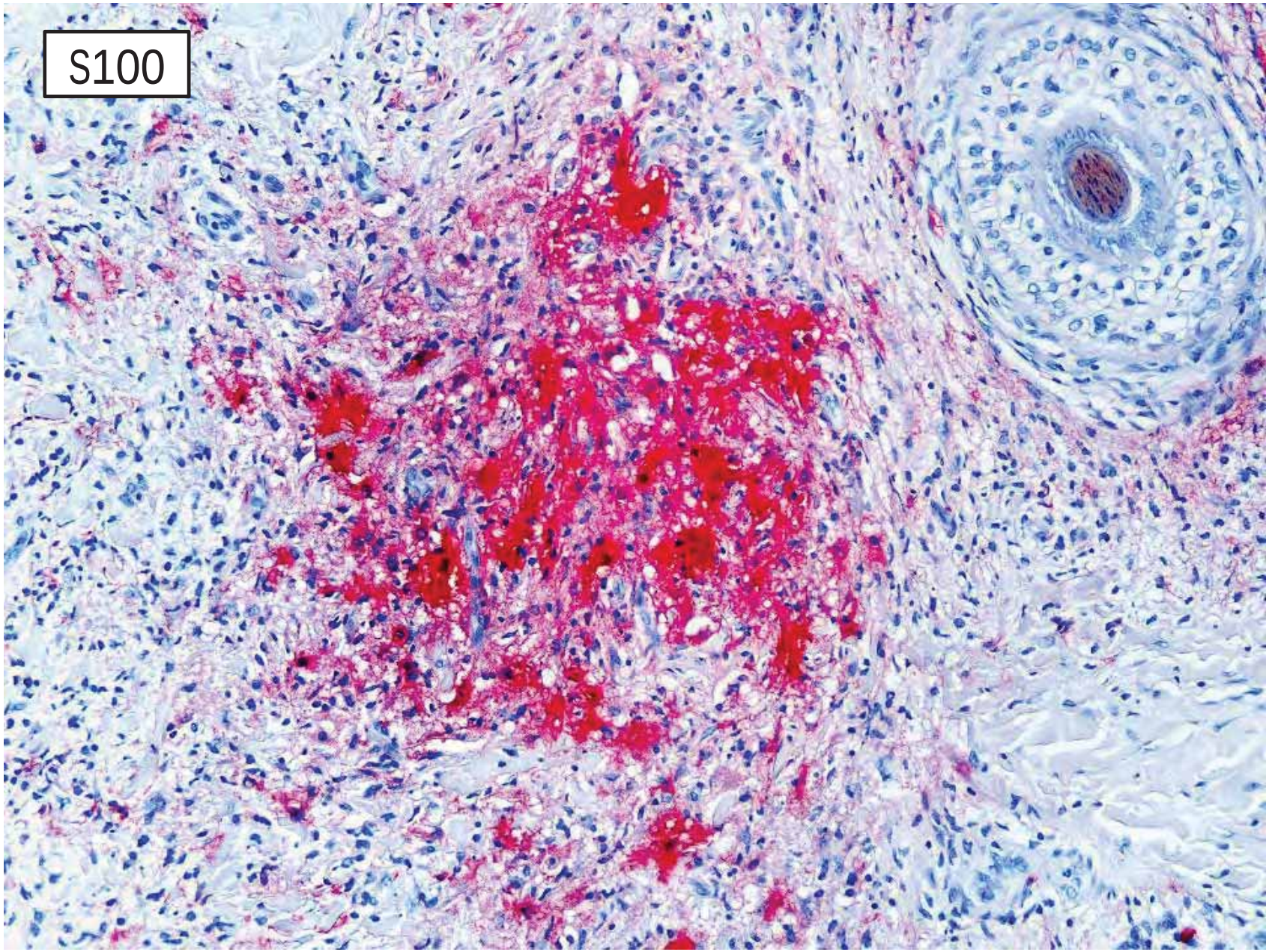








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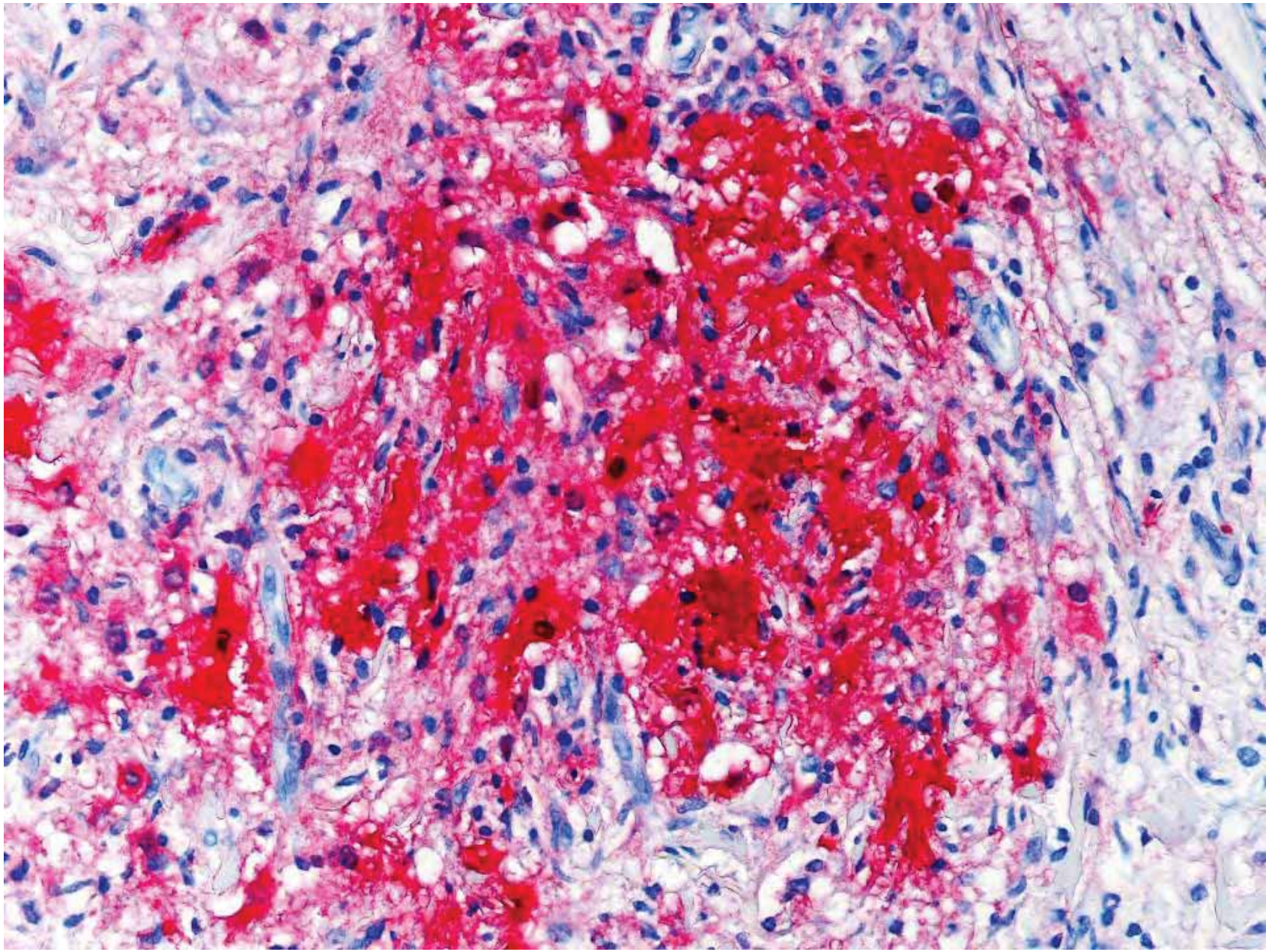
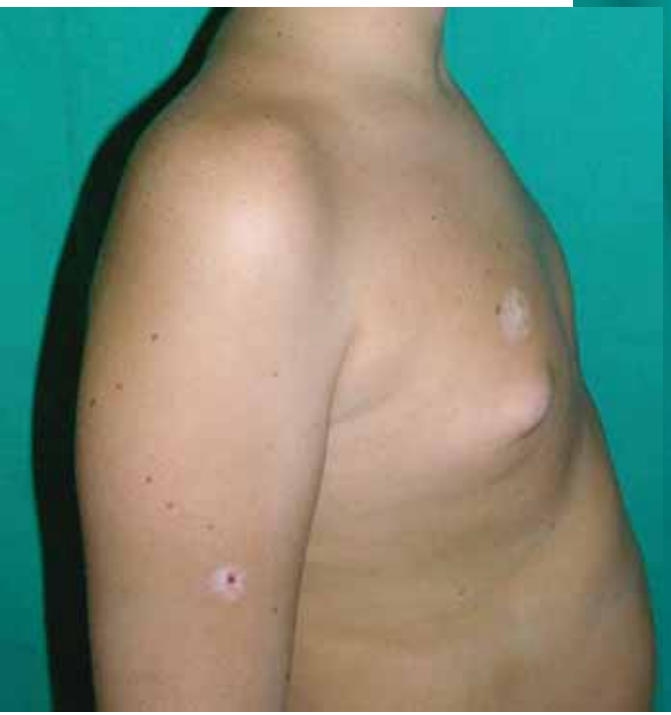
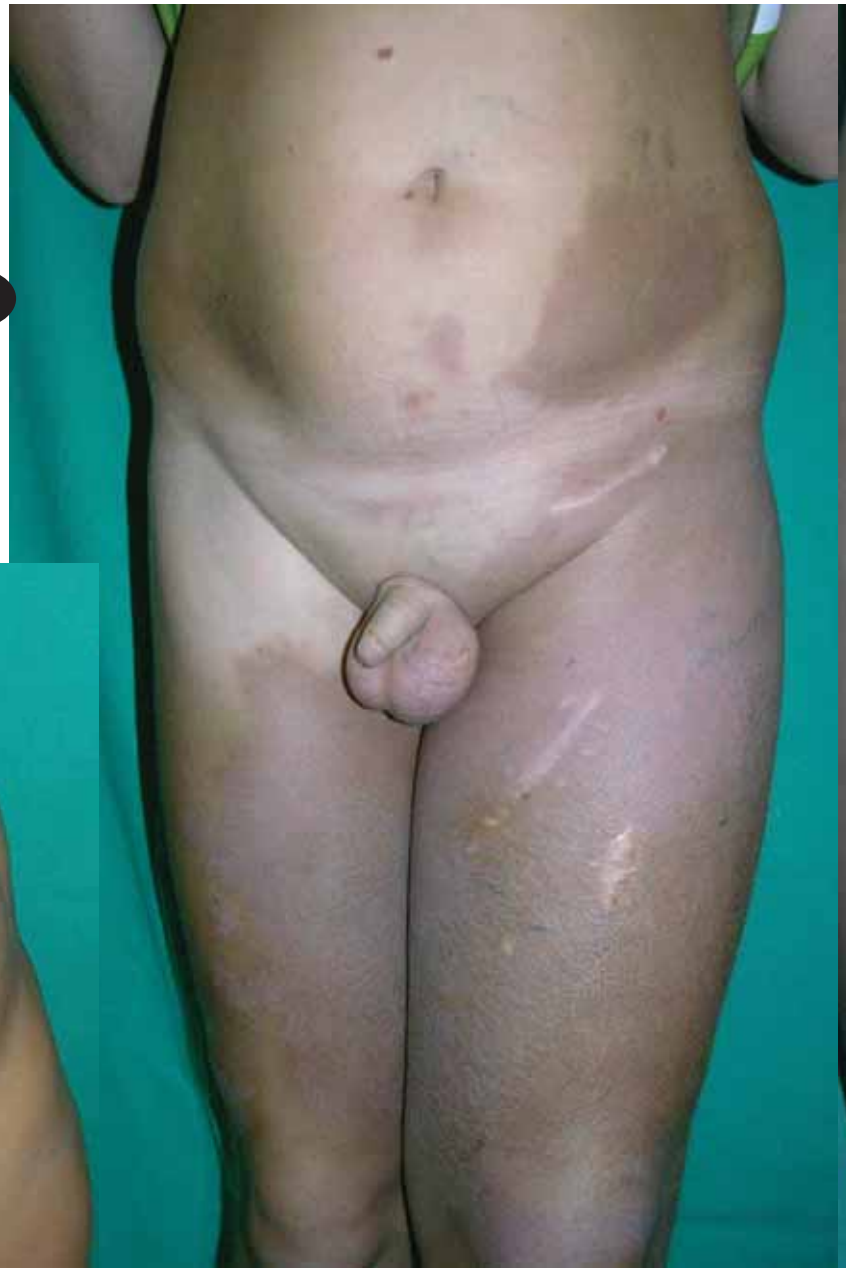
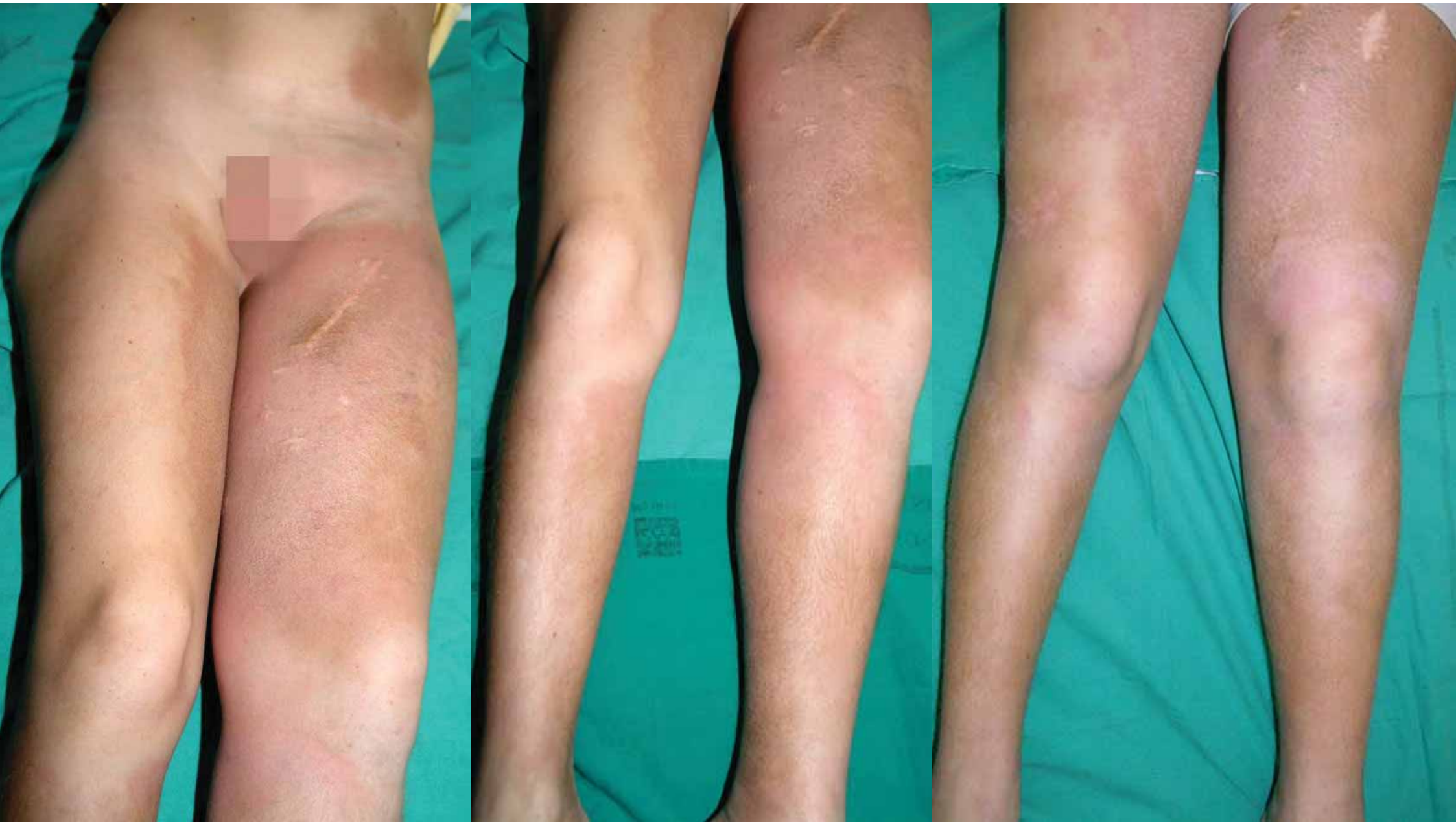
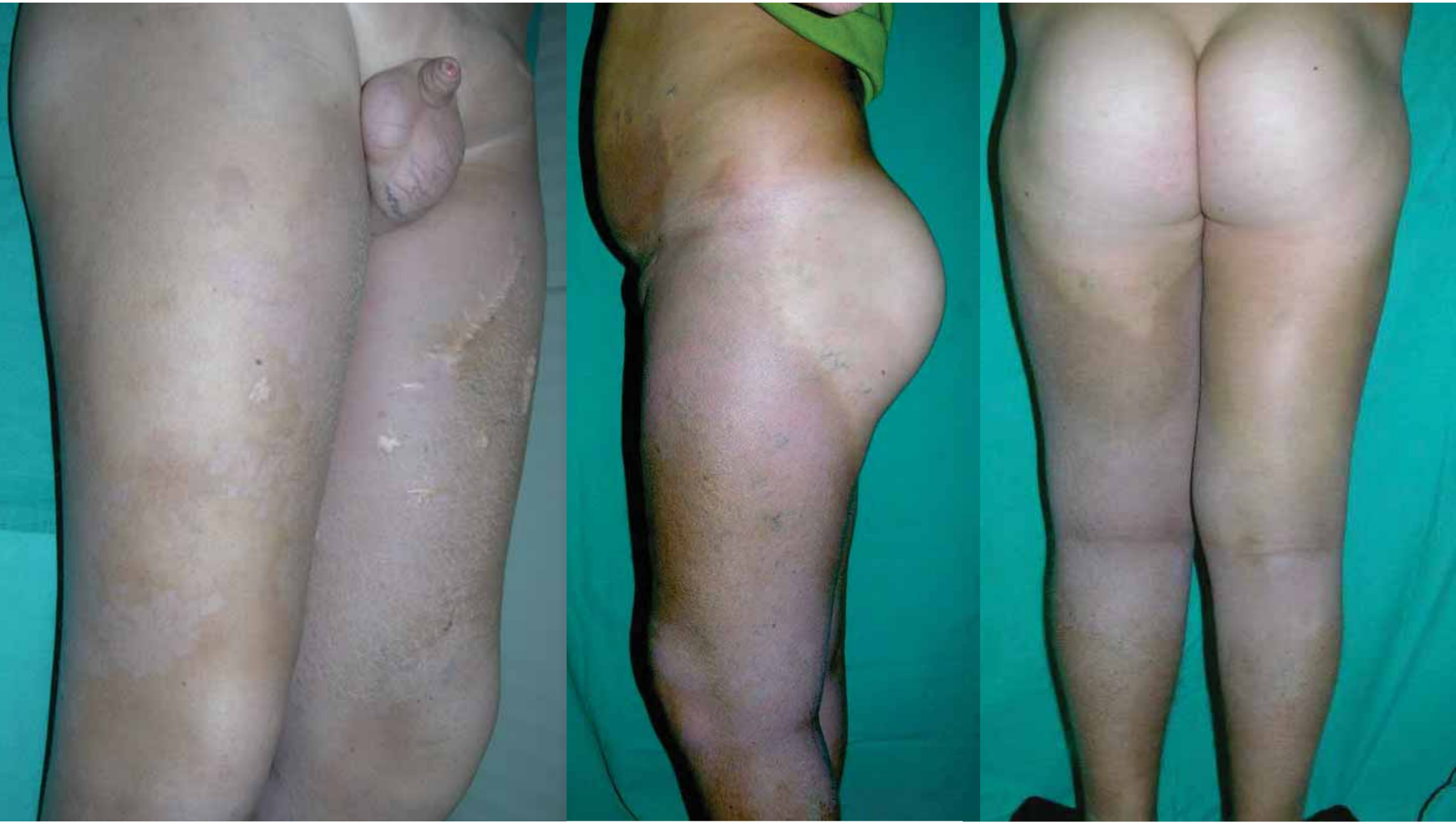






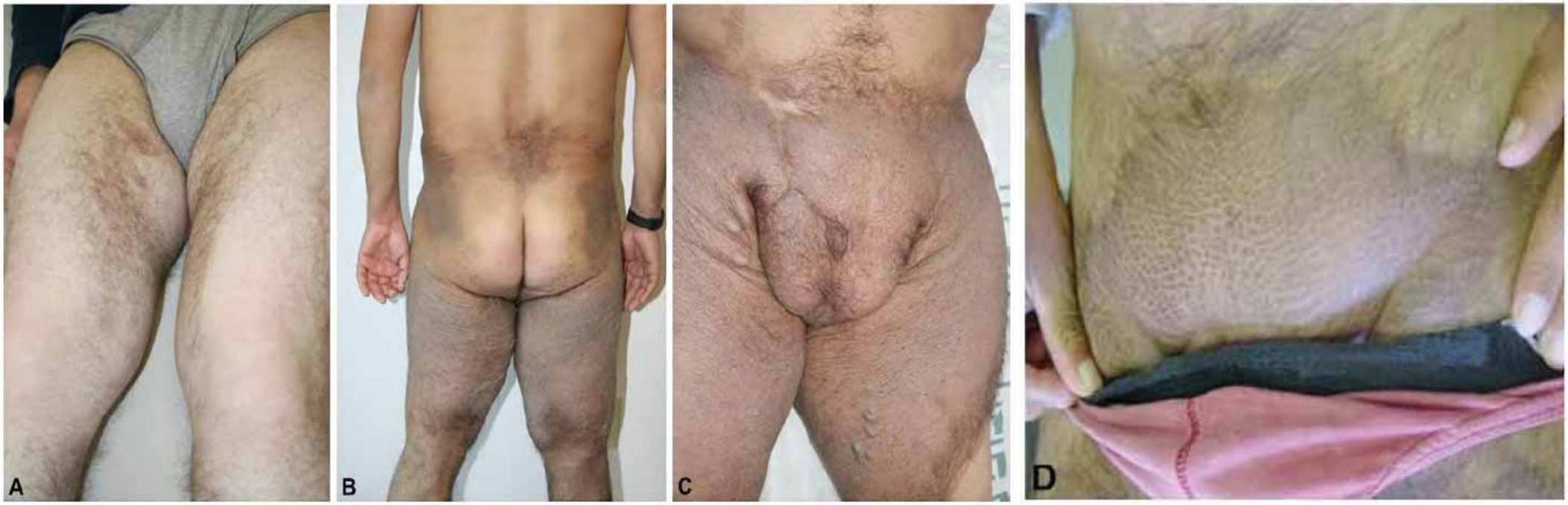




The H syndrome: A genodermatosis characterized by indurated, hyperpigmented, and hypertrichotic skin with systemic manifestations

Vered Molho-Pessach, MD,[a,b] Ziad Agha, MD,[a] Suhail Aamar, MD,[c] Benjamin Glaser, MD,[d] Victoria Doviner, MD,[e] Nurith Hiller, MD,[f] David Haim Zangen, MD,[g] Annick Raas-Rothschild, MD,[h] Ziva Ben-Neriah, MD,[h] Shaher Shweiki, MD,[i] Orly Elpeleg, MD,[j] and Abraham Zlotogorski, MD[a,b]
Jerusalem, Israel

- Hyperpigmented, hypertrichotic, indurated plaques
- Hearing loss
- Short stature
- Hepatosplenomegaly
- Heart: cardiac anomalies
- Scrotal masses
- Hypogonadism



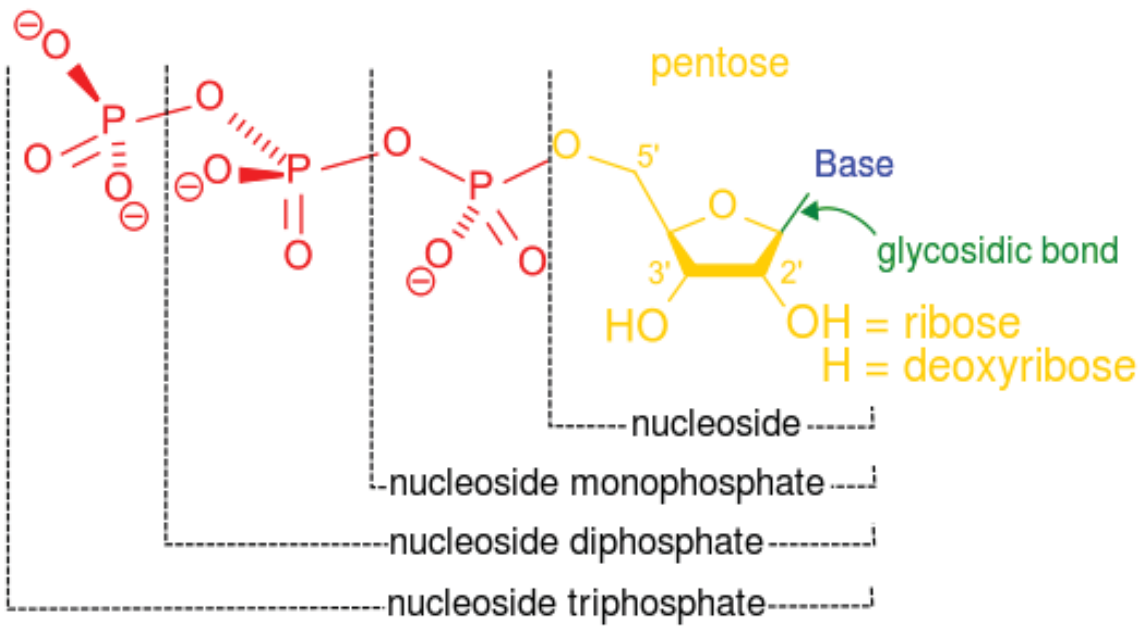
The H Syndrome Is Caused by Mutations in the Nucleoside Transporter hENT3

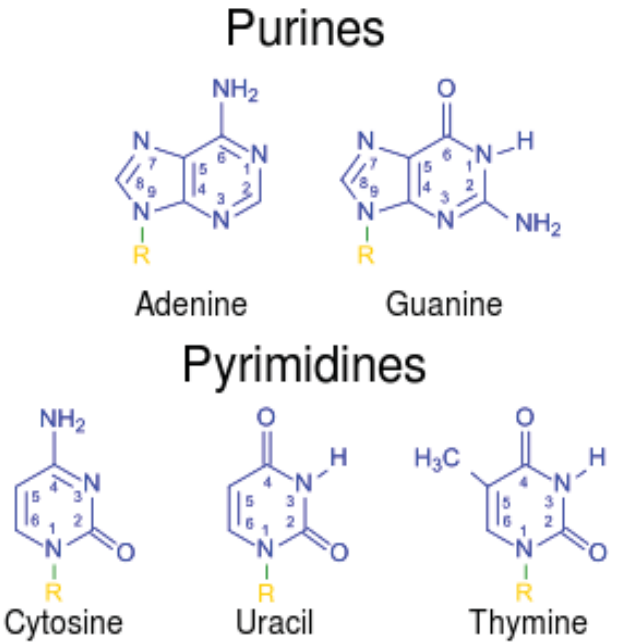
Vered Molho-Pessach,[1,4] Israela Lerer,[2] Dvorah Abeliovich,[2] Ziad Agha,[1] Abdulasalam Abu Libdeh,[5] Valentina Broshtilova,[6] Orly Elpeleg,[3] and Abraham Zlotogorski[1,4,*]

De novo synthesis (liver)

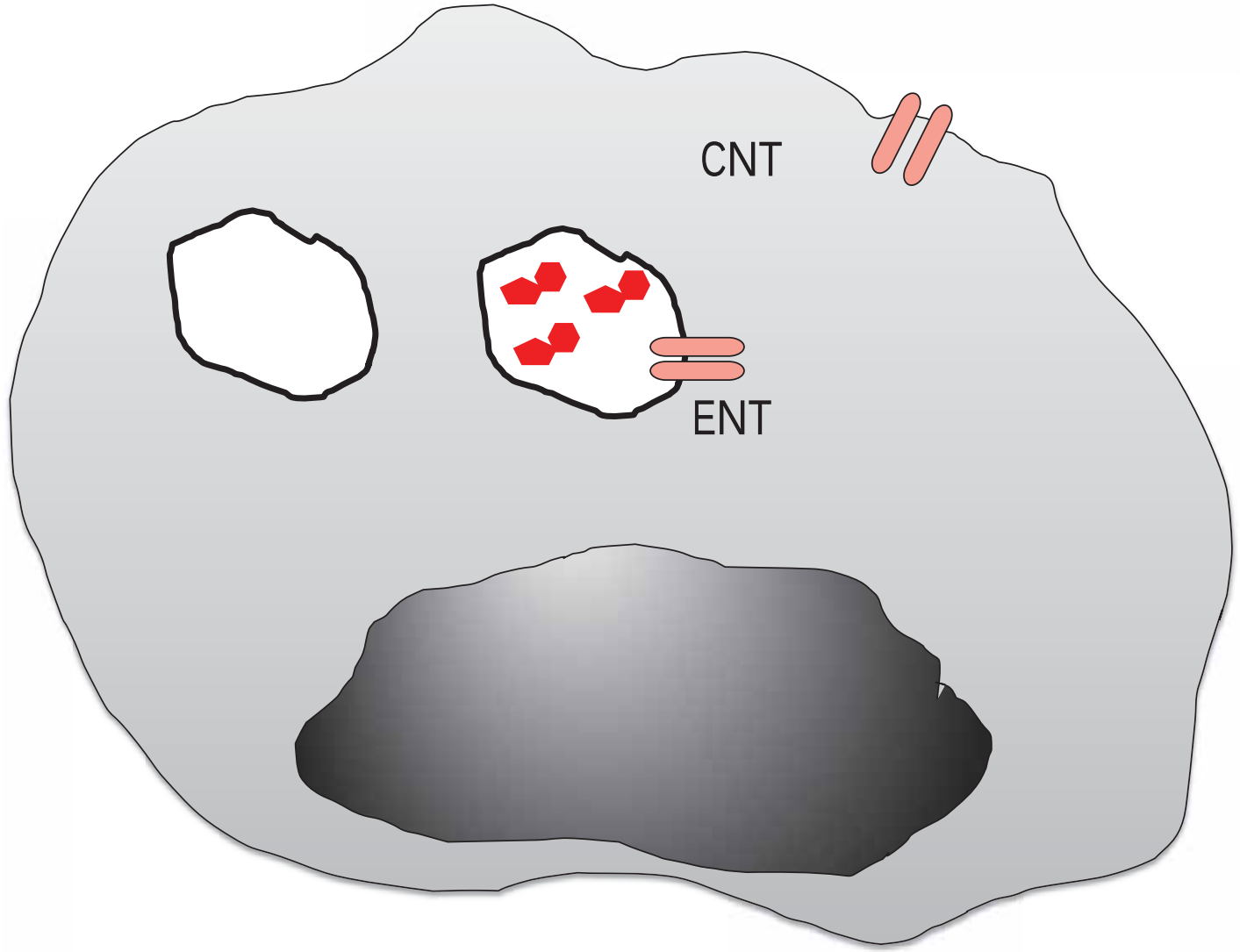
Ingestion (dietary nucleic acids)

Recycling by degradation of NAs (macrophages)

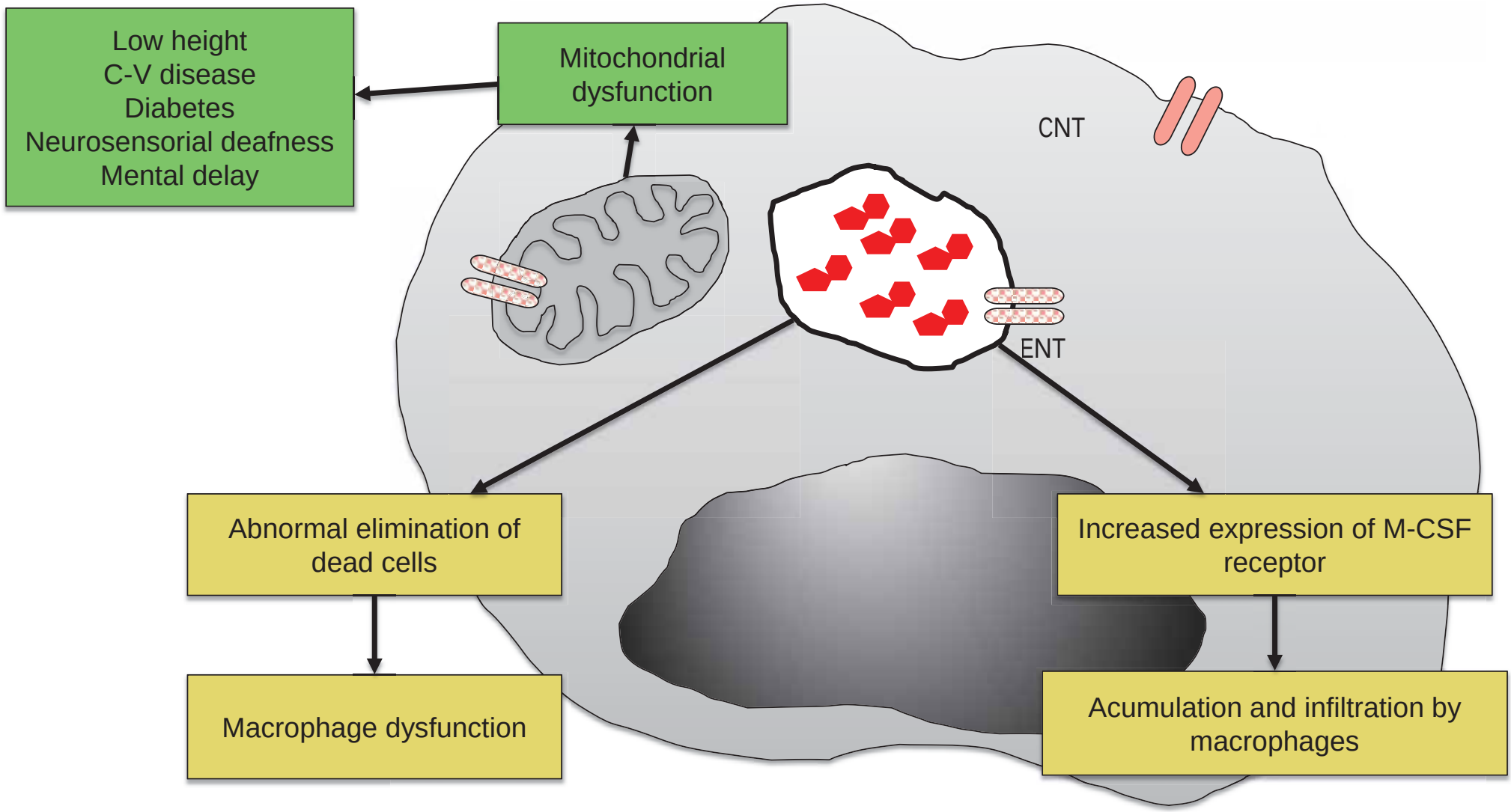




Recycling by degradation of NAs (macrophages)



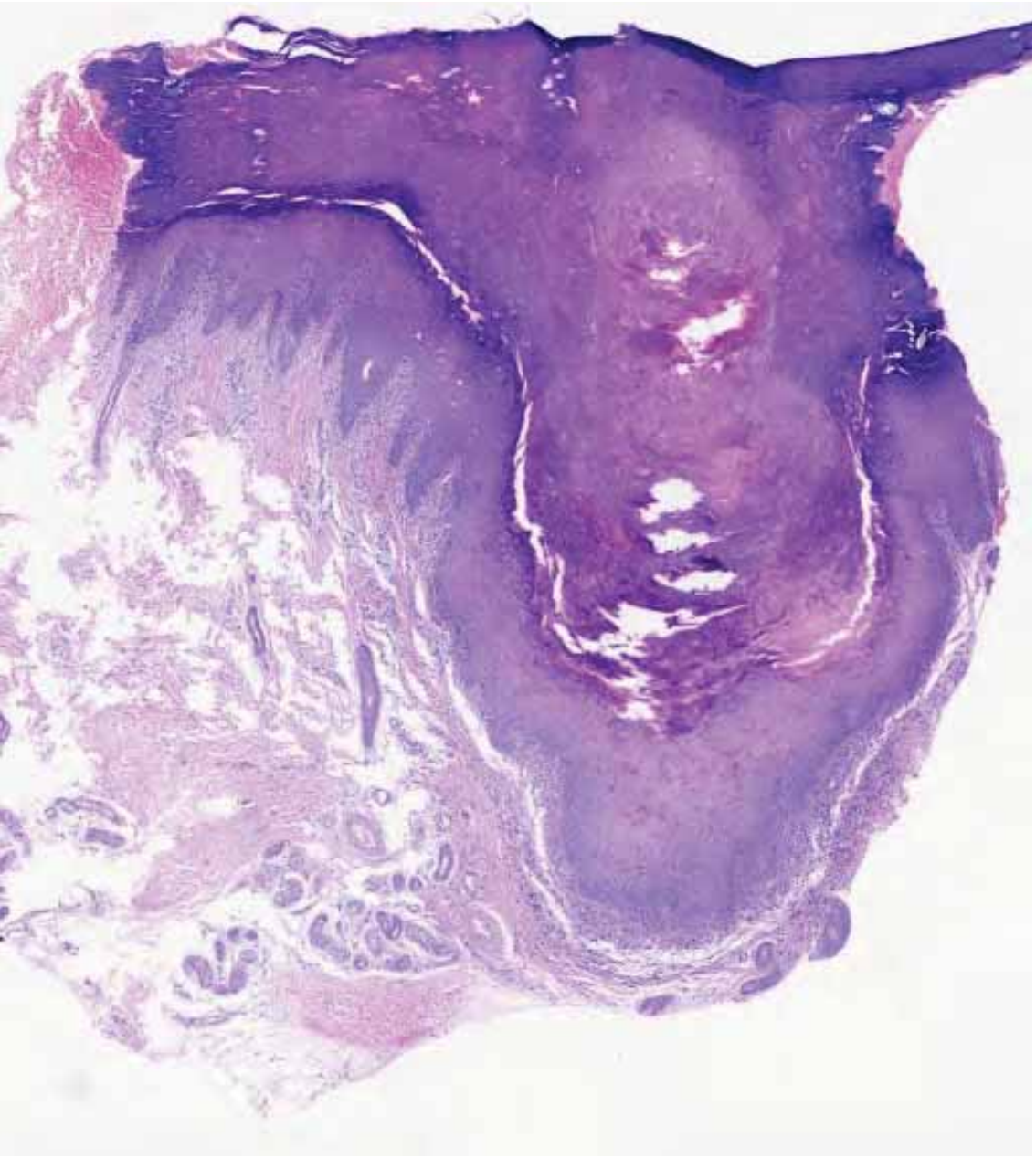
Defective nucleoside recycling in H-syndrome macrophages

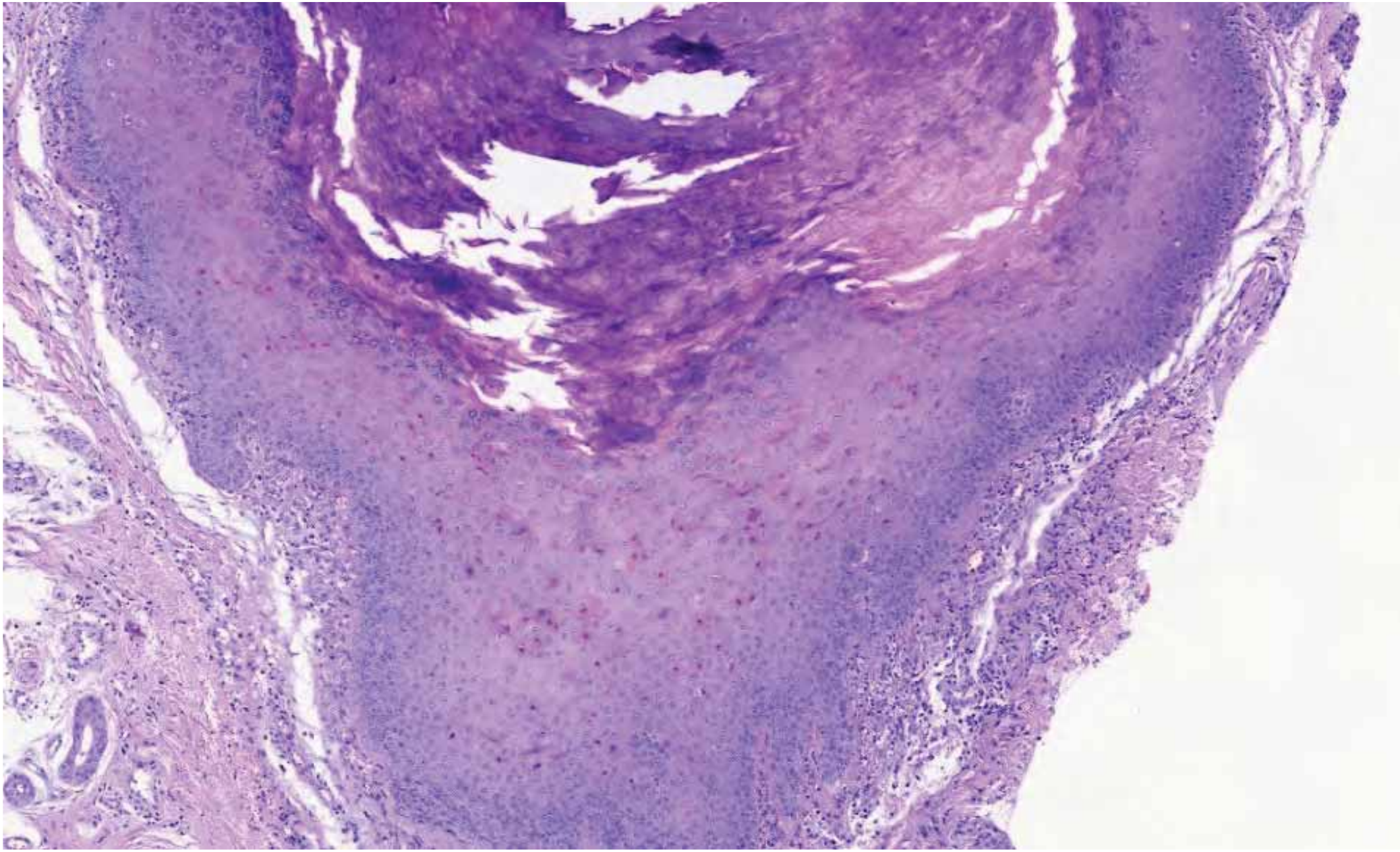


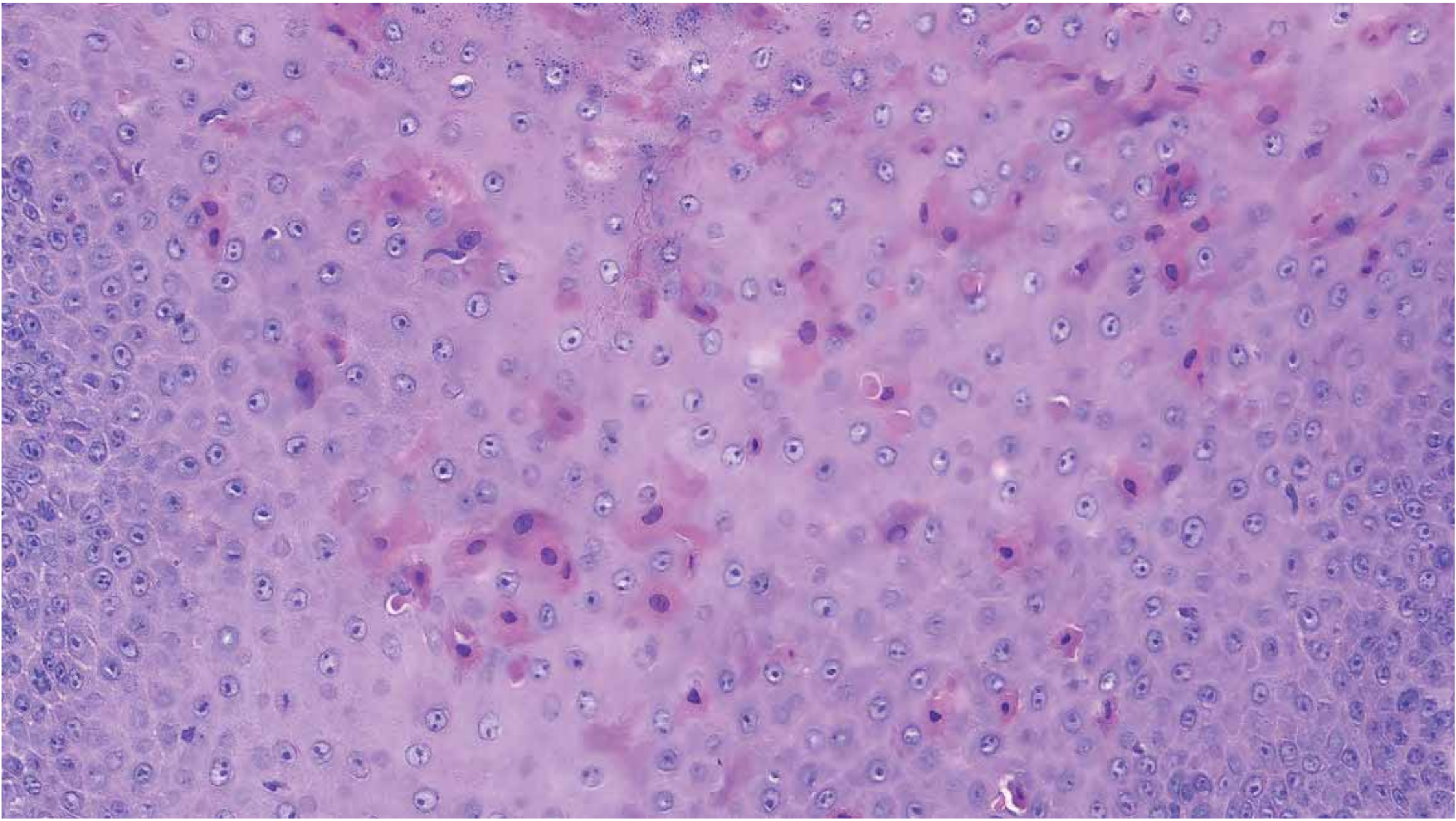
Dermatopathologic clue #7

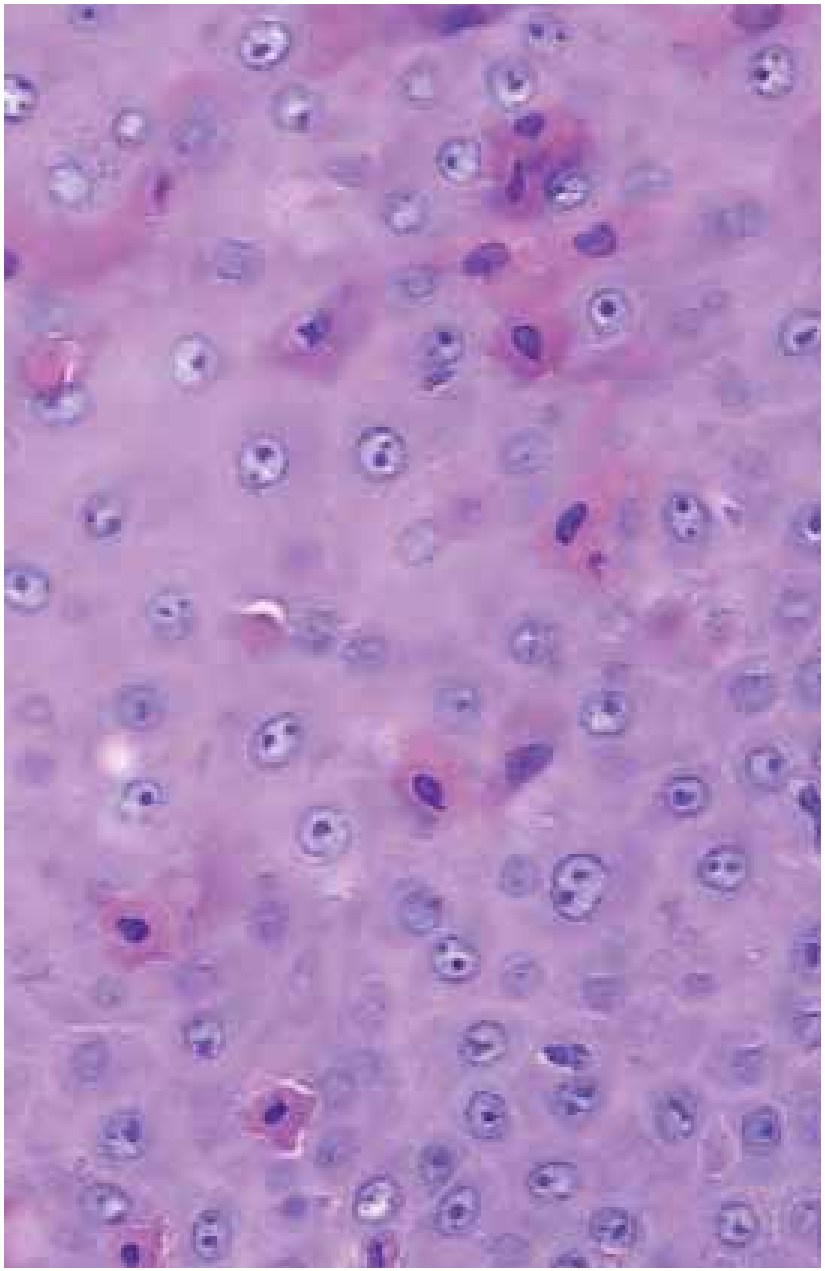
Deep dermatitis & panniculitis
histocytic & emperipolesis

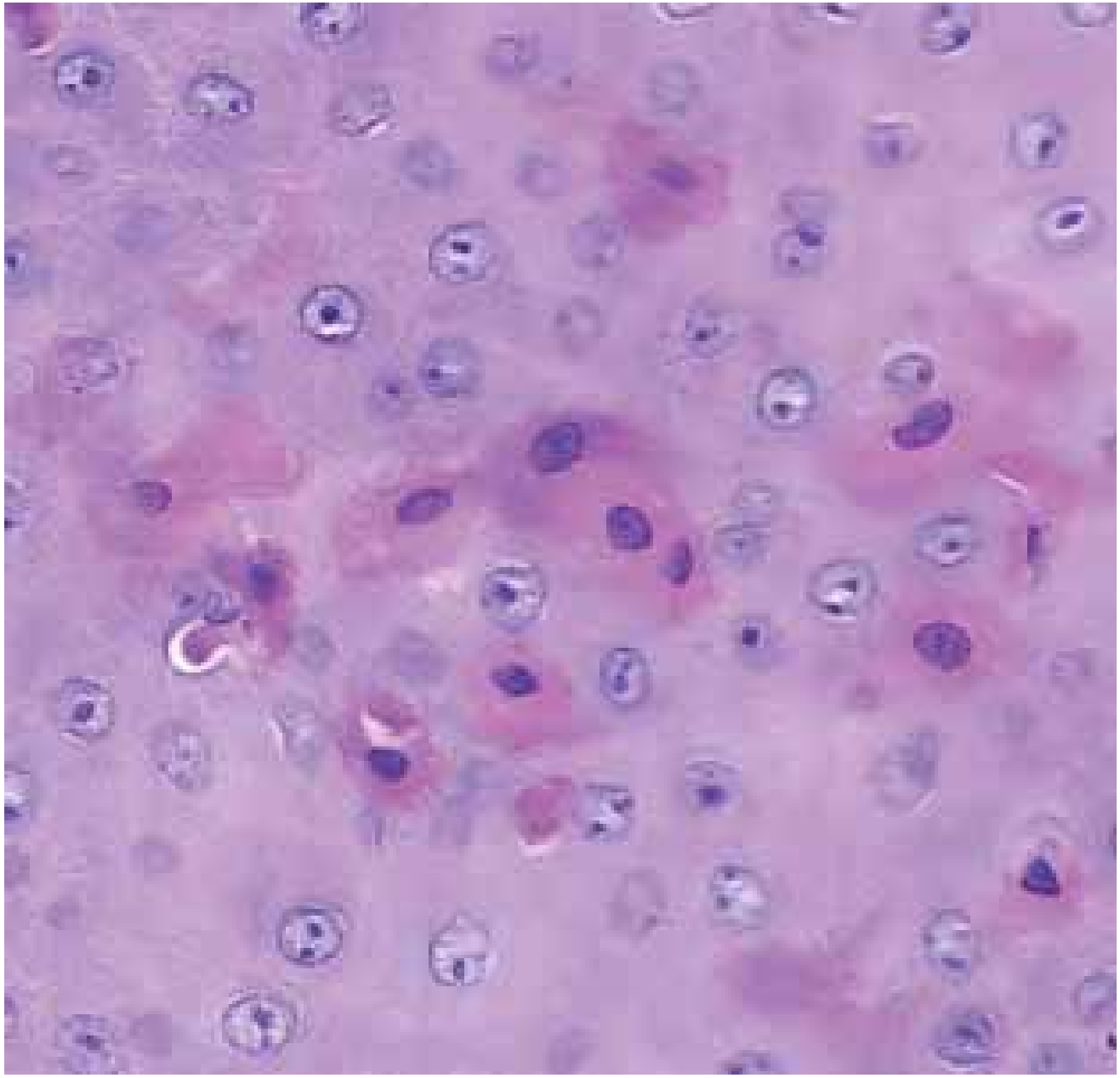
The H syndrome
(hENT3 mutations)

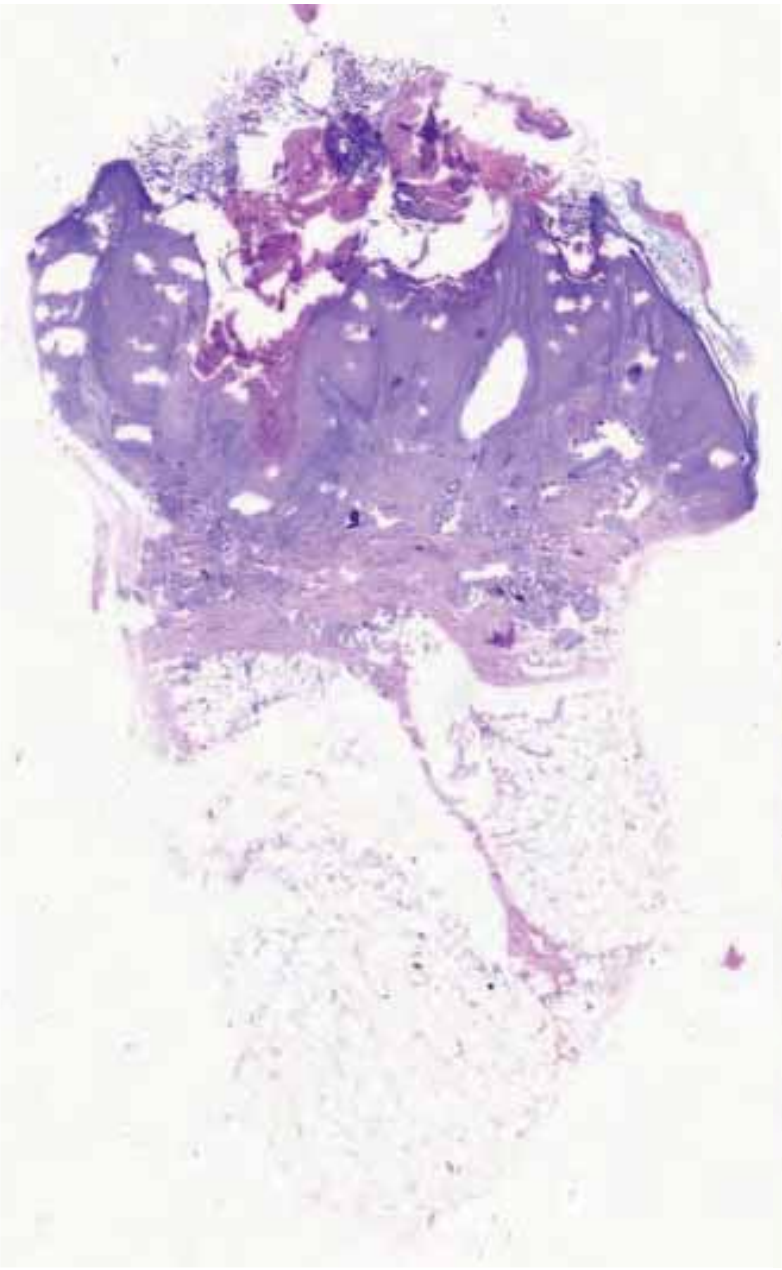


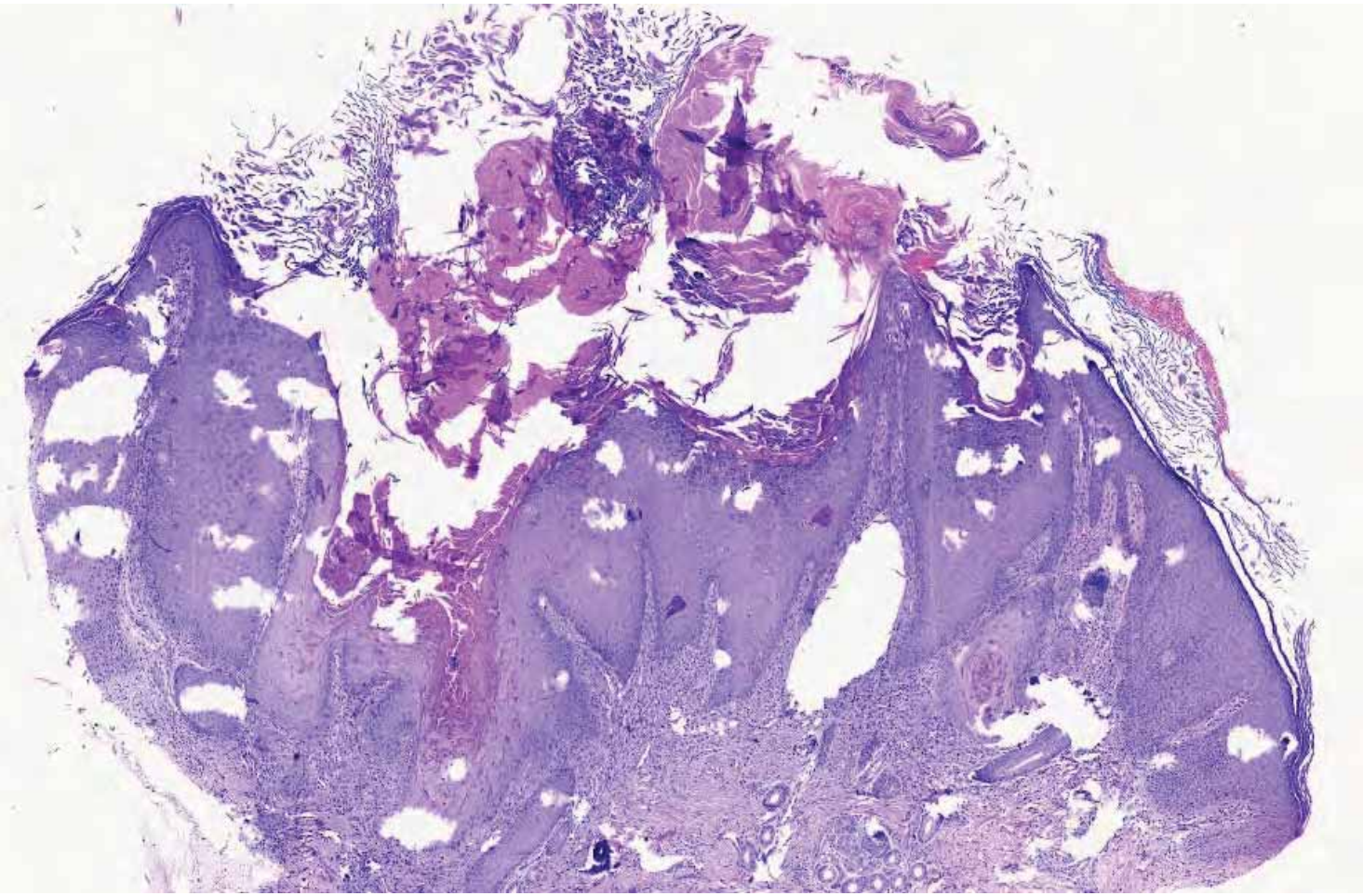


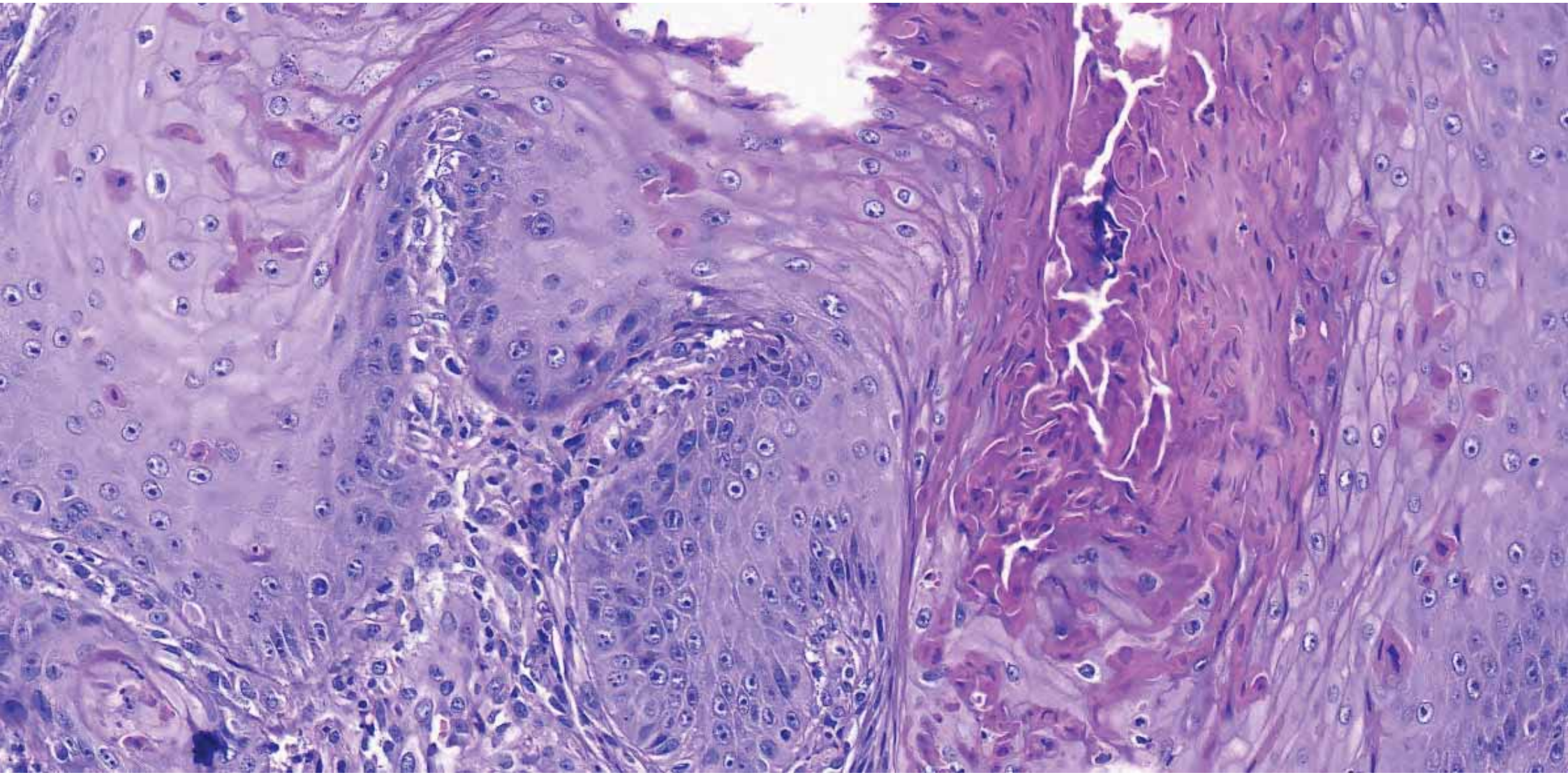


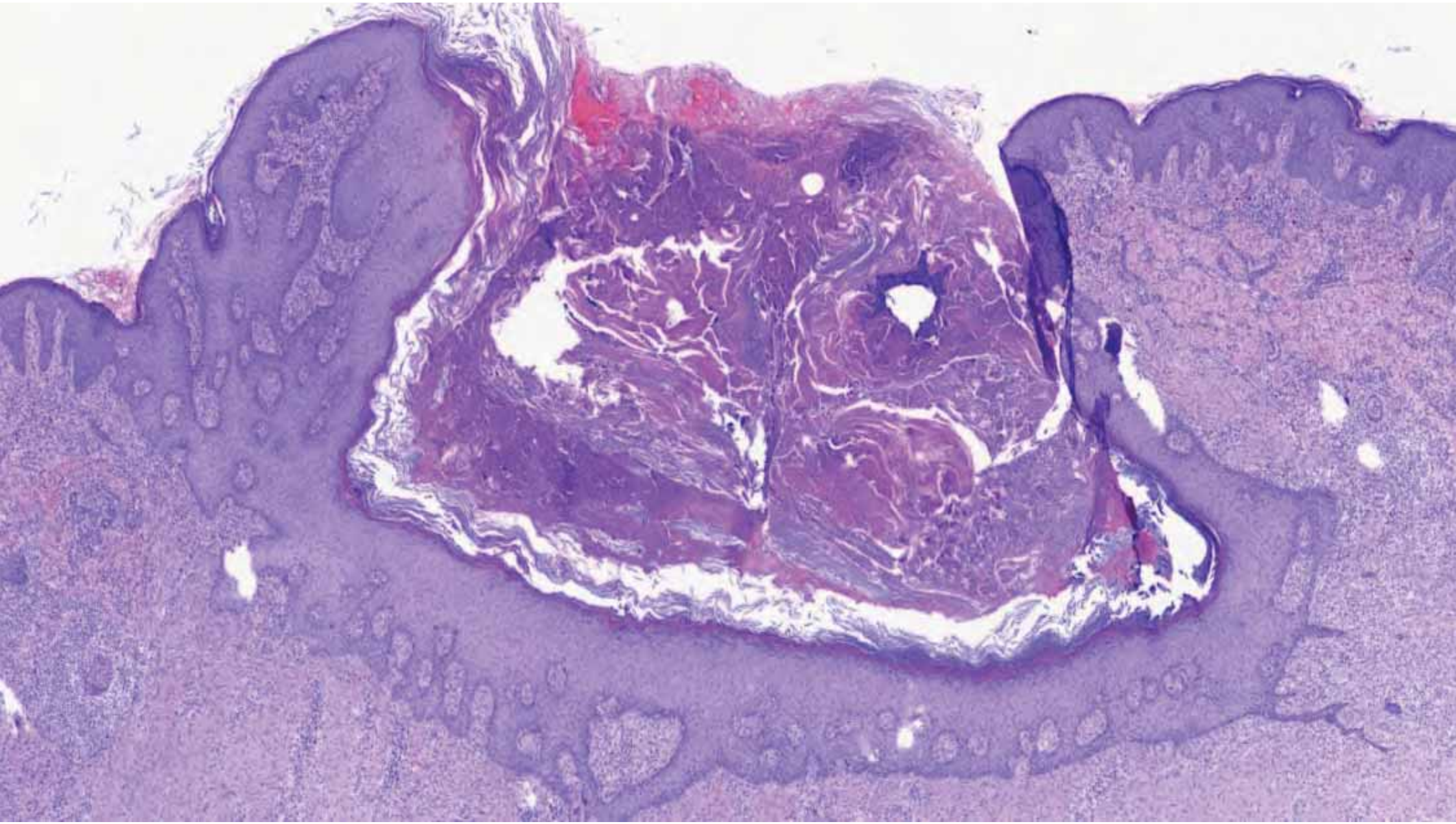


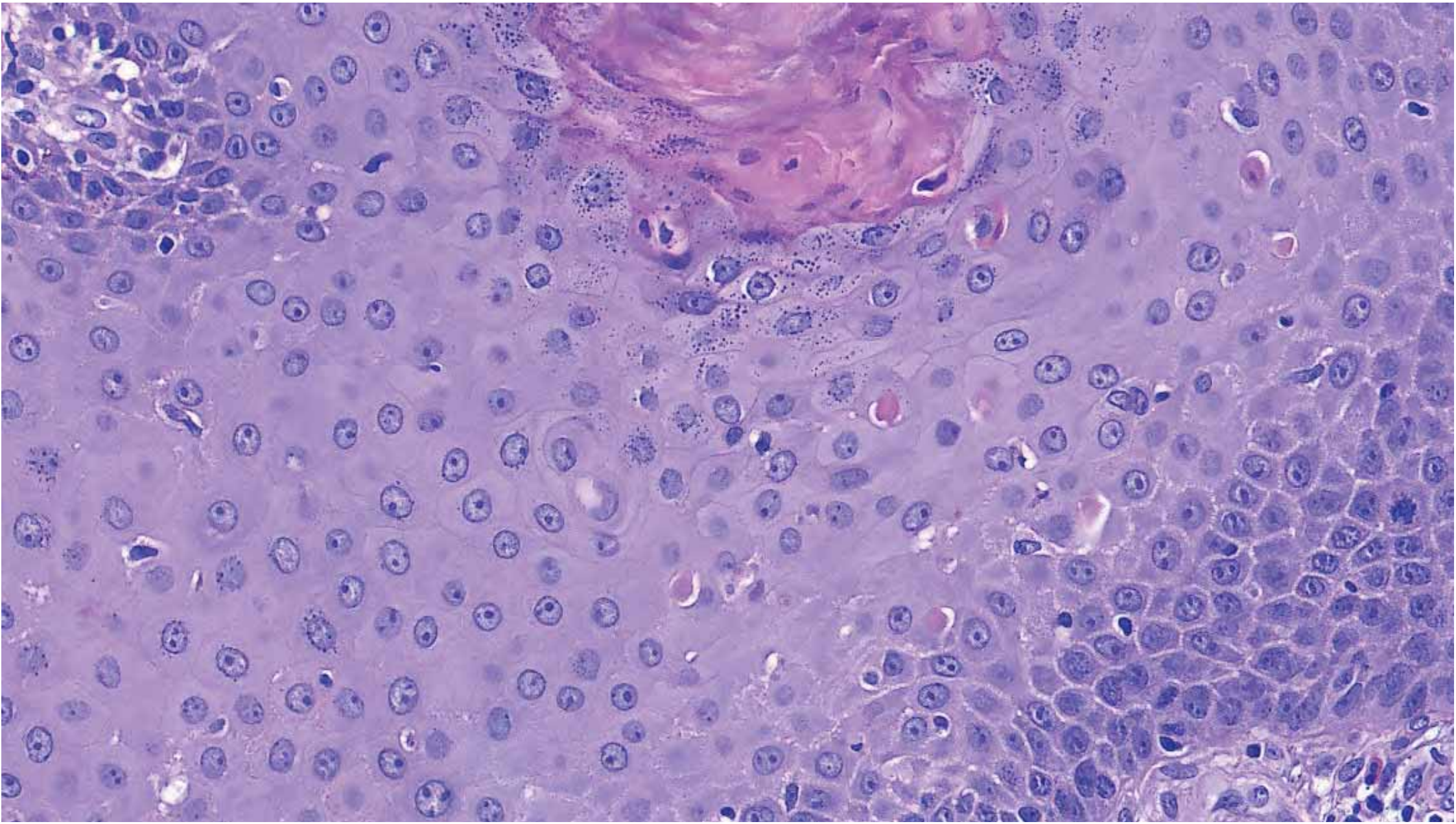


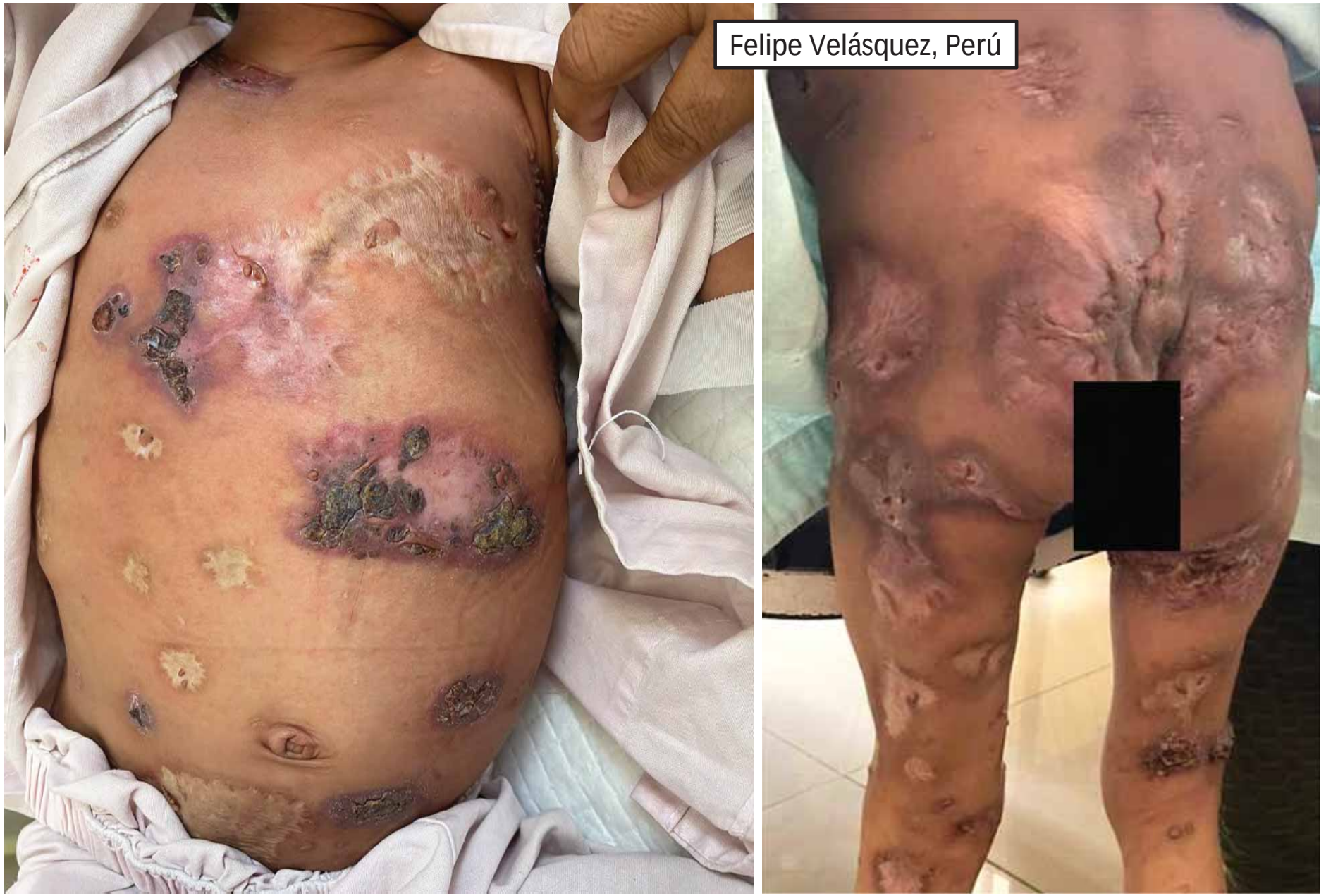


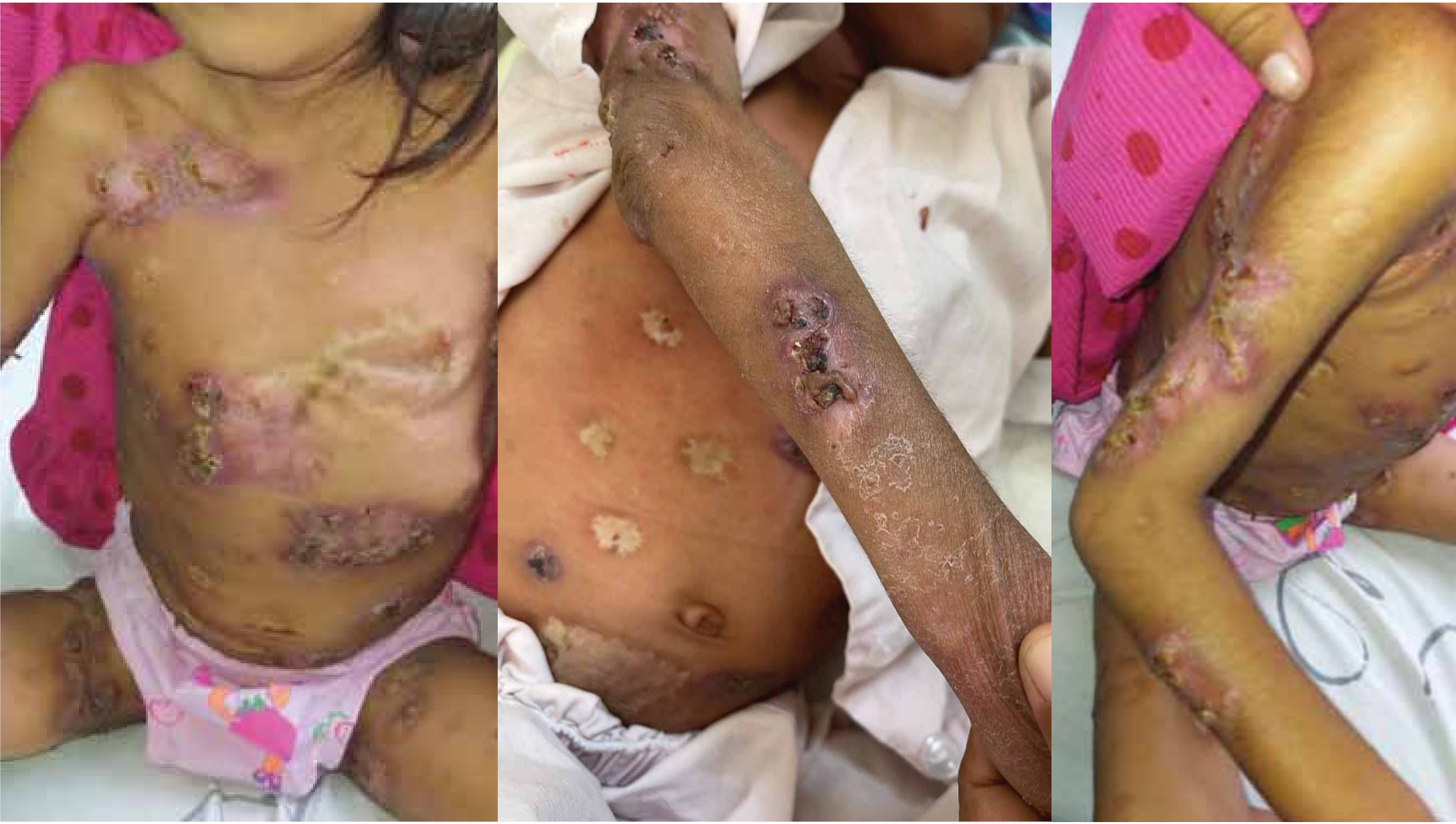


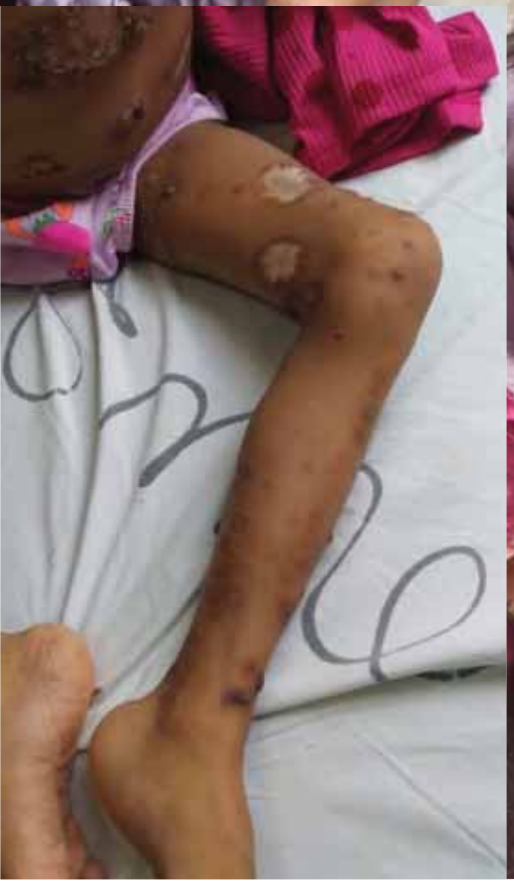
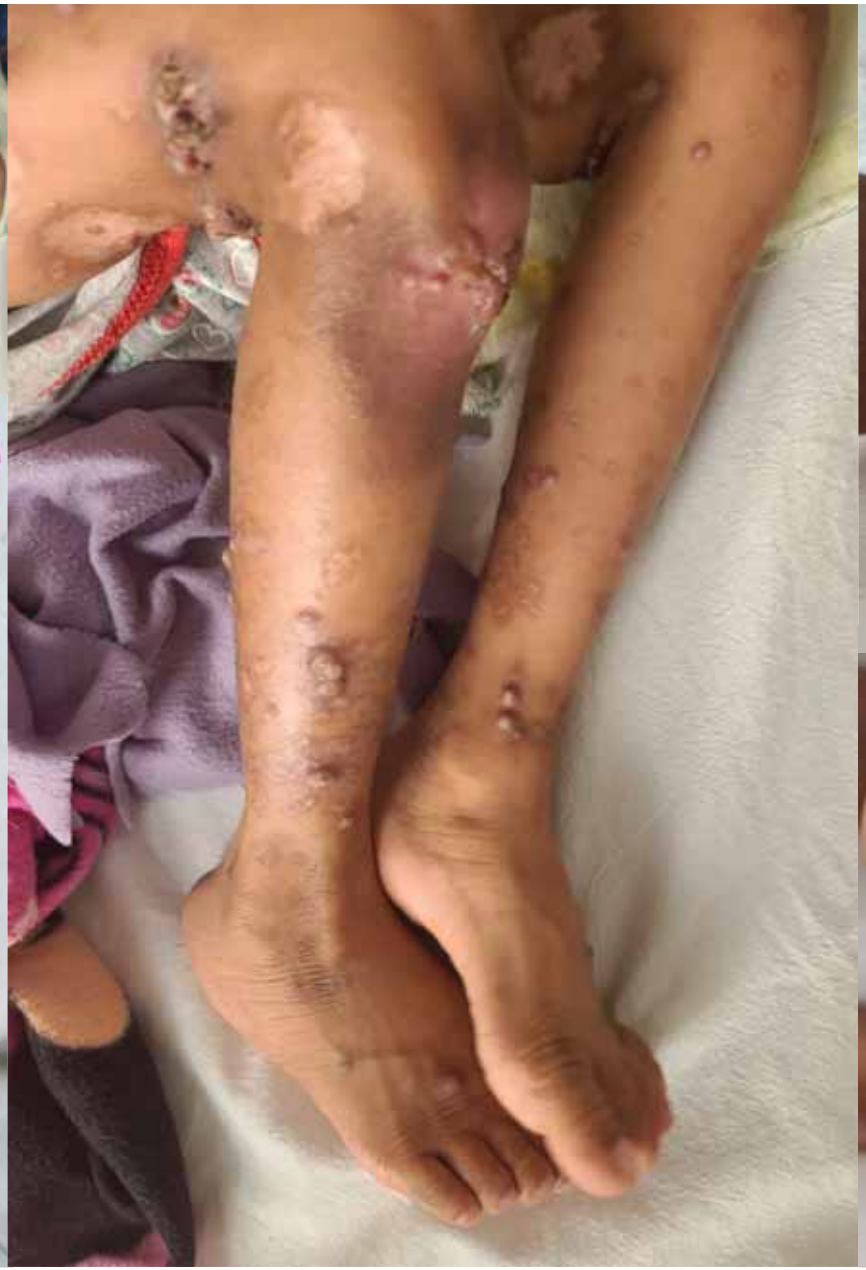


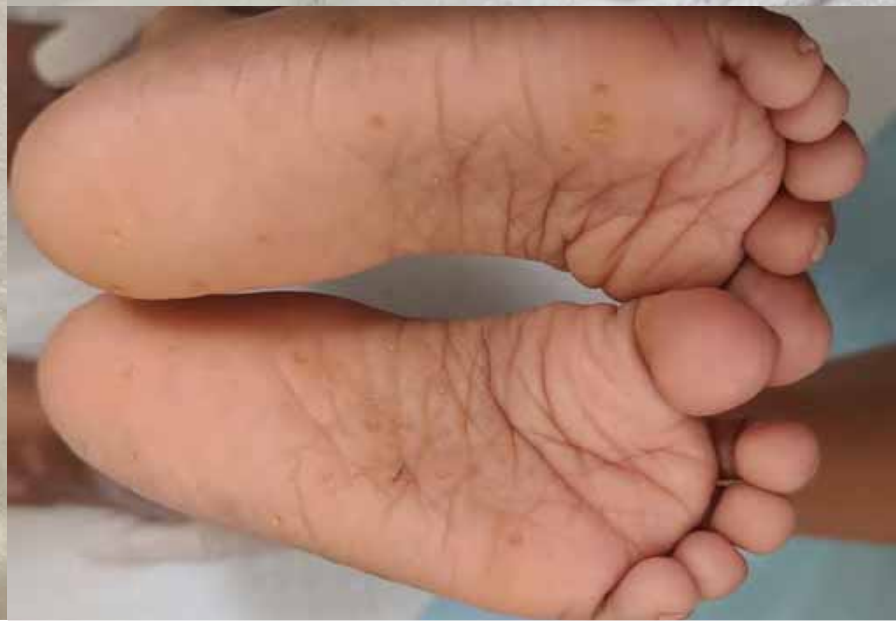





Felipe Velásquez, Perú

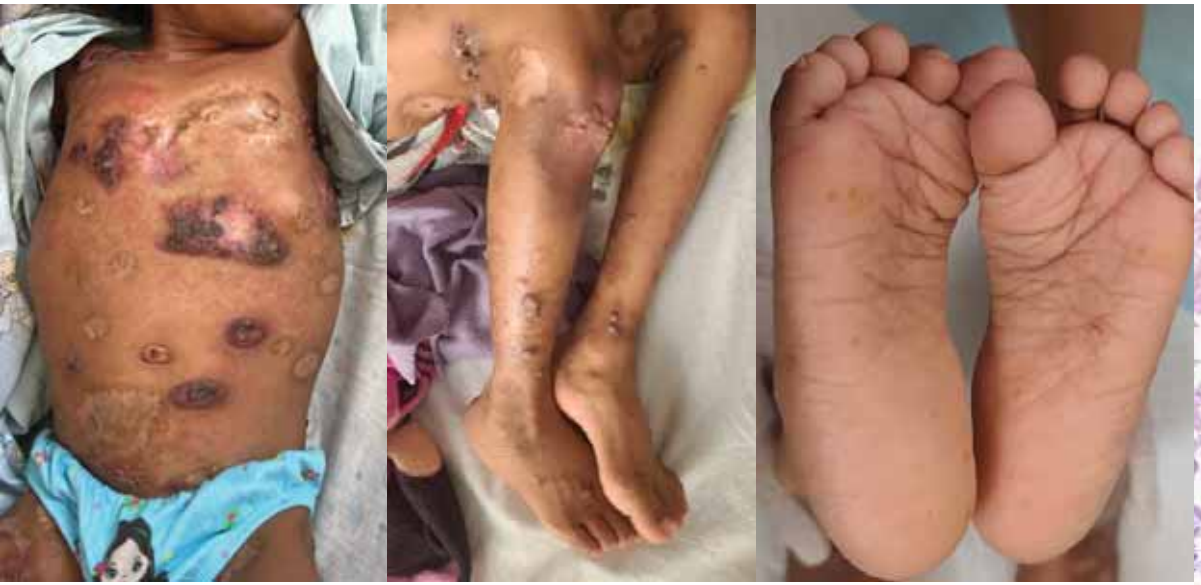


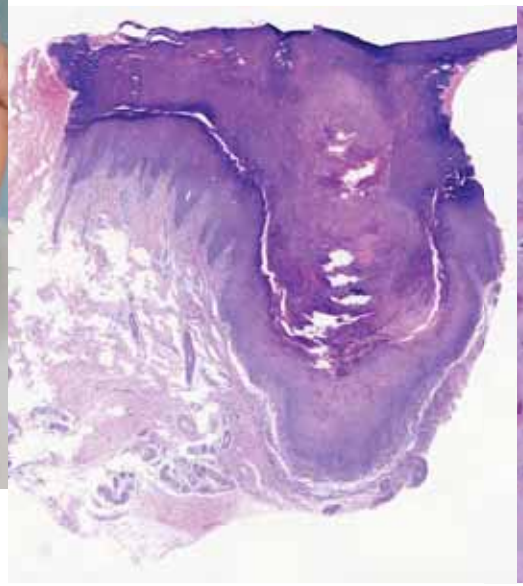




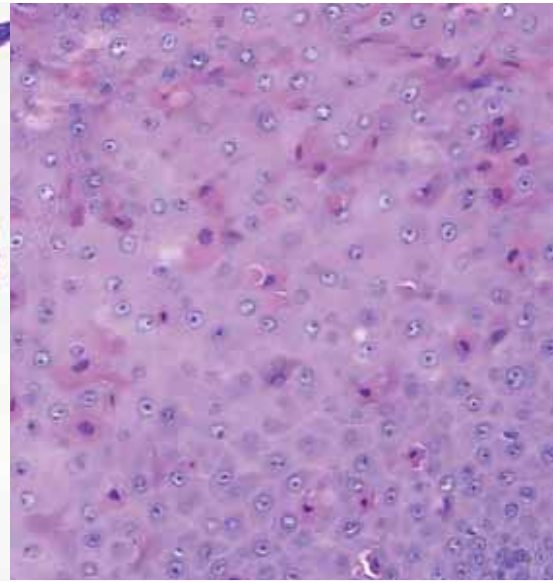


NLRP1-associated autoinflammatory disease with epithelial dyskeratosis

Kevin Lemus-Arteaga MD[1,2,3] | Rosalía Ballona-Chambergo MD[1,4]
Wilmer Córdova-Calderón MD[1,5] | Alex Ventura-León MD[6,7] |
Antonio Torrelo MD[8] | Felipe Velásquez-Valderrama MD[1,4]







Number of cases	Variant identified	Inheritance	Status	Reference
17 members of a family	A54T	AD	Heterozygous	3
4 family members	A59P	AD	Heterozygous	13,16
Several Family members	A66V	AD	Heterozygous	3
2 (mother and son)	M77T	AD	Heterozygous	14
2 cousins	R726W	AR	Homozygous	12
2 brothers	T755N	AR	Homozygous	15
2 siblings	F787_R5843del	AR	Homozygous	3
2 sisters	L813P	AR	Homozygous	17
2 (unrelated)	P1214R	AD	Heterozygous	12, present case

FIGURE 4 A schematic view of the *NLRP1* gene, indicating the site of described genetic variants. CARD, caspase activation and recruitment domain; FIIND, function-to-find domain; LRR, leucine-rich repeats; NACHT, NACHT domain; PYD, pyrin domain.

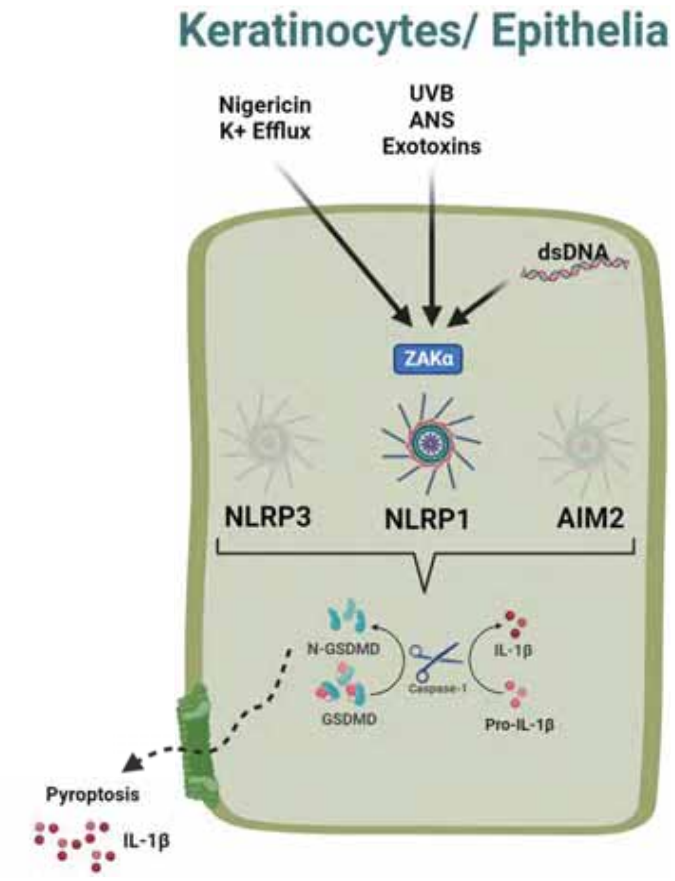
NLRP1-associated autoinflammatory disease with epithelial dyskeratosis (NADED)

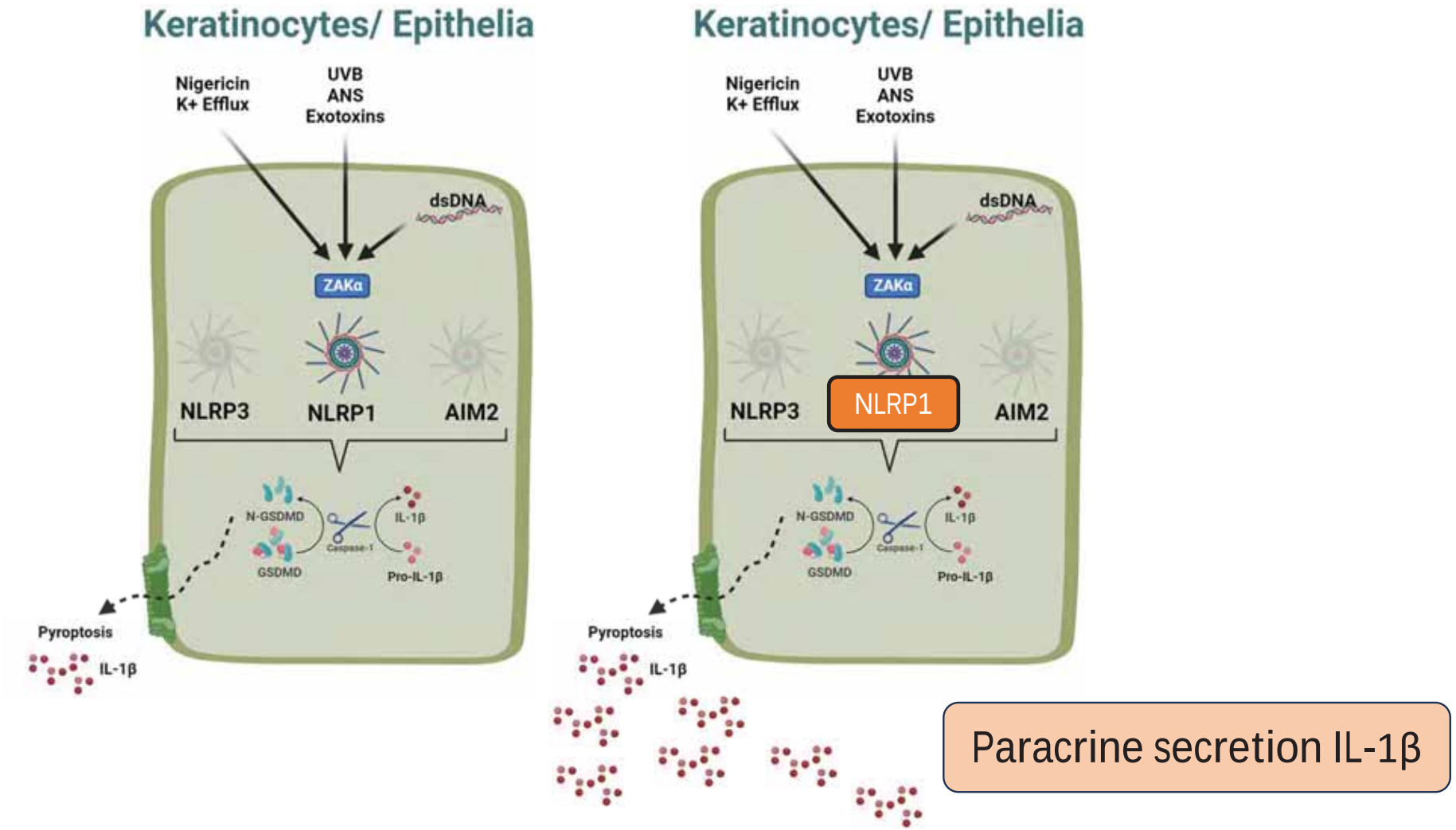
RESULT: POSITIVE

One Likely Pathogenic variant identified in NLRP1. NLRP1 is associated with autosomal dominant NLRP1 gain of function syndrome.

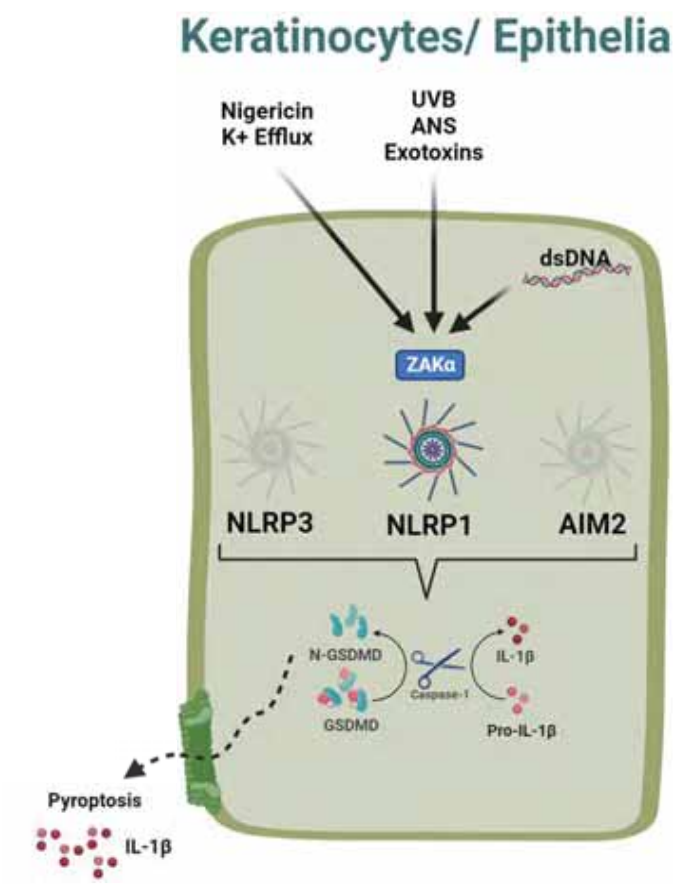
Additional Variant(s) of Uncertain Significance identified.

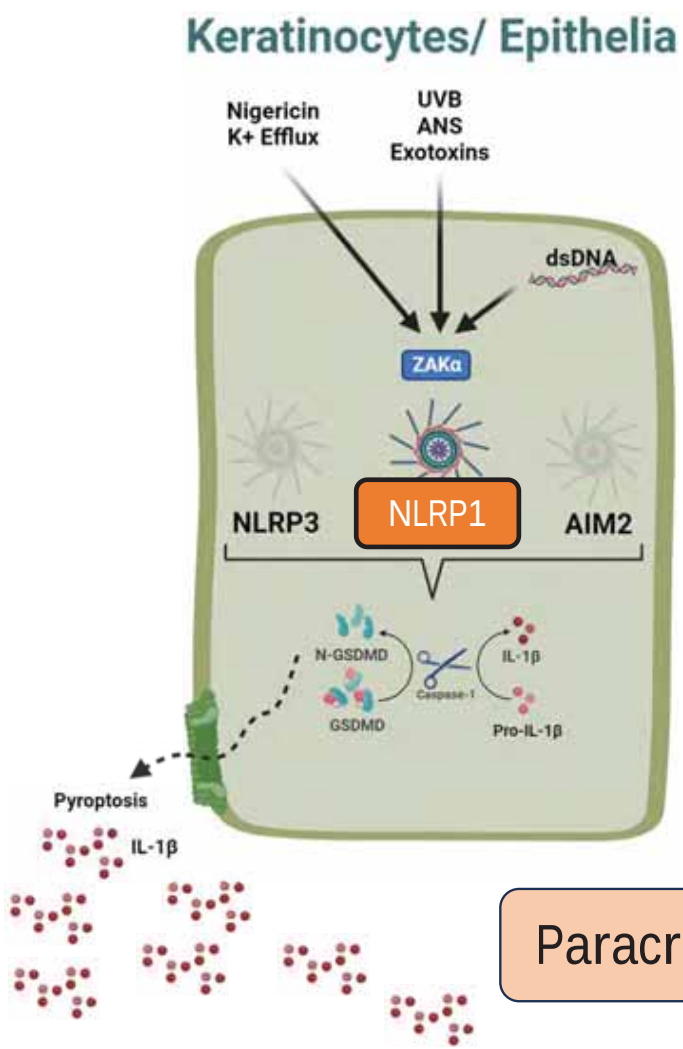
GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
TGFB1	c.466C>T (p.Arg156Cys)	heterozygous	PATHOGENIC
NLRP1	c.3641C>G (p.Pro1214Arg)	heterozygous	Likely Pathogenic
CFI	Deletion (Exons 8-13)	heterozygous	Uncertain Significance
DOCK2	c.167A>G (p.Gln56Arg)	heterozygous	Uncertain Significance
LYST	c.8306A>G (p.His2769Arg)	heterozygous	Uncertain Significance
NLRP12	c.753C>G (p.Asn251Lys)	heterozygous	Uncertain Significance
RAB27A	c.425T>C (p.Val142Ala)	heterozygous	Uncertain Significance
TAP2	c.730A>G (p.Thr244Ala)	heterozygous	Uncertain Significance
TOP2B	c.2510T>C (p.Val837Ala)	heterozygous	Uncertain Significance
UNC13D	c.271G>A (p.Val91Met)	heterozygous	Uncertain Significance


Keratinocytes/ Epithelia
Nigericin
K+ Efflux
UVB
ANS
Exotoxins
dsDNA
ZAKα
NLRP3
NLRP1
AIM2
N-GSDMD
GSDMD
Caspase-1
IL-1β
Pro-IL-1β
Pyroptosis
IL-1β



Paracrine secretion IL-1β





Inflammation

Dyskeratosis

Cancer SCC

Paracrine secretion IL-1β

NLRP1-associated autoinflammatory disease with epithelial dyskeratosis (NADED)

Number of cases	Variant identified	Inheritance	Status
17 members of a family	A54T	AD	Heterozygous
4 family members	A59P	AD	Heterozygous
Several family members	A66V	AD	Heterozygous
2 (mother and son)	M77T	AD	Heterozygous
2 cousins	R726W	AR	Homozygous
2 brothers	T755N	AR	Homozygous
2 siblings	F787_R843del	AR	Homozygous
2 sisters	L813P	AR	Homozygous
2 (unrelated)	P1214R	AD	Heterozygous

ORIGINAL ARTICLE

Whole exome sequencing identifies a mutation for a novel form of corneal intraepithelial dyskeratosis

Vincent José Soler,[1,2] Khanh-Nhat Tran-Viet,[1] Stéphane D Galiacy,[2] Vachiranee Limviphuvadh,[3] Thomas Patrick Klemm,[4] Elizabeth St Germain,[1] Pierre R Fournié,[2,5] Céline Guillaud,[2,5] Sebastian Maurer-Stroh,[3,6] Felicia Hawthorne,[1] Cyrielle Suarez,[2,5] Bernadette Kantelip,[7] Natalie A Afshari,[8] Isabelle Creveaux,[9] Xiaoyan Luo,[1] Weihua Meng,[2] Patrick Calvas,[2] Myriam Cassagne,[2,5] Jean-Louis Arné,[5] Steven G Rozen,[4] François Malecaze,[2,5] Terri L Young[1,8]

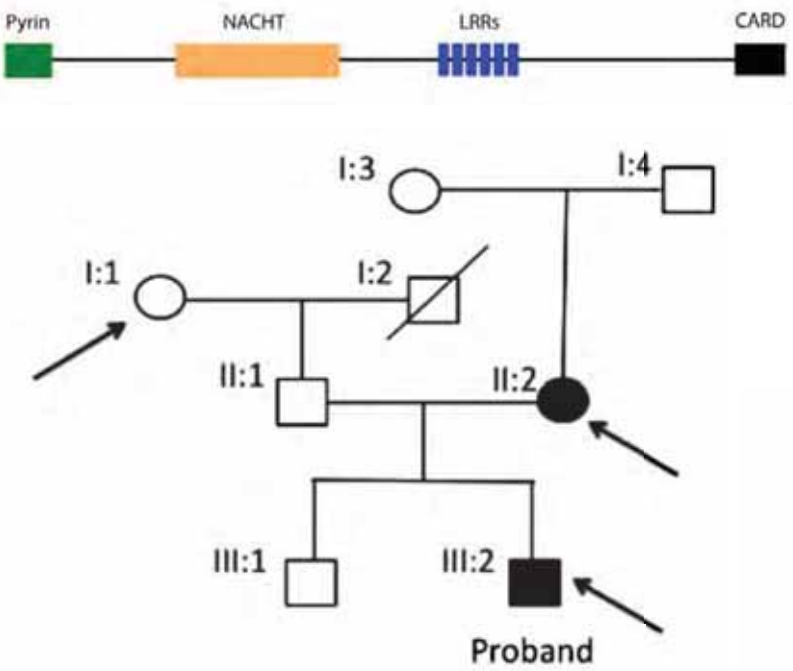


Figure 1 Corneal dystrophy pedigree. Arrows depict samples that were chosen for exome sequencing: individuals I:1 (unaffected), II:2 (affected) and the proband III:2 (affected).

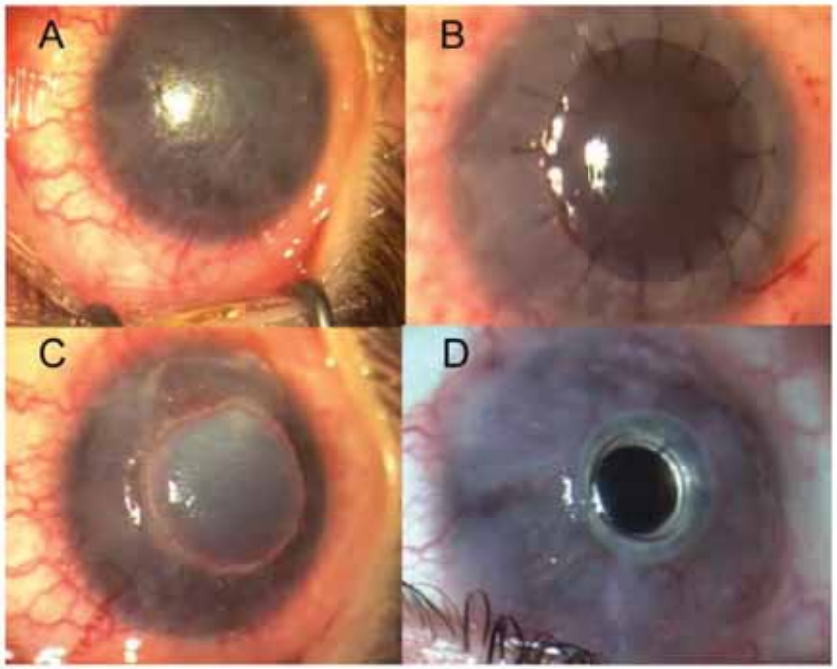


Figure 2 Preoperative corneal examination of the right eye and postoperative clinical follow-up. Preoperatively, the patient presented with corneal opacification, corneal thickening, and circumferential corneolimbal neovascularisation (A). An initial deep anterior lamellar keratoplasty (DALK) (B) was performed; the disease recurred resulting in corneal graft opacification noted at a 2 month postoperative clinic session (C). After three DALK failures, the patient underwent a type 1 Boston keratoprosthesis procedure (D) approximately 7 months later.

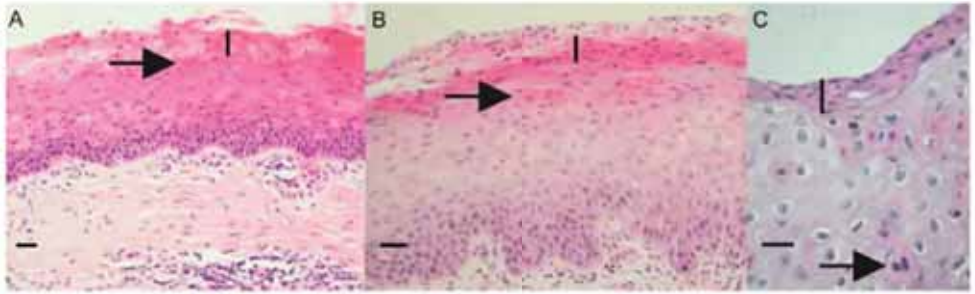


Figure 3 Histopathological features of the original cornea sample, the first failed corneal graft, and vocal chord tissue. The original cornea (panel A, horizontal bold scale: 100 μm), first corneal graft (panel B, horizontal bold scale: 60 μm), and vocal chord tissue (panel C, horizontal bold scale: 25 μm) show similar epithelial features: parakeratosis (vertical bold line), dyskeratosis (arrows), and acanthosis. Other histological characteristics are the absence of Bowman's layer and the presence of a stromal inflammatory infiltrate.

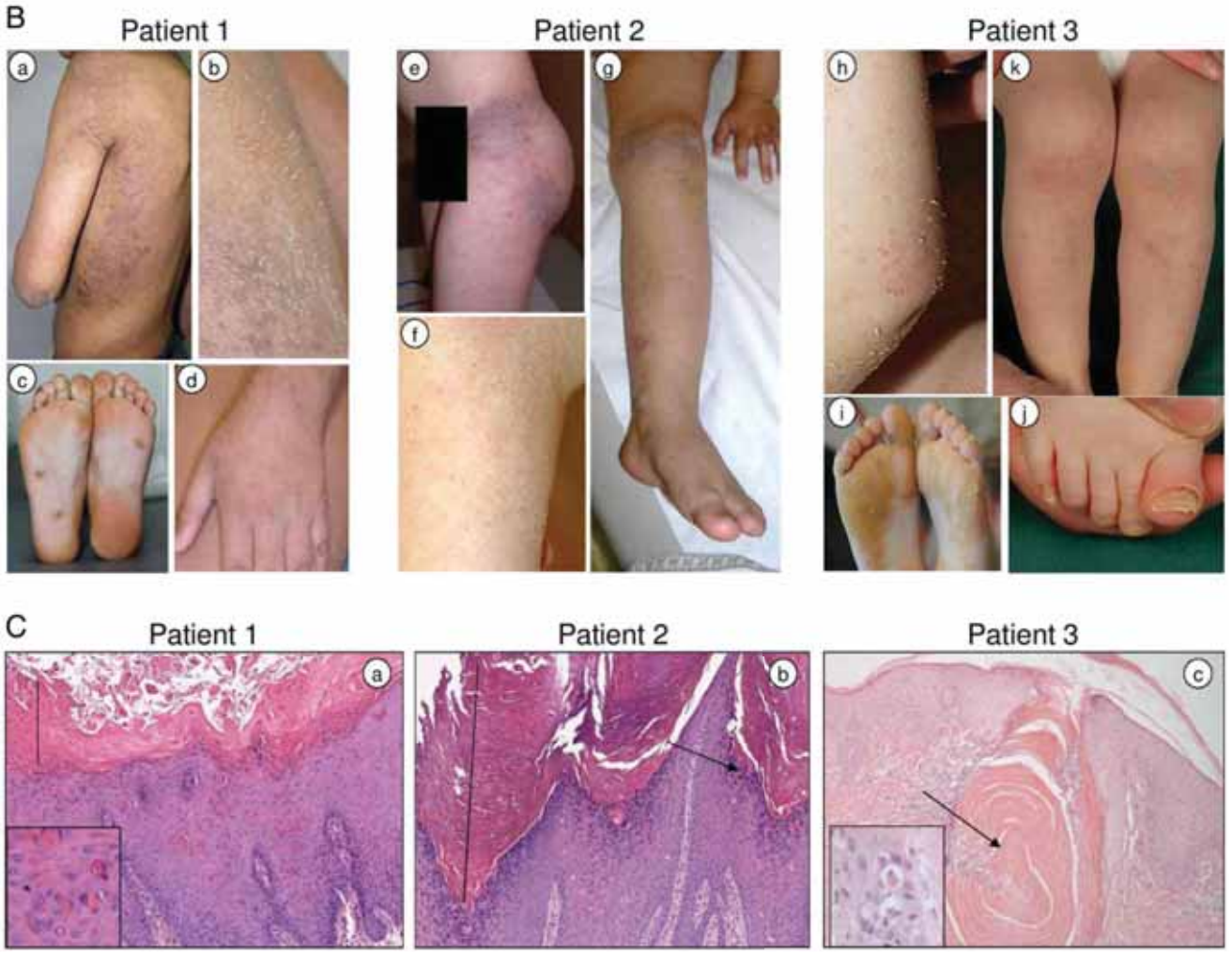
EXTENDED REPORT

A new autoinflammatory and autoimmune syndrome associated with NLRP1 mutations: NAIAD (*NLRP1*-associated autoinflammation with arthritis and dyskeratosis)

Sylvie Grandemange,[1,2] Elodie Sanchez,[2,3] Pascale Louis-Plence,[2,4] Frédéric Tran Mau-Them,[2,3] Didier Bessis,[4,5] Christine Coubes,[3] Eric Frouin,[6] Marieke Seyger,[7] Manon Girard,[3] Jacques Puechberty,[3] Valérie Costes,[4,6] Michel Rodière,[8] Aurélia Carbasse,[8] Eric Jeziorski,[4,8] Pierre Portales,[9] Guillaume Sarrabay,[1,2,4] Michel Mondain,[4,10] Christian Jorgensen,[2,4,11] Florence Apparailly,[2,4,11] Esther Hoppenreijs,[12] Isabelle Touitou,[1,2,4] David Geneviève[2,3,4]

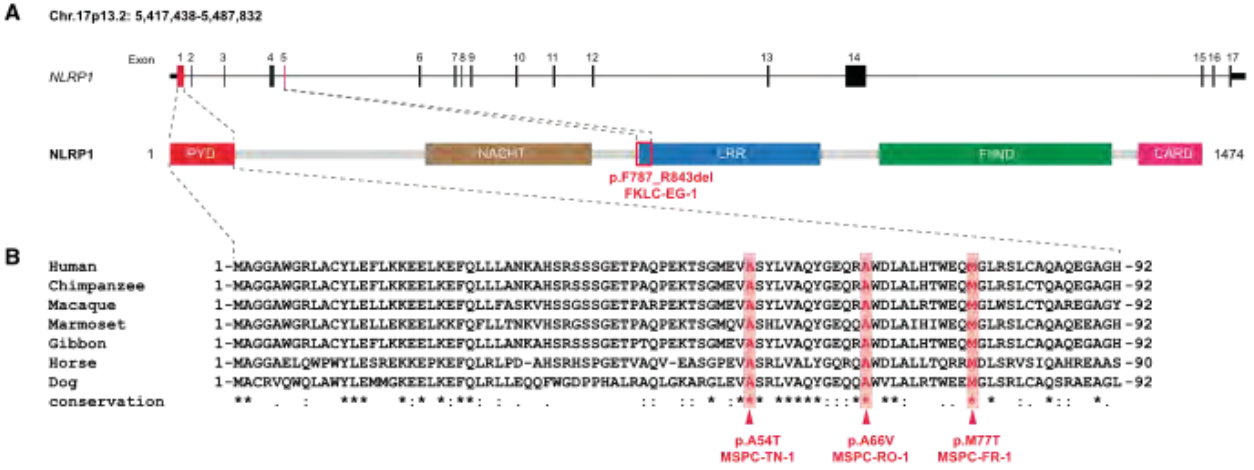
Table 1 Summary of the main clinical and biological features of patients

	Patient 1	Patient 2	Patient 3
Dyskeratosis	+	+	+
Arthritis	+	+	+
Recurrent fever	+	+	+
Chronic infection	+	–	+
Recurrent elevated CRP	+	+	+
ANA	–	+	+
Vitamin A deficiency	+	+	+
High transitional B cells	+	–	+

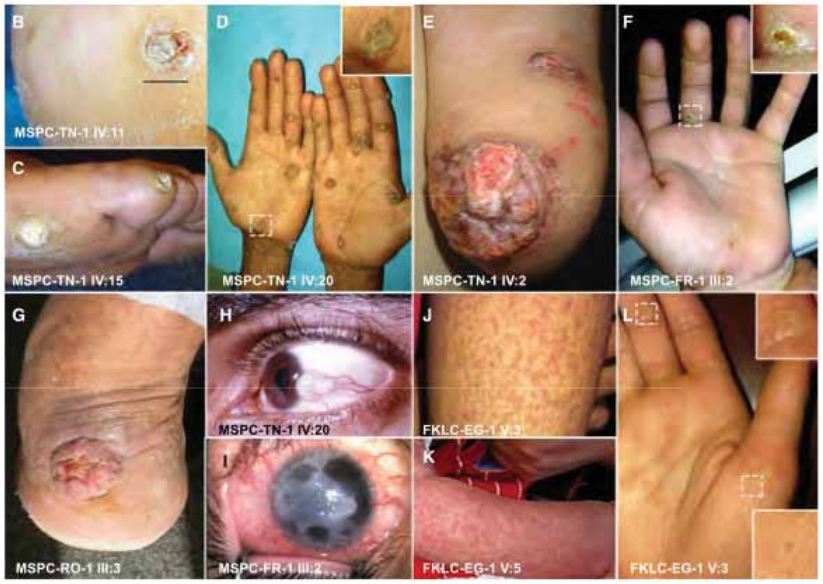


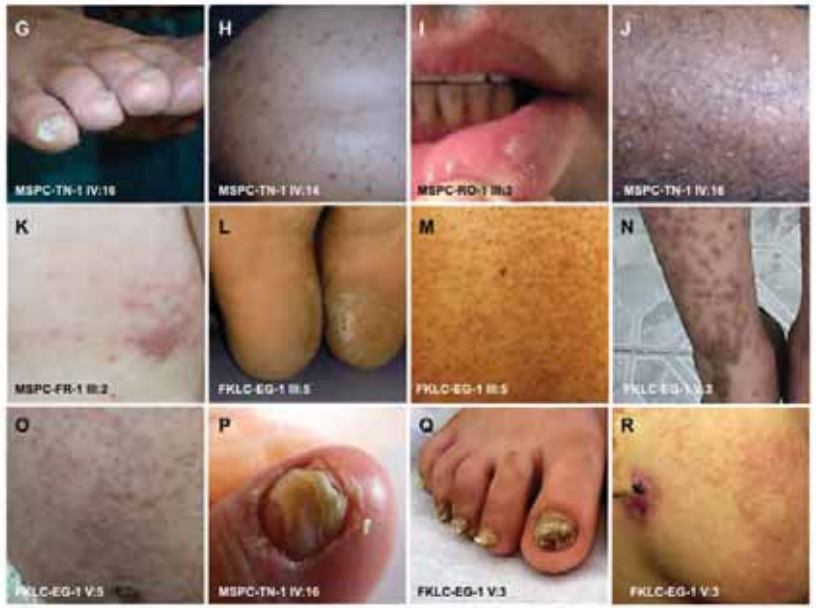
Germline NLRP1 Mutations Cause Skin Inflammatory and Cancer Susceptibility Syndromes via Inflammasome Activation

Franklin L. Zhong,[1,2,17,*] Ons Mamaï,[1,4,17] Lorenzo Sborgi,[3] Lobna Boussofara,[5] Richard Hopkins,[2] Kim Robinson,[1] Ildikó Szeverényi,[1] Takuya Takeichi,[6,14] Reshmaa Balaji,[1] Aristotle Lau,[1] Hazel Tye,[10,11] Keya Roy,[1] Carine Bonnard,[1] Patricia J. Ahl,[2] Leigh Ann Jones,[2] Paul Baker,[10,11] Lukas Lacina,[1] Atsushi Otsuka,[7] Pierre R. Fournie,[8,9] François Malecaze,[8,9] E. Birgitte Lane,[1] Masashi Akiyama,[6] Kenji Kabashima,[1,7] John E. Connolly,[2] Seth L. Masters,[10,11] Vincent J. Soler,[8,9] Salma Samir Omar,[12] John A. McGrath,[13] Roxana Nedelcu,[14] Moez Gribaa,[4] Mohamed Denguezli,[5] Ali Saad,[4] Sebastian Hiller,[3] and Bruno Reversade[1,2,15,16,18,*]



- Germline, gain-of-function *NLRP1* mutations cause MSPC and FKLC syndromes.
- The Pyrin (PYD) and LRR domains of NLRP1 inhibit its self-oligomerization.
- NLRP1 mutants cause skin hyperplasia via paracrine inflammatory signaling.





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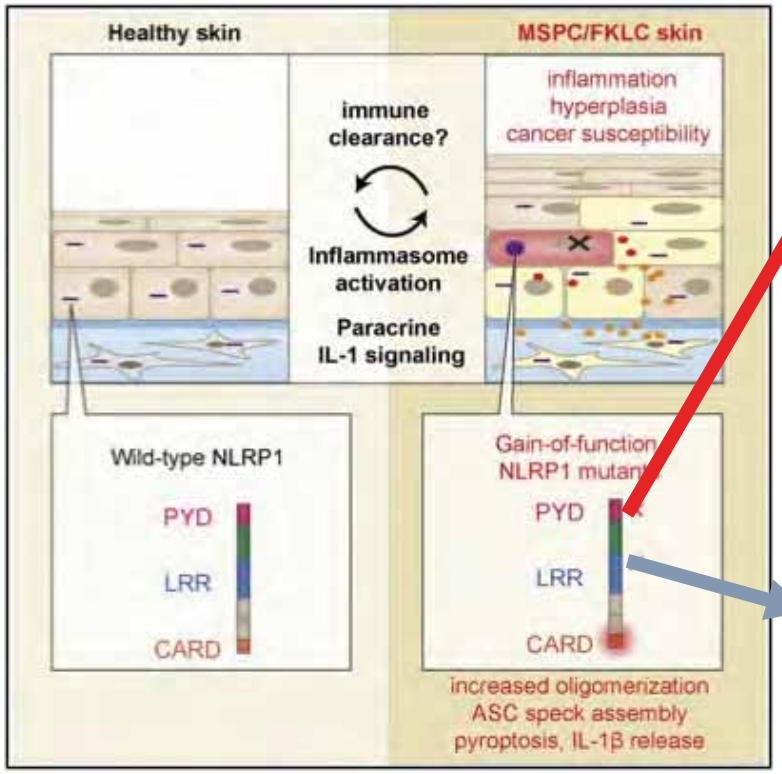
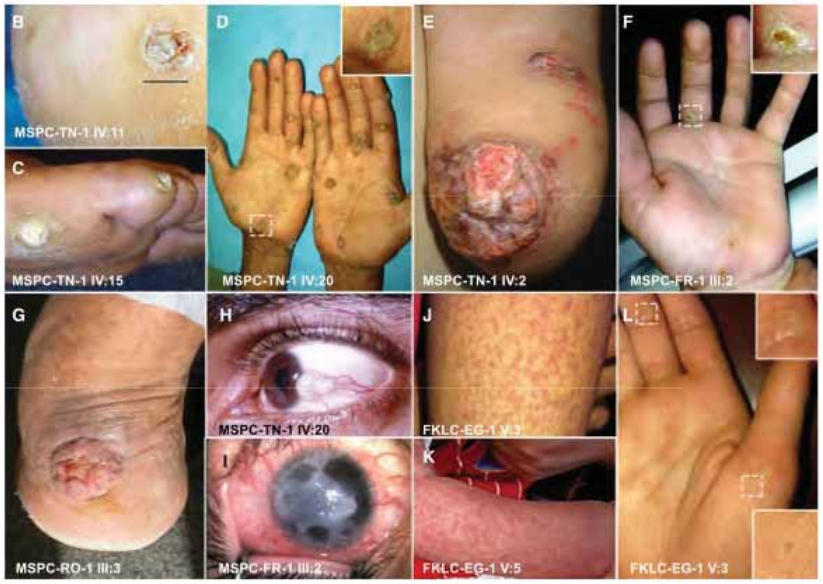


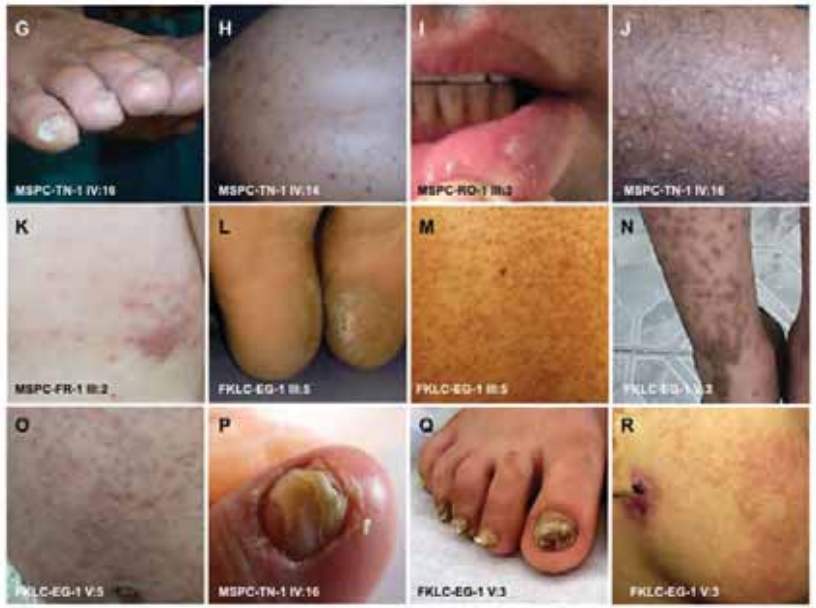
A54T/wt
A66V/wt
M77T/wt

Multiple self-healing palmoplantar carcinoma

p.F787_R843del/wt

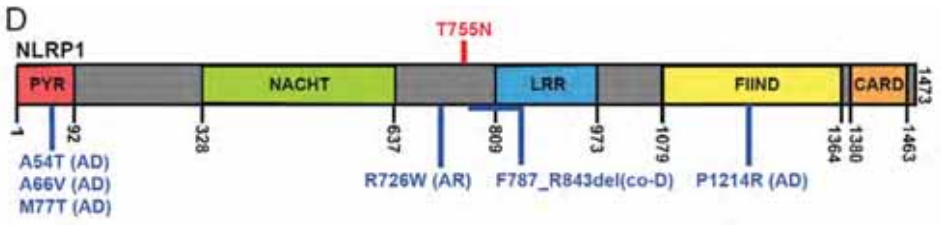
Familial keratosis lichenoides chronica

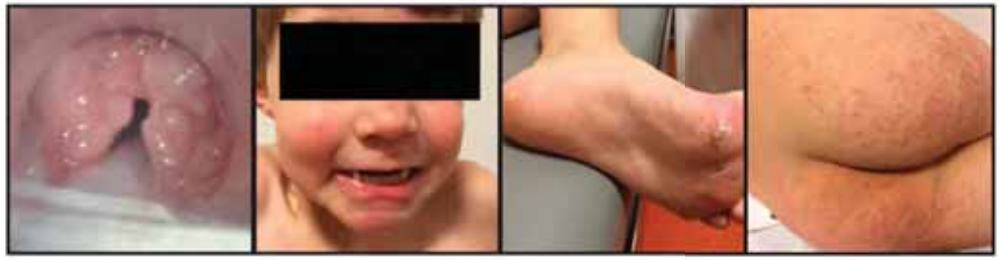


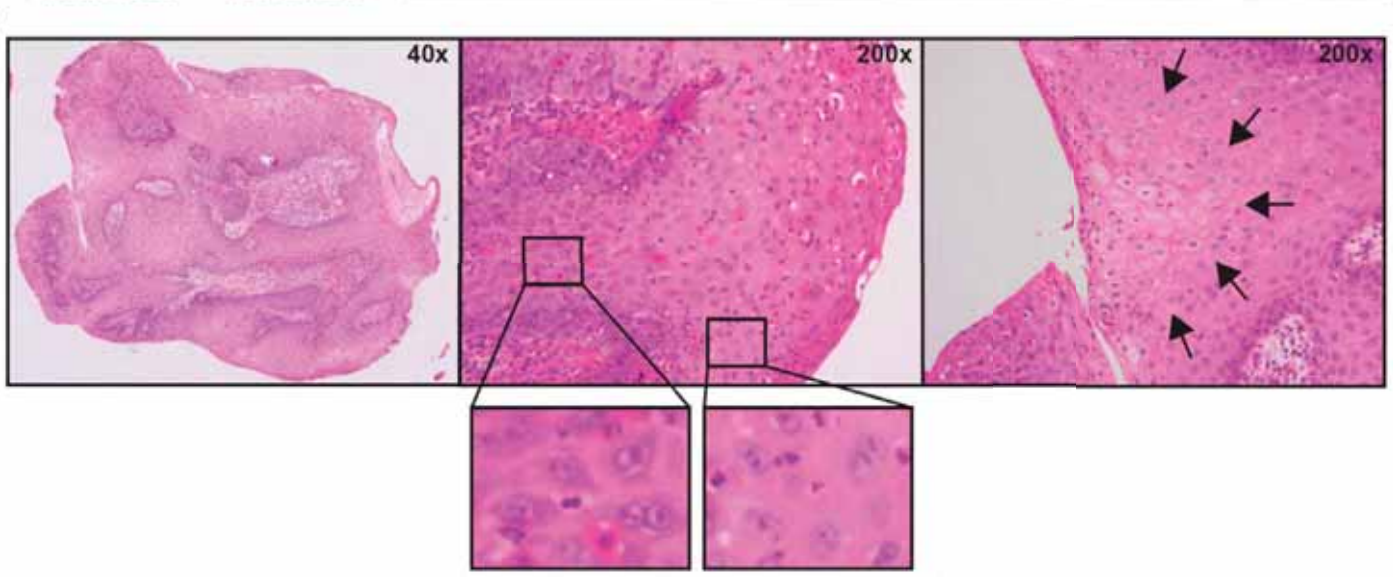


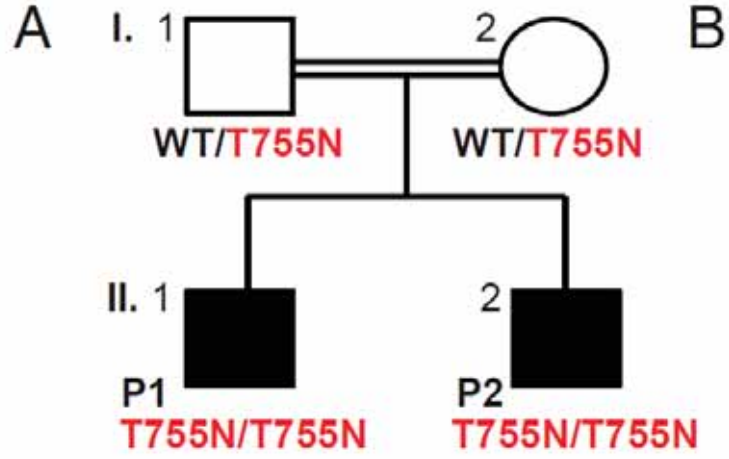
Homozygous *NLRP1* gain-of-function mutation in siblings with a syndromic form of recurrent respiratory papillomatosis

Scott B. Drutman[a], Filomeen Haerynck[b,1], Franklin L. Zhong[c,d,e,f,1], David Hum[a,1], Nicholas J. Hernandez[a], Serkan Belkaya[a], Franck Rapaport[a], Sarah Jill de Jong[a], David Creytens[g,h], Simon J. Tavernier[b,i,j], Katrien Bonte[k], Sofie De Schepper[l], Jutte van der Werff ten Bosch[m], Lazaro Lorenzo-Diaz[n,o], Andy Wullaert[j,p,q], Xavier Bossuyt[r,s], Gérard Orth[t], Vincent R. Bonagura[u,v], Vivien Béziat[a,n,o], Laurent Abel[a,n,o], Emmanuelle Jouanguy[a,n,o], Bruno Reversade[c,d,w,x], and Jean-Laurent Casanova[a,n,o,y,z,2]







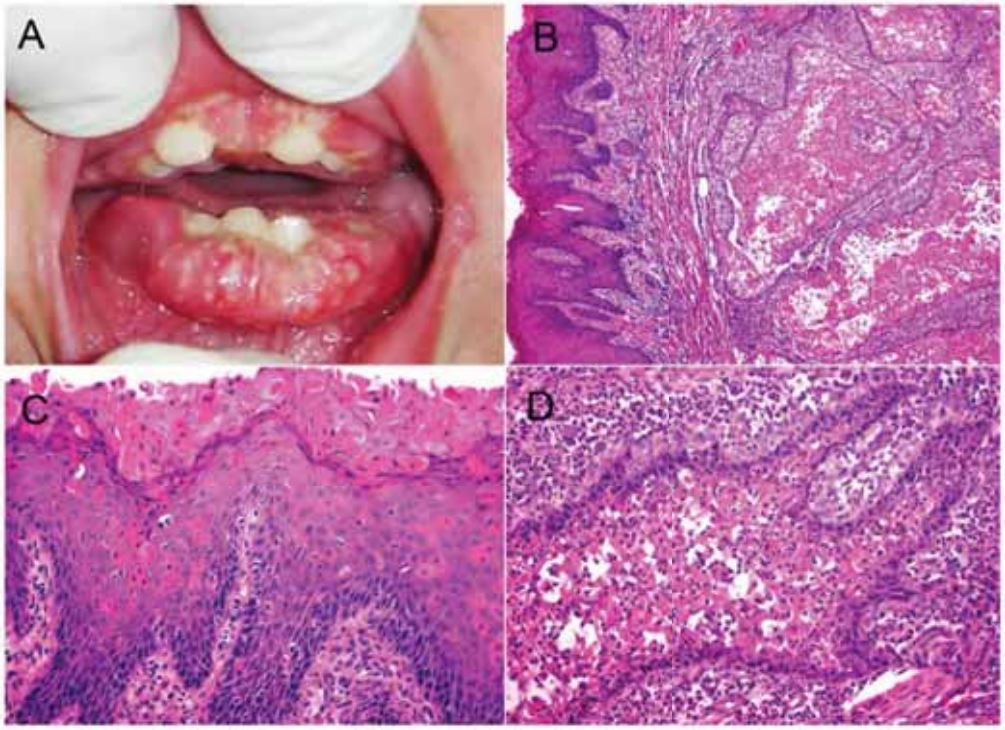


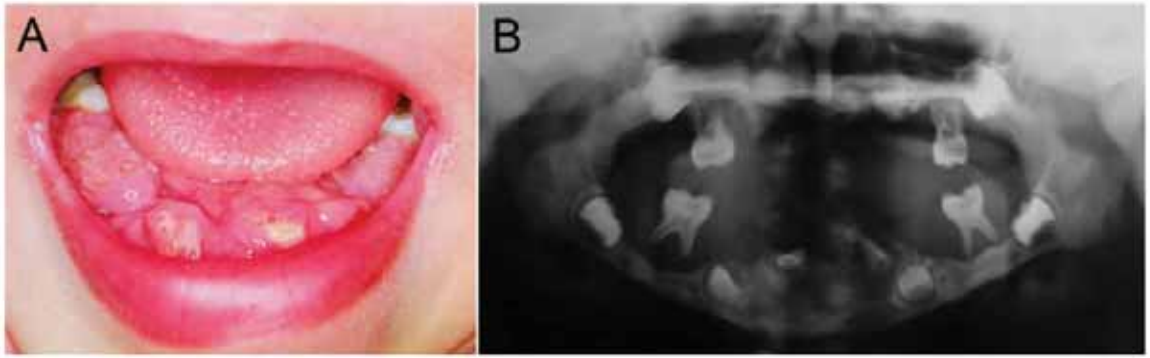
CASE REPORT

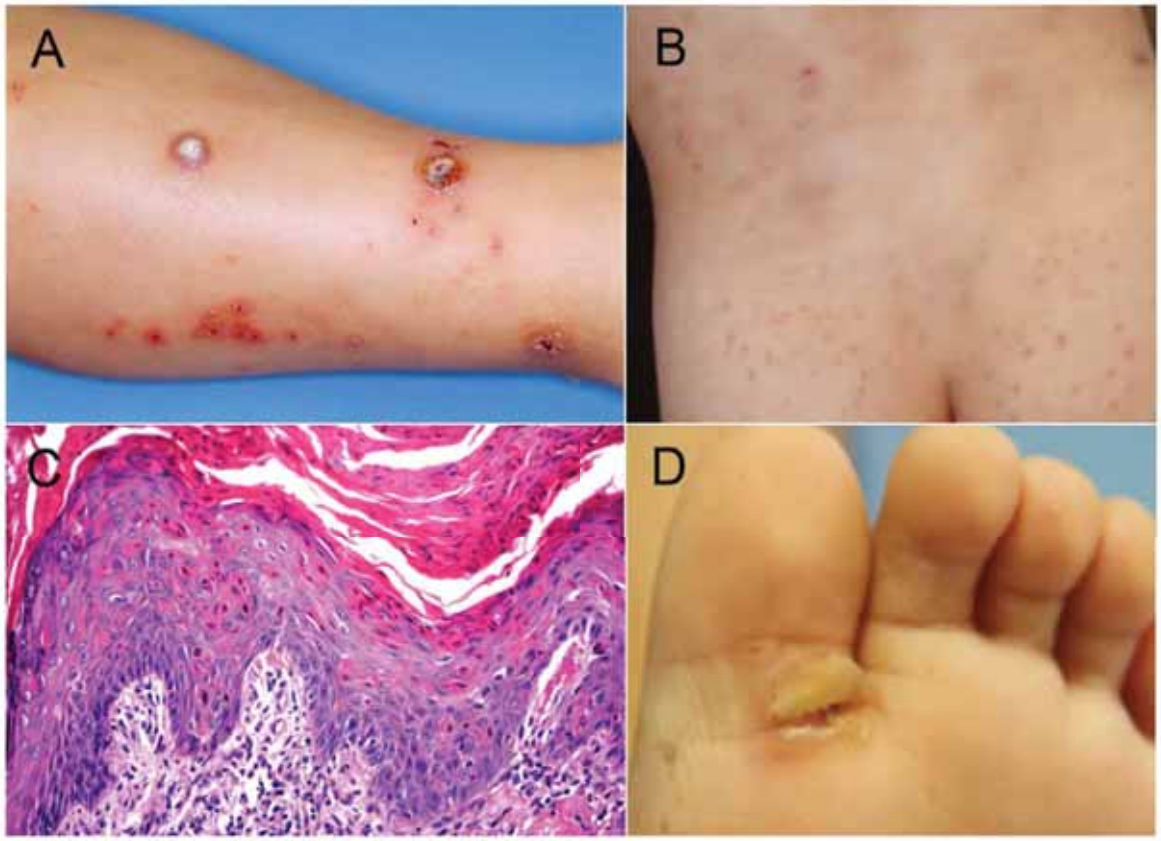
Mucocutaneous dyskeratosis with periodontal destruction and premature tooth loss

Michelle Agostini, DDS, PhD,[a,b] Renato Valiati, DDS, PhD,[b] Jorge Esquiche León, DDS, PhD,[a] Mário José Romañach, DDS, MSc,[a] Crispian Scully, MD, PhD,[c] and Oslei Paes de Almeida, DDS, PhD[a]
University of Campinas, Piracicaba, Brazil; and University of Planalto Catarinense, Lages, Brazil; and
UNIVERSITY COLLEGE LONDON AND UNIVERSITY OF BRISTOL, UNITED KINGDOM

We report the case of a 16-month-old boy who presented an exuberant erythematous gingival swelling and severe tooth mobility. Radiographic examination confirmed alveolar bone loss, and gingival biopsy showed epithelium containing numerous dyskeratotic cells. Because of feeding difficulties, the enlarged gingival tissue and involved teeth were removed. One year later, similar problems were encountered during the eruption of the deciduous second molars. The patient also exhibited papular skin lesions. Histopathologic features on biopsies of the skin and oral lesions were similar. The oral and cutaneous lesions presented by this patient were similar to those described by From et al. in 1978 in a father and son, reported as dyskeratosis benigna intraepithelialis mucosae et cutis hereditaria—the sole report in the English language. To avoid confusion with hereditary benign intraepithelial dyskeratosis (Witkop–von Sallmann syndrome) we have renamed the condition as mucocutaneous dyskeratosis with periodontal destruction and tooth loss. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:254-259)







Journal of Cutaneous Pathology 1978: 5, 105–115

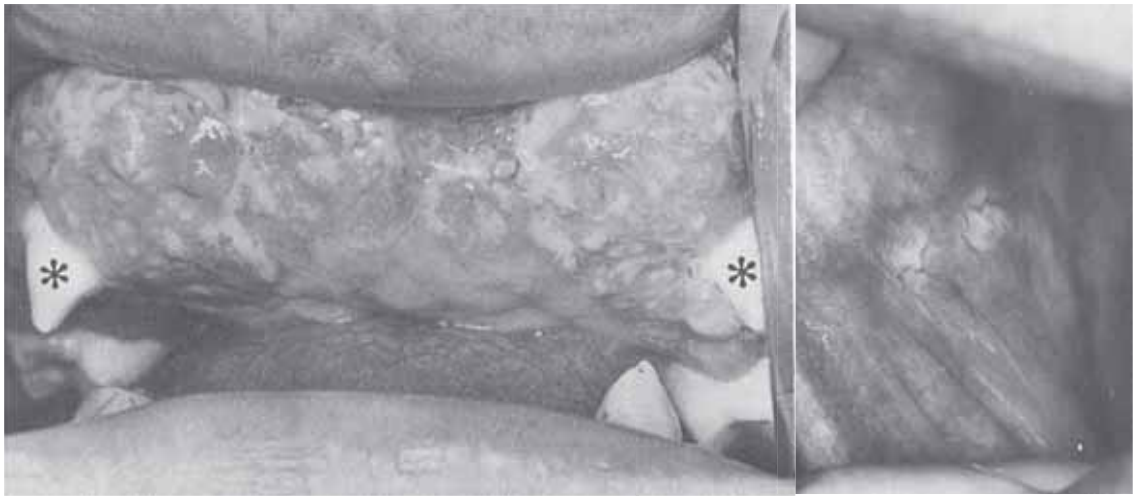
Dyskeratosis Benigna Intraepithelialis Mucosae et Cutis Hereditaria

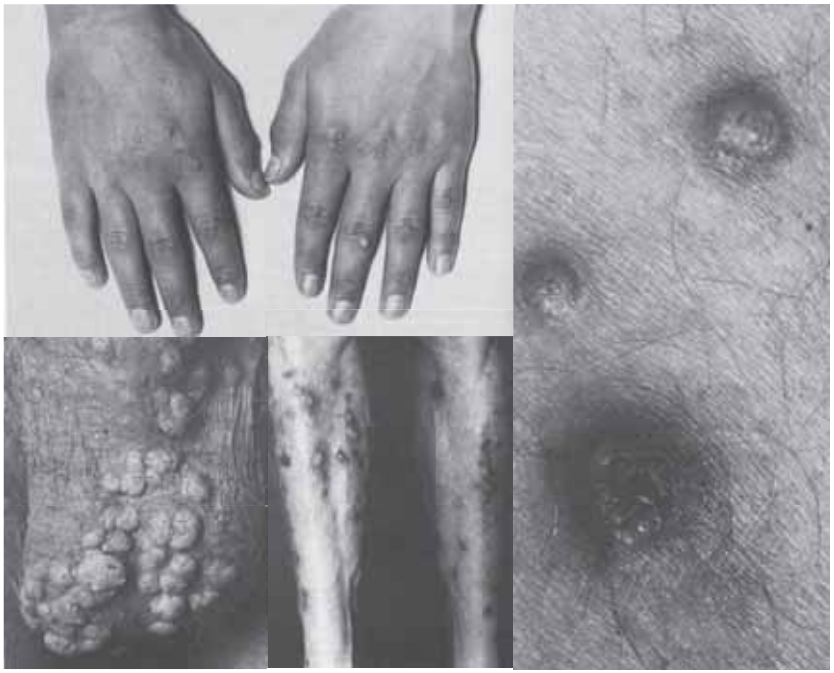
A Report of this Disorder in Father and Son

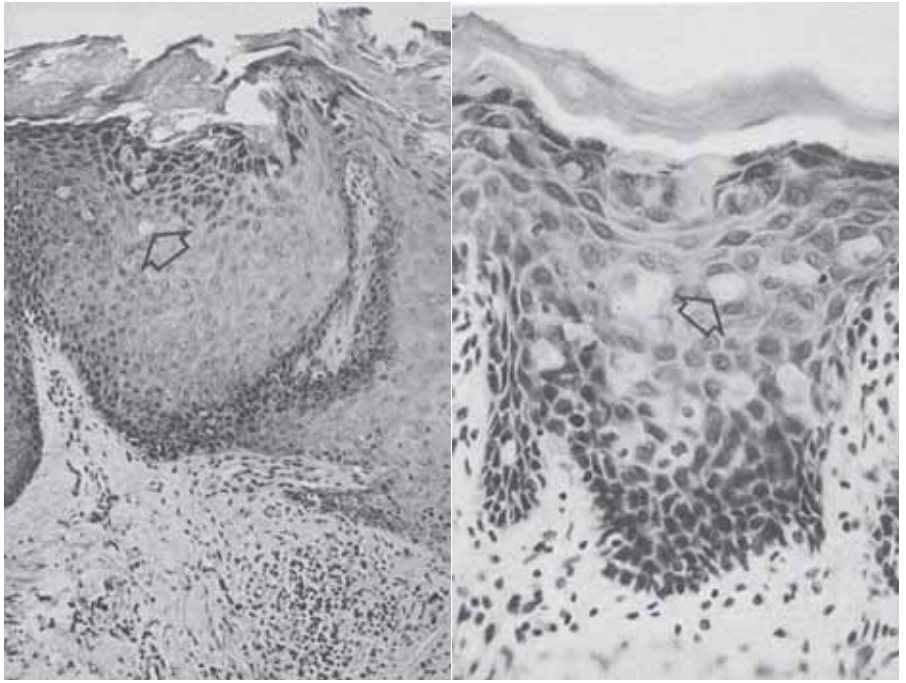
E. FROM, H. P. PHILIPSEN AND J. THORMANN

Department of Dermatology, Marselisborg Hospital, University of Aarhus, and Department of Oral Pathology, Royal Dental College, Aarhus, Denmark

A congenital syndrome affecting the skin, oral mucosa and bulbar conjunctiva is reported in father and son. Skin lesions consisted of brownish papules with central keratotic plugs. Trauma was able to provoke lesions. In addition, changes of oral mucosa with premature loss of the teeth, and recurrent eye symptoms with conjunctivitis were present. Histological examination of specimens from skin, oral mucosa and conjunctiva revealed a uniform picture of dyskeratosis (single cell keratinization). The symptoms reported do not seem to fit into any of the existing muco-cutaneous syndromes. An autosomal dominant mutation is suggested as the cause of the disease.







REVIEW

Autoinflammatory Keratinization Diseases—The Concept, Pathophysiology, and Clinical Implications

Leszek Blicharz[1] · Joanna Czuwara[1] · Lidia Rudnicka[1] · Antonio Torrelo[2]

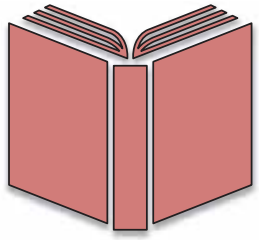
Pathomechanism	Resulting phenotype
Aberrant IL-1-family signaling	
Deficiency of the IL-36 receptor antagonist (DITRA)	Pustular psoriasis
Deficiency of the IL-1 receptor antagonist (DIRA)	Pustular psoriasis
NLRP1 hyperactivation	Epithelial dyskeratosis
Disorders of NFκB and/or aberrant TNF activity	
CARD14 hyperactivation;	PRP; CAPE
Adaptor protein complex 1 subunit σ1C (AP1S3) deficiency	Pustular psoriasis, PPPP
Other miscellaneous mechanisms	
Mevalonate pathway abnormalities	Porokeratoses
Janus kinase 1 hyperactivity	Eczematous & ichthyosiform
Proteasome maturation protein deficiency	KLICK
Epidermal growth factor receptor deficiency	GI and cutaneous 1
ADAM17	GI and cutaneous 2
Mixed mechanisms	Hidradenitis suppurativa

Dermatopathologic clue #8

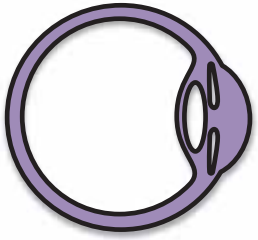
Keratoacanthoma-like & dyskeratotic keratinocytes

NLRP1-associated AID with epithelial dyskeratosis

Take-home messages

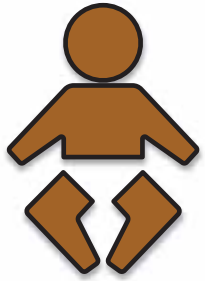


Study as much as you can



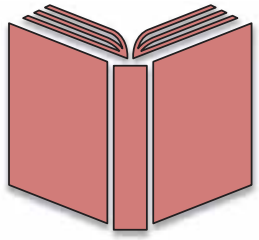
Look sharp

Think a lot

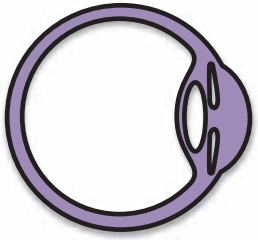


Remember they’re kids

Take-home messages

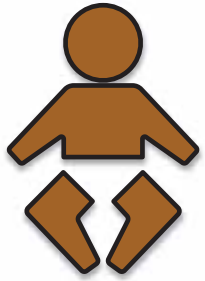


Study as much as you can



Look sharp

Think a lot



Remember they're kids

Stay alert, never trust…