Nuevas entidades descritas en el Hospital Niño Jesús 2010-2011

Isabel Colmenero
Servicio de Anatomía Patológica

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2011 ZARAGOZA

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome

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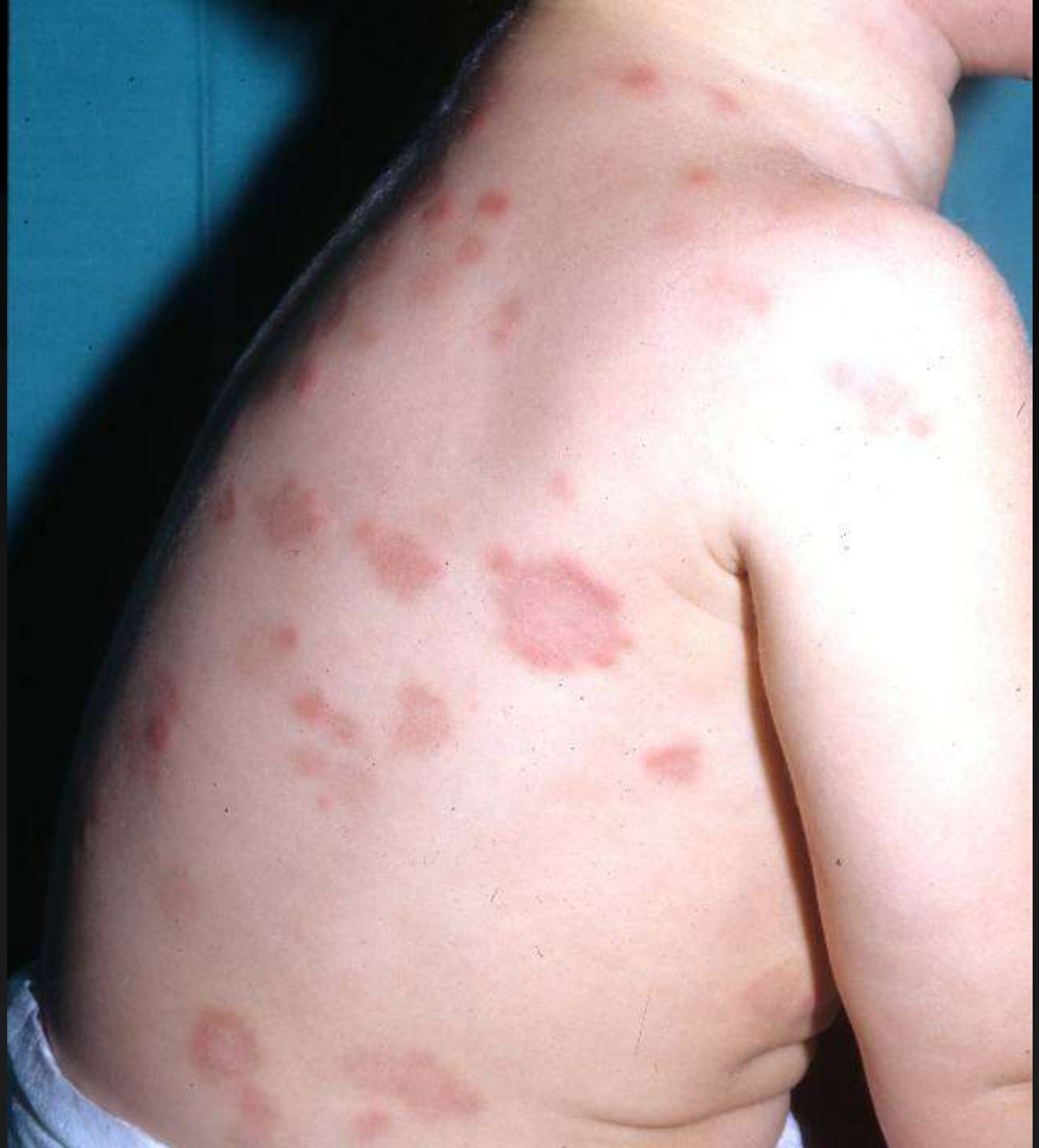
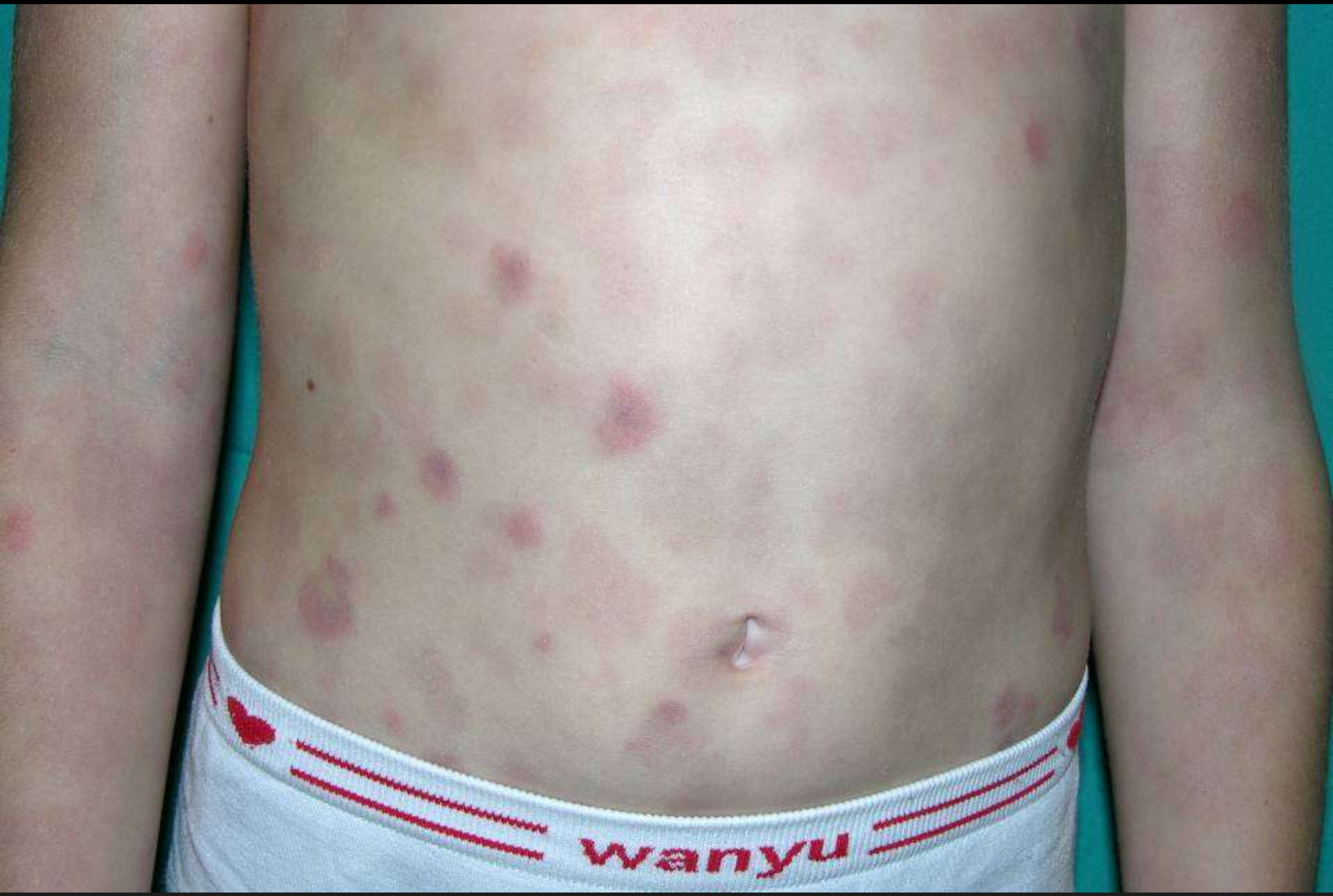
Madrid and Almería, Spain; Chicago, Illinois; and Amiens, France

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 (*c*hronic *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.)

Feature	Patient 1	Patient 2	Patient 3	Patient 4
Early onset	+	+	+	+
Fever (daily or recurrent)	+	+	+	+
Annular violaceous plaques	+	+	+	+
Persistent eyelid violaceous swelling	+	+	+	
Perioral swelling	+	+		
Ear and nose chondritis	+			
Low weight and height	+	+	+	+
Lipodystrophy	+	+	+	+
Prominent abdomen	+		+	
Acanthosis nigricans and hirsutism			+	
Lymphadenopathy	+			
Hepatomegaly	+		+	+
Splenomegaly	+		+	

Feature	Patient 1	Patient 2	Patient 3	Patient 4
Arthralgia	+	+	+	
Conjunctivitis and nodular episcleritis	+	+		
Epididymitis	+			
Aseptic meningitis	+		+	
Parotitis			+	
Interstitial lung disease			+	
Nephritis			+	
Otitis			+	
Increased ESR and CRP	+	+	+	+
Hypochromic anemia	+	+	+	+
Increased platelet counts	+			+
Elevated AST and ALT	+	+	+	+
Increased triglyceride levels			+	+
Basal ganglia calcifications	+		+	

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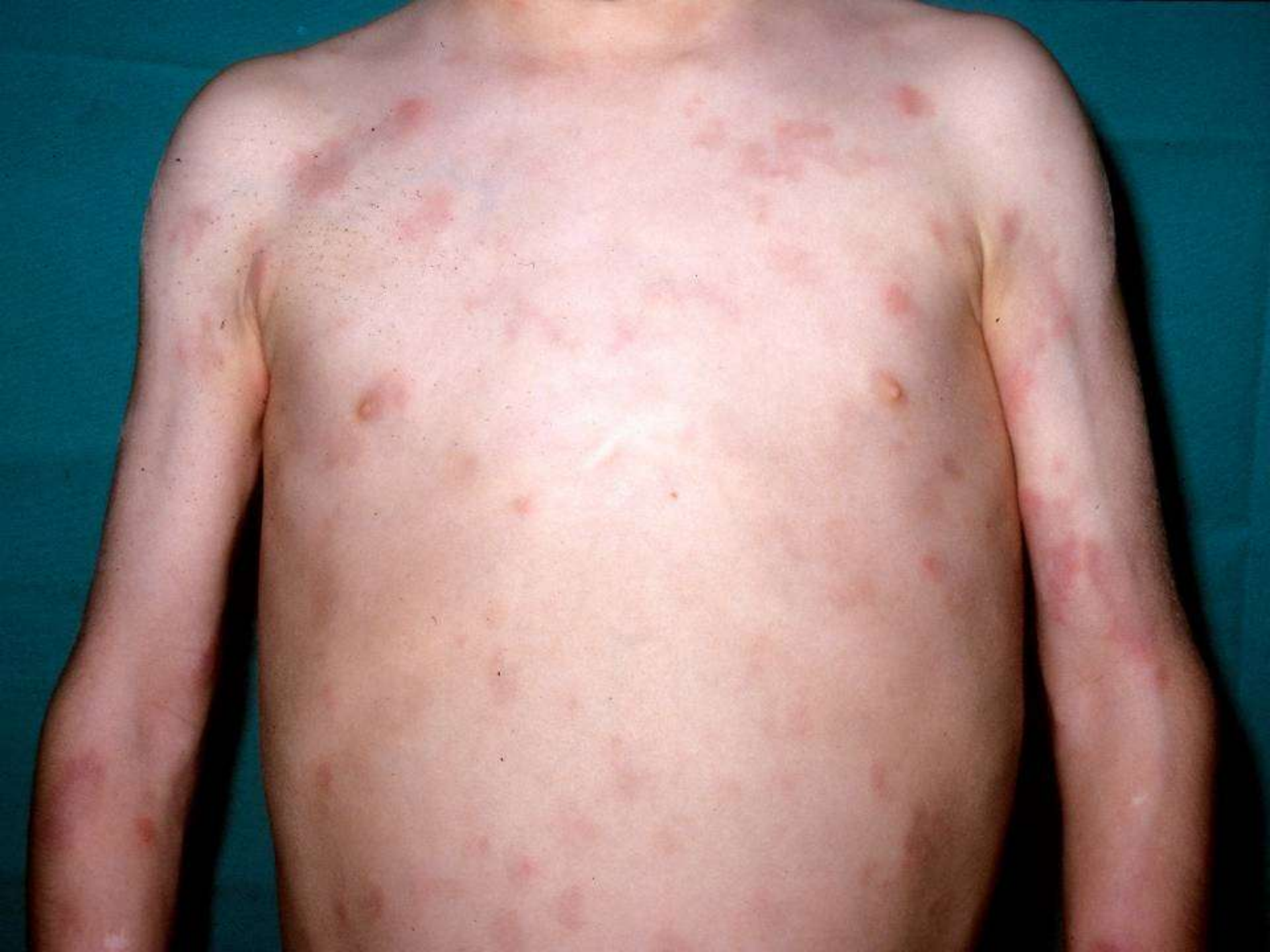

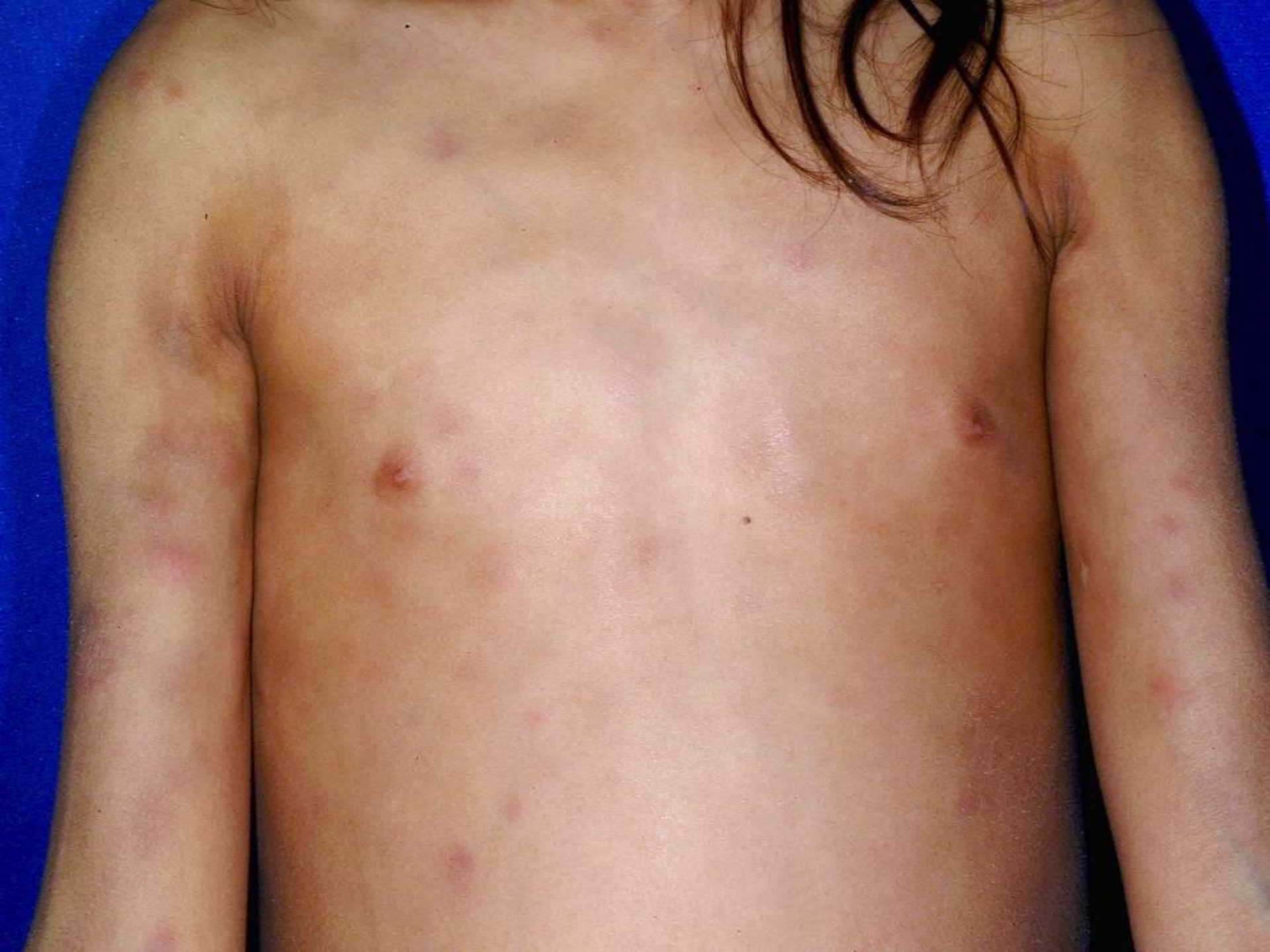

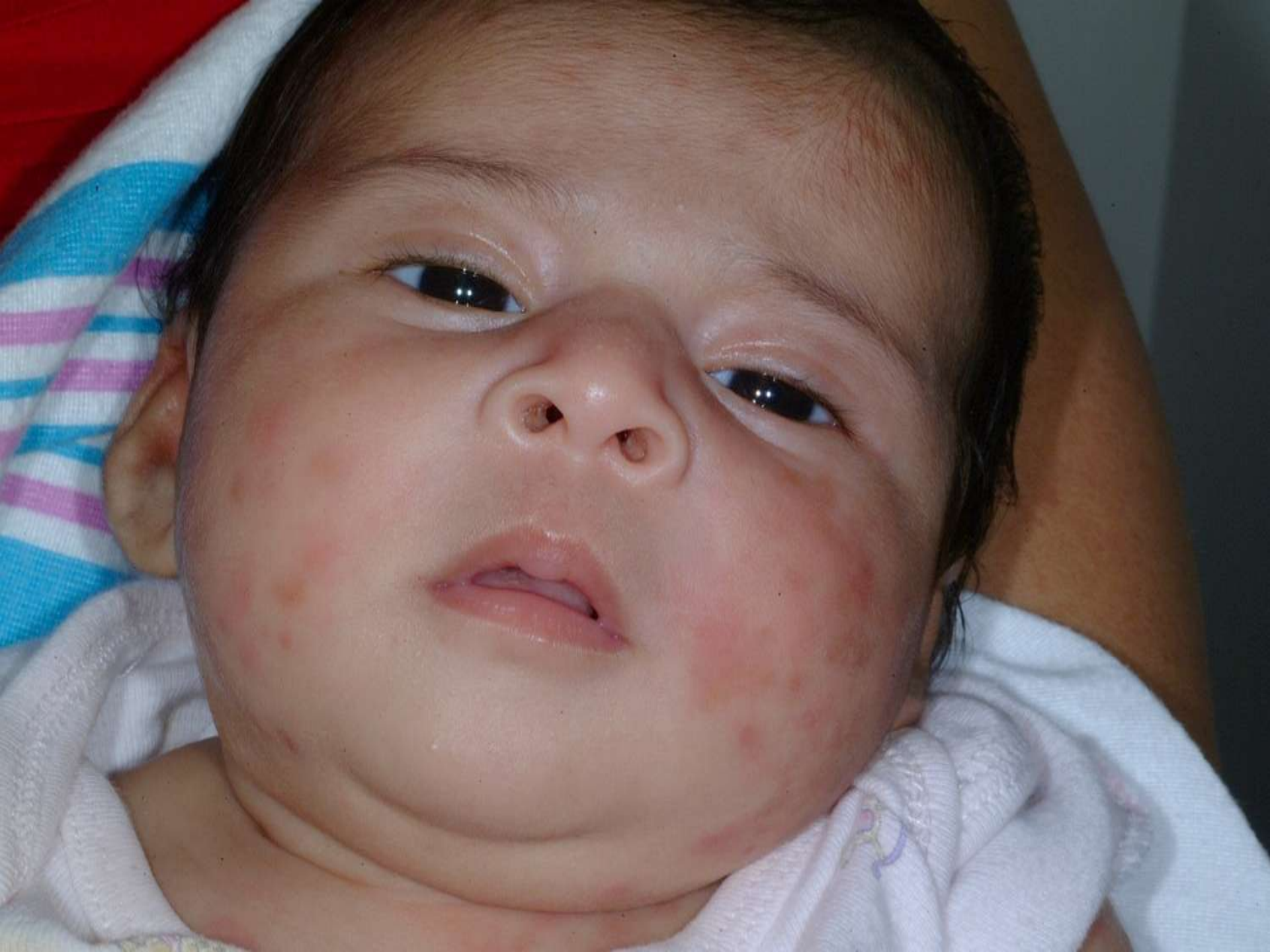

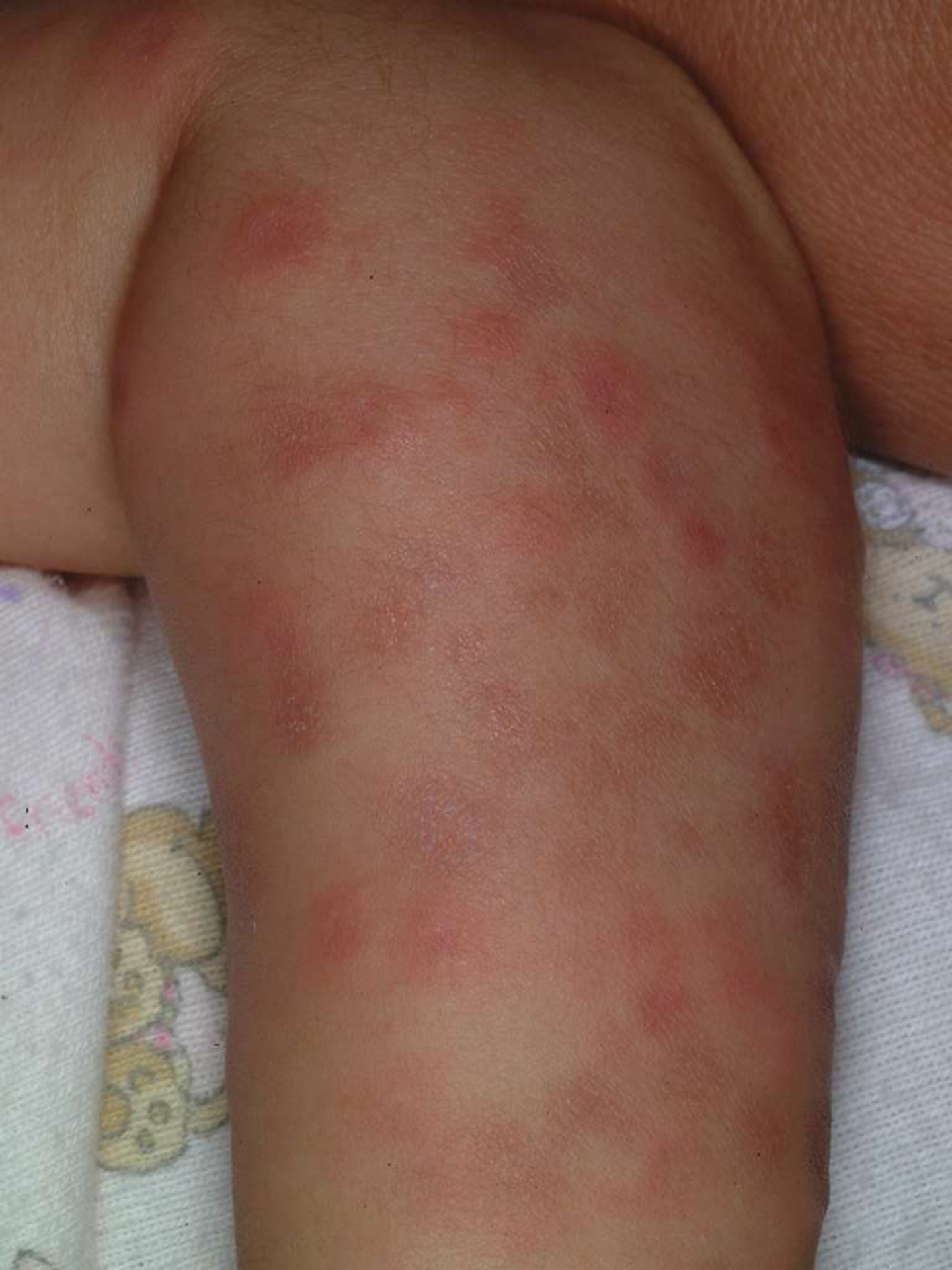

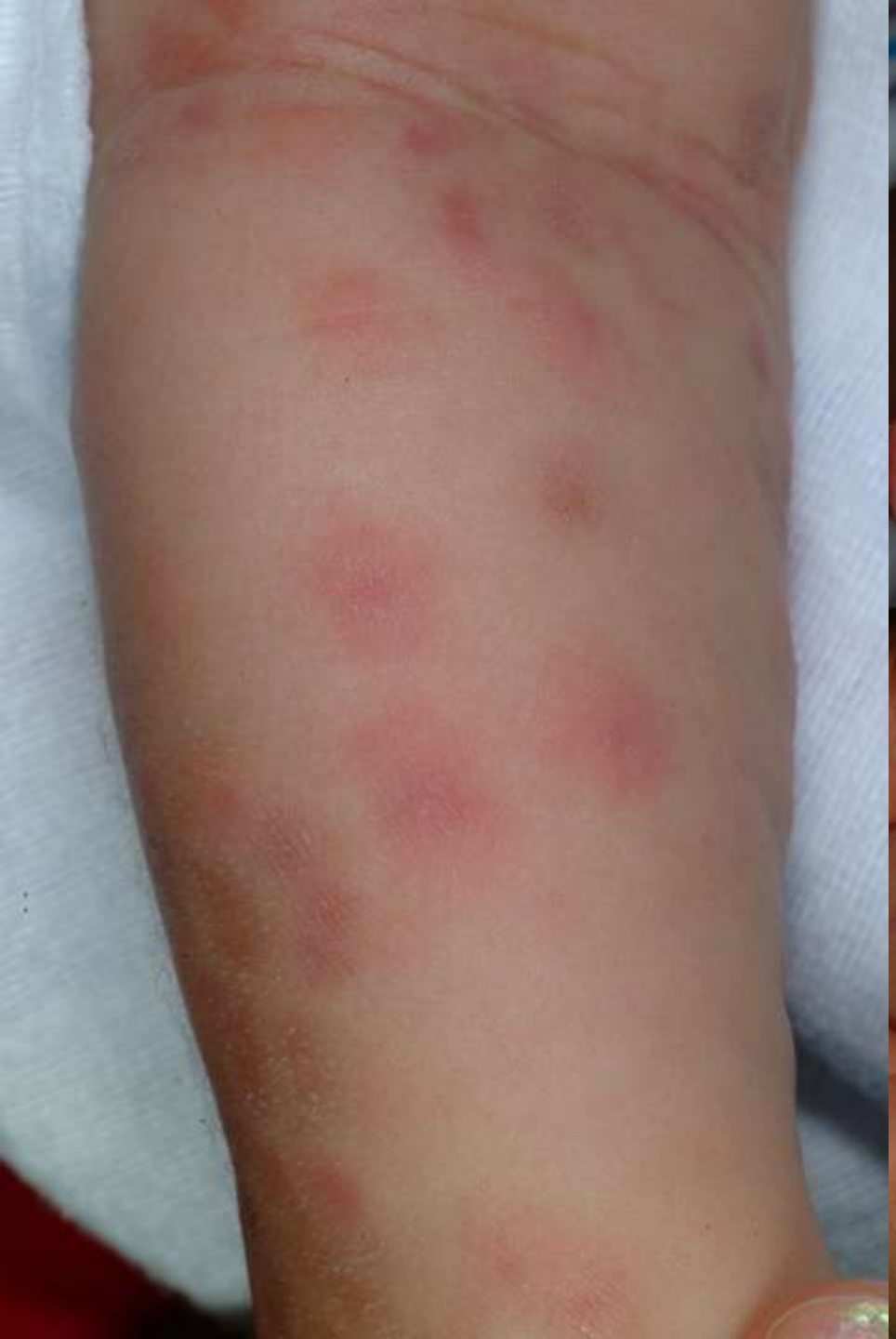
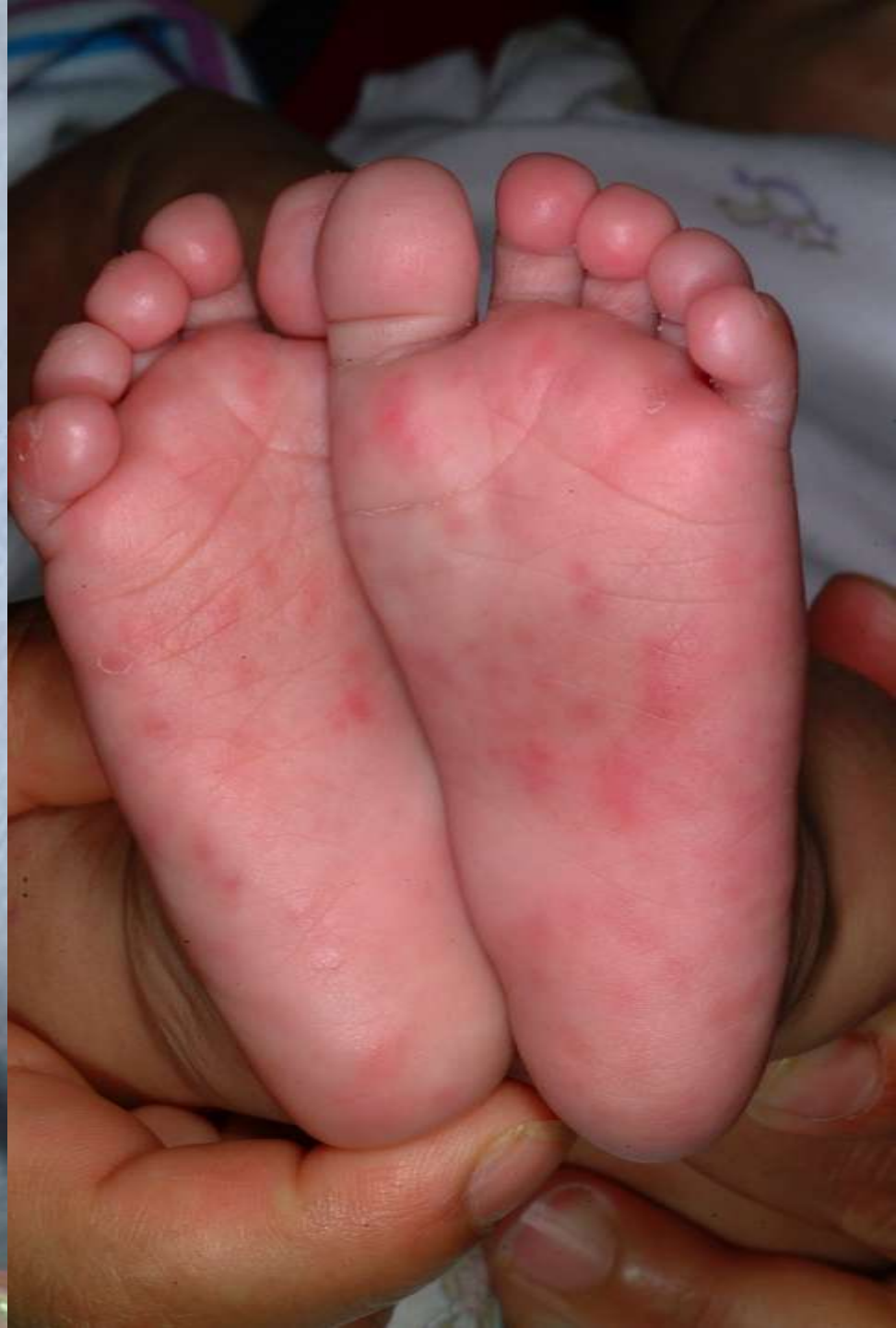

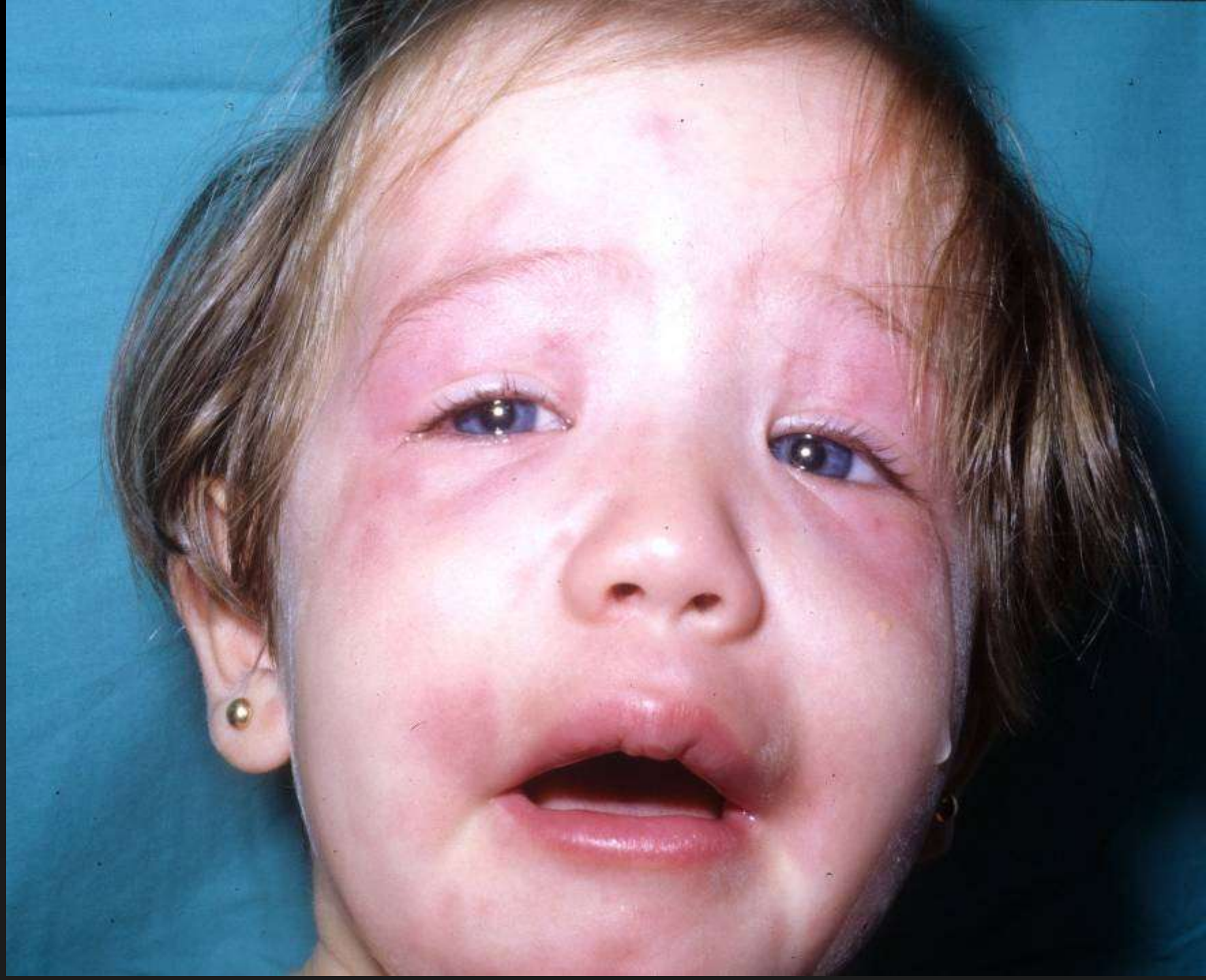

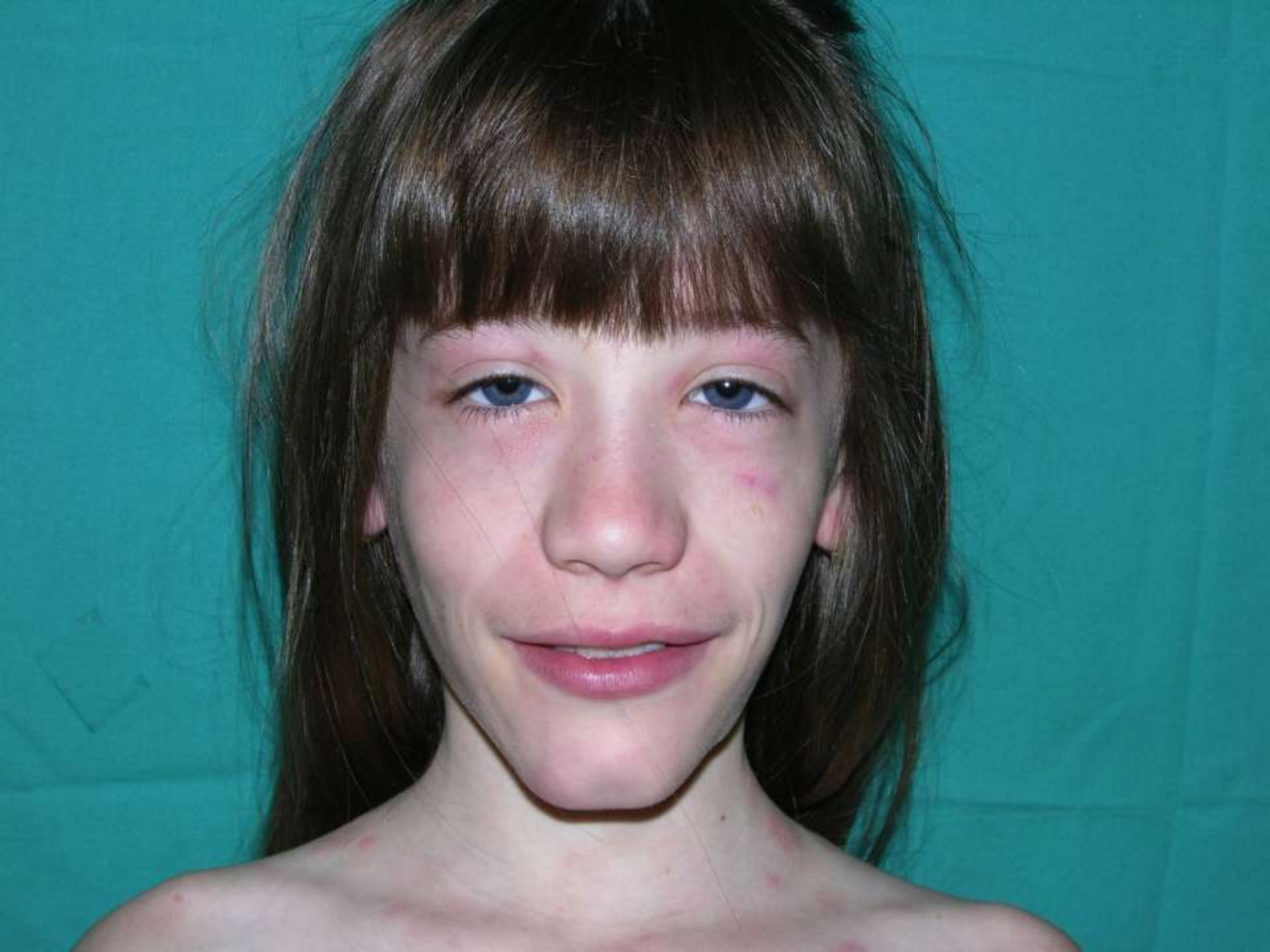

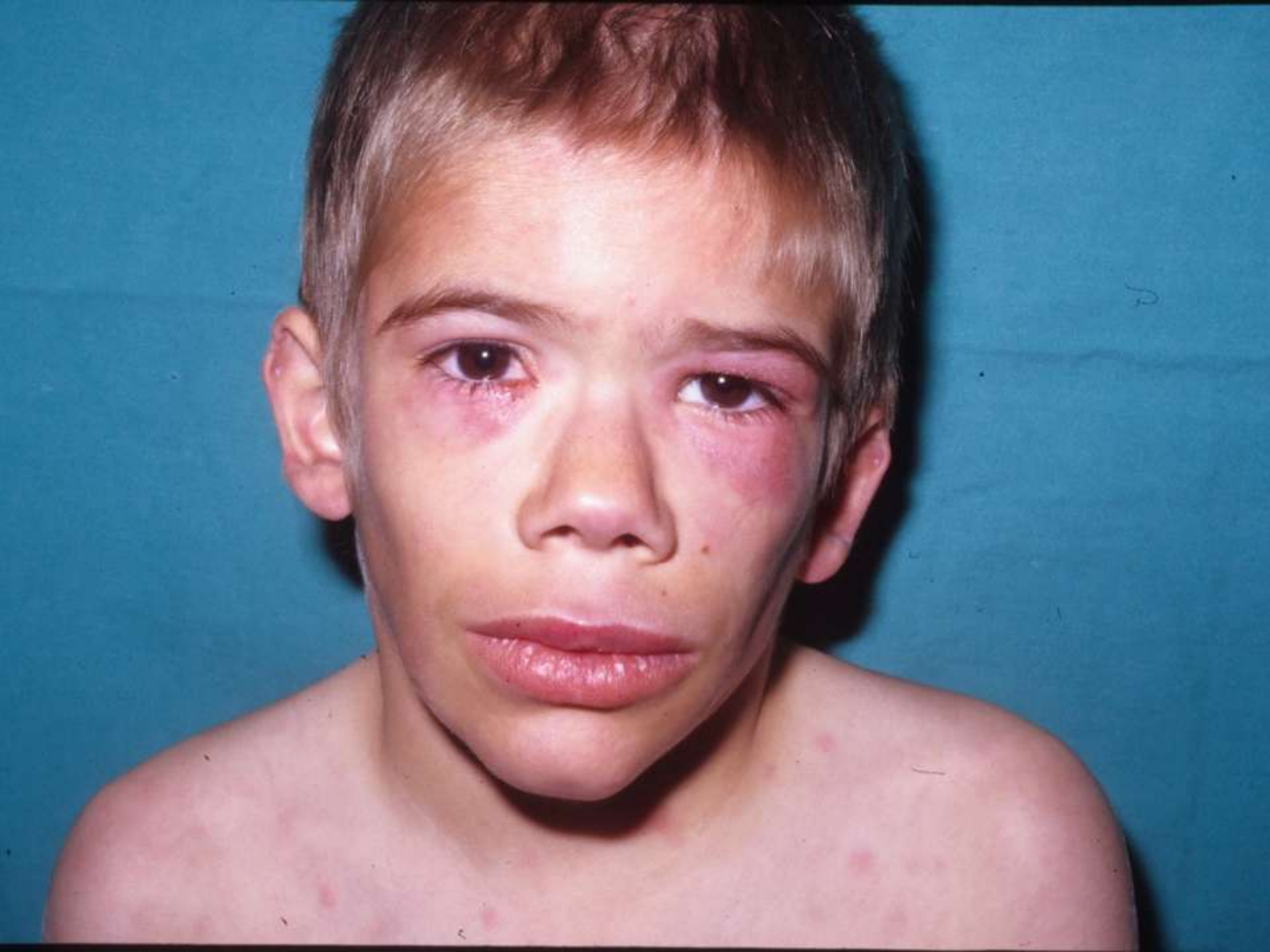


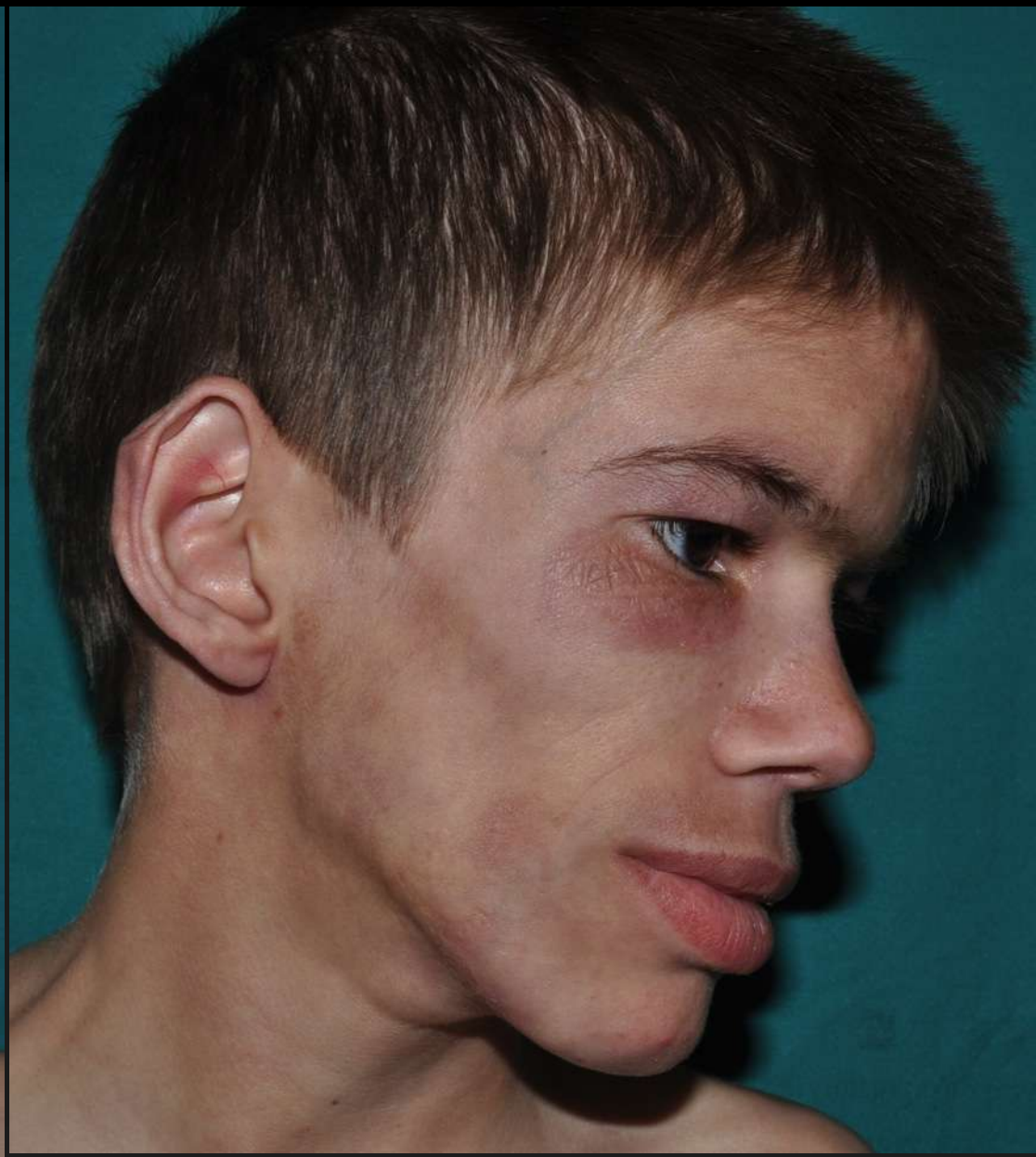

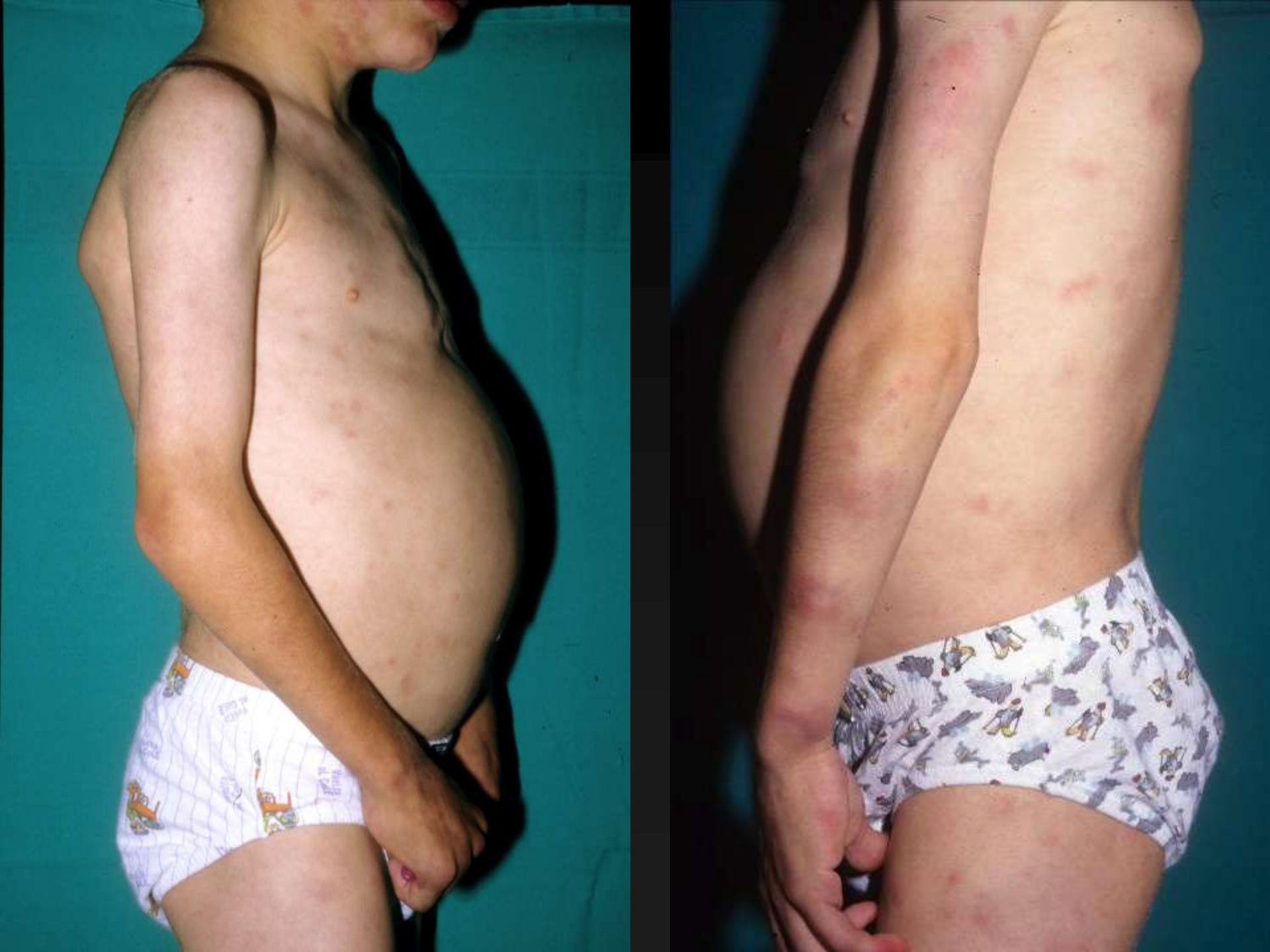

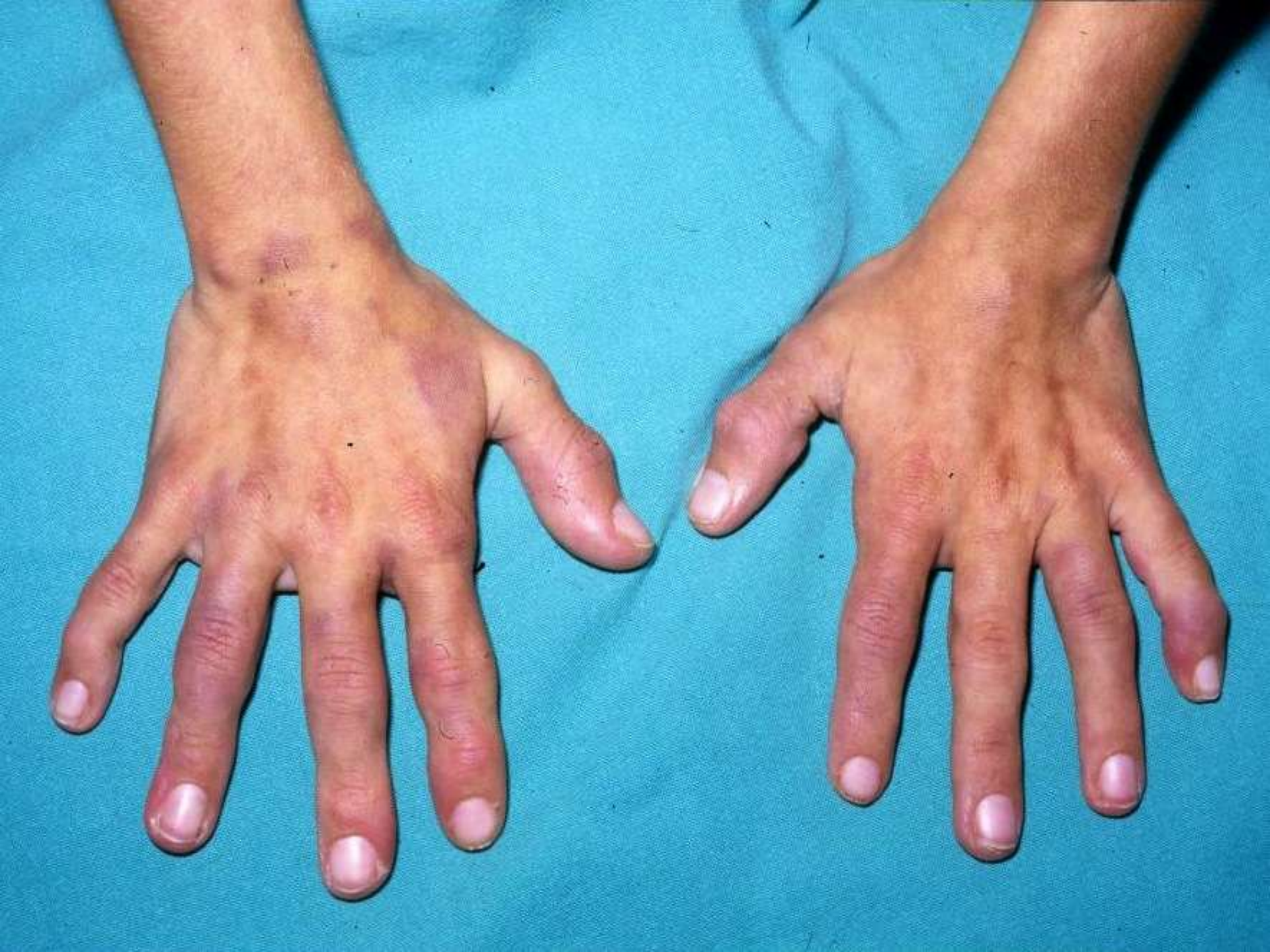

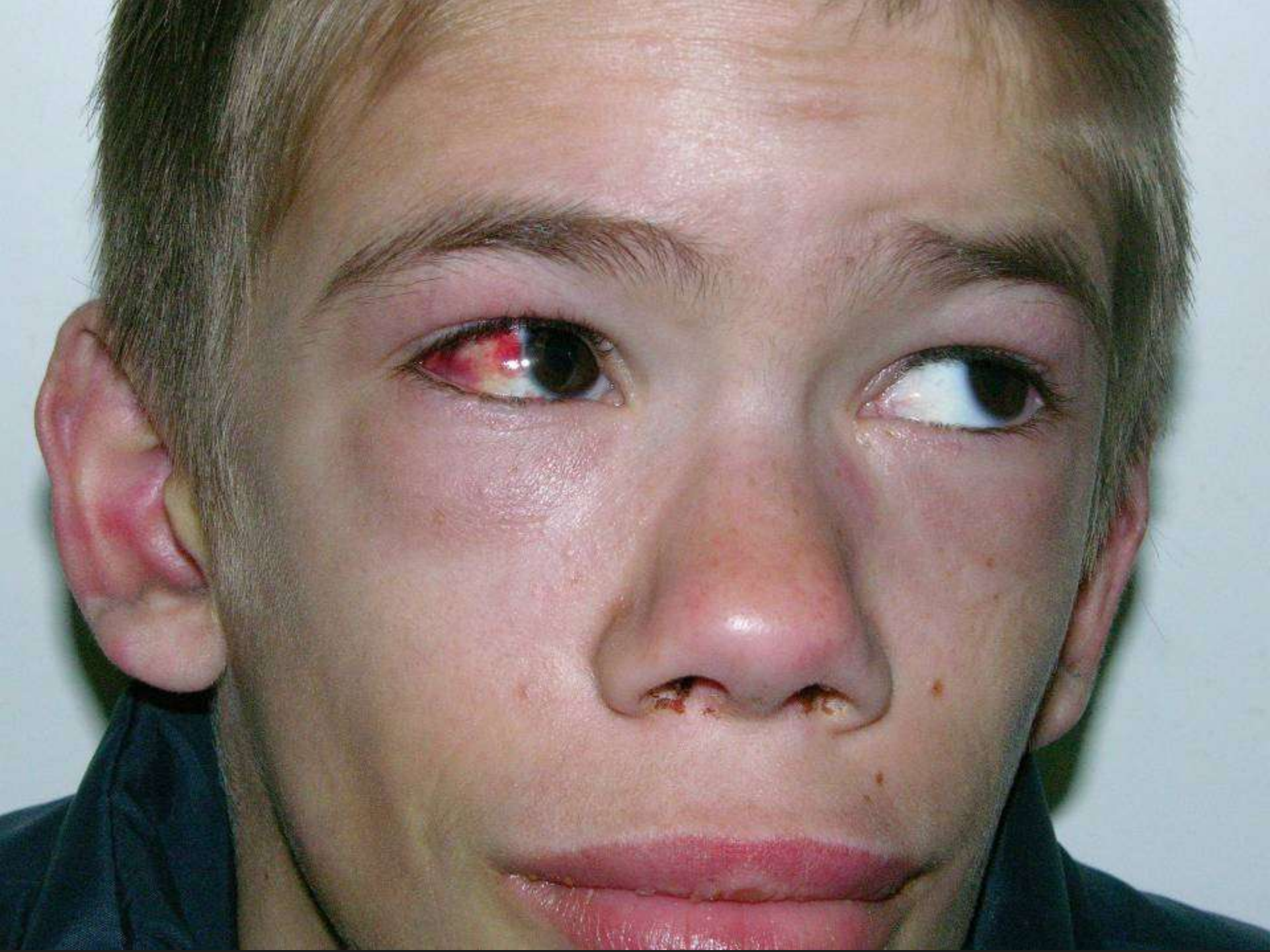

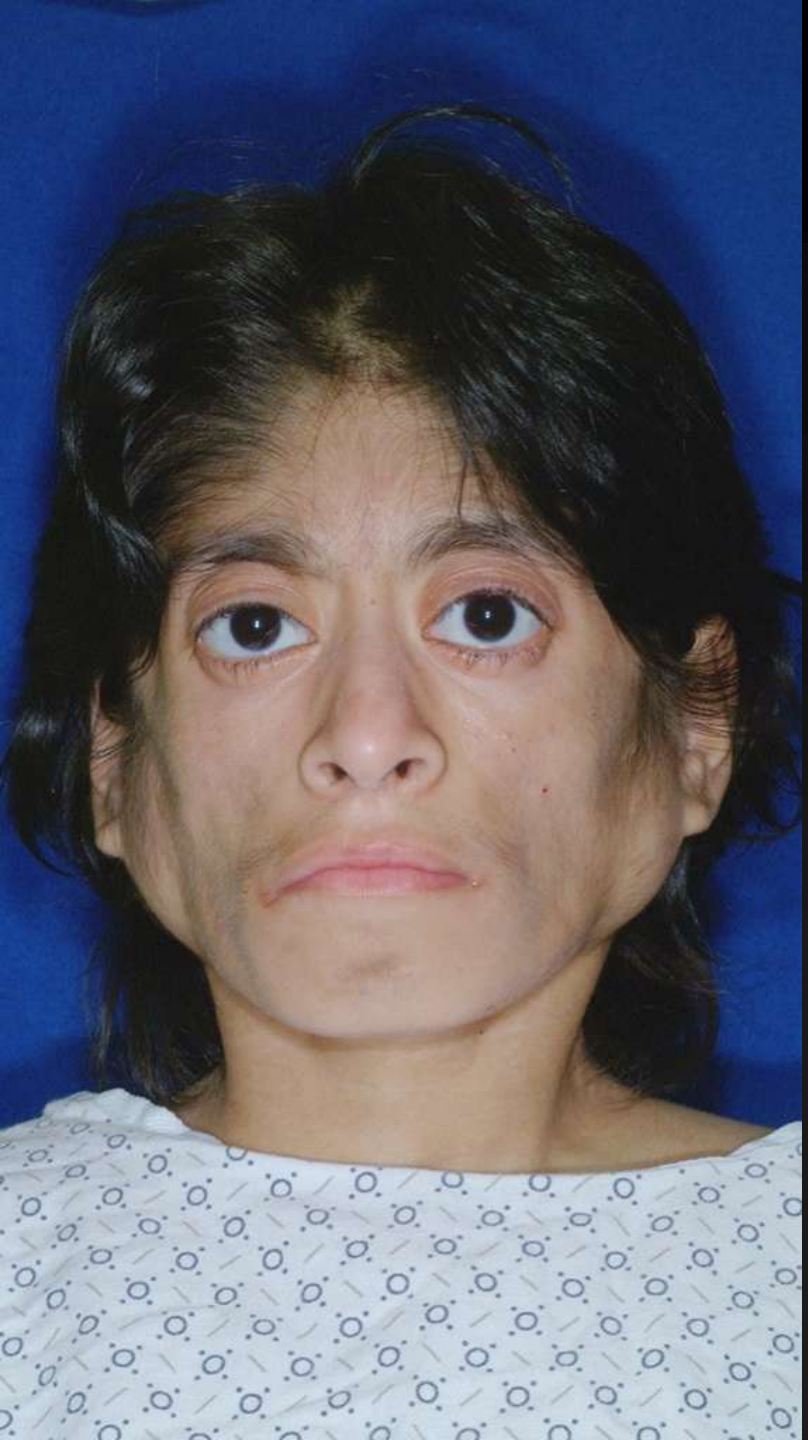

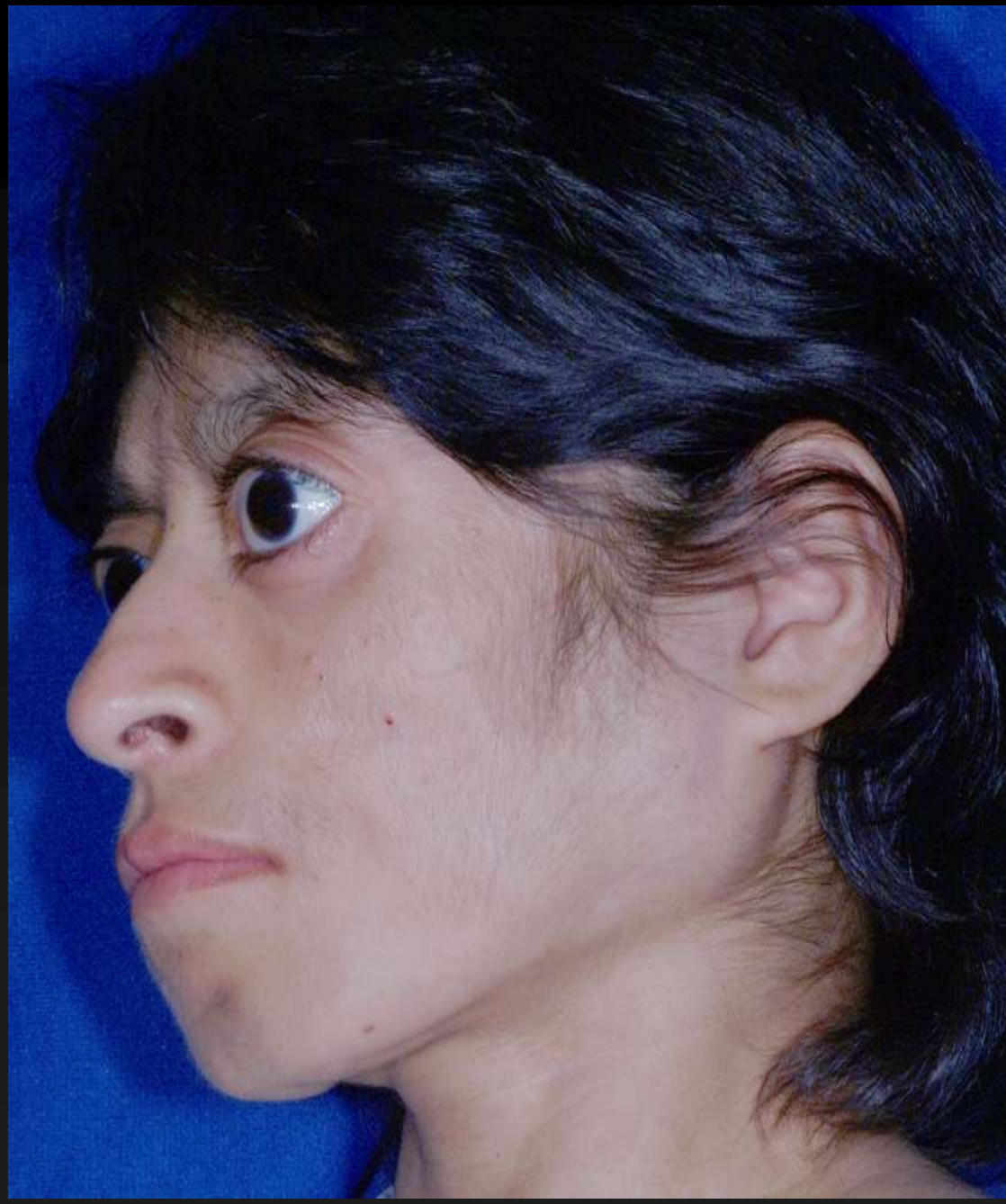

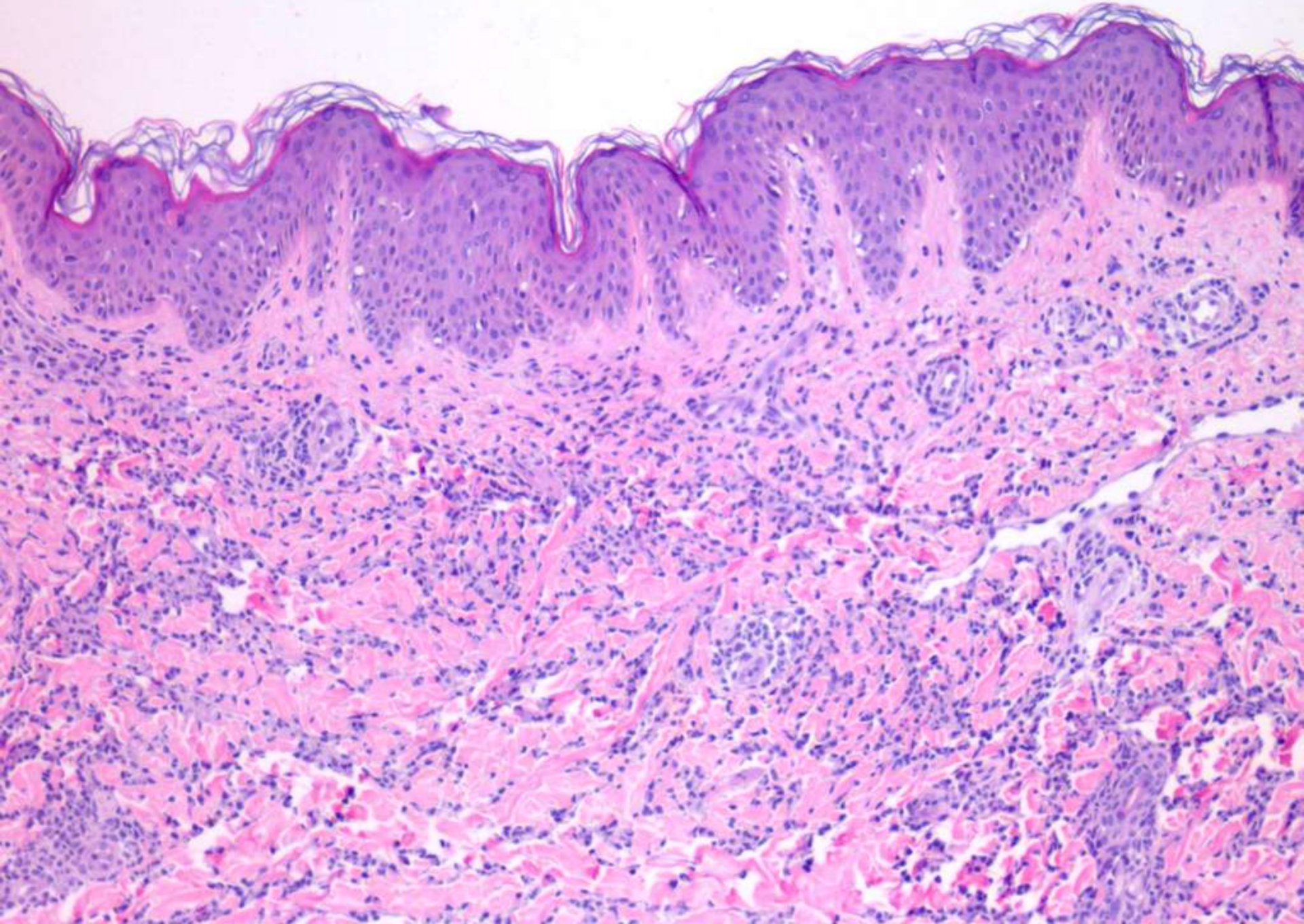

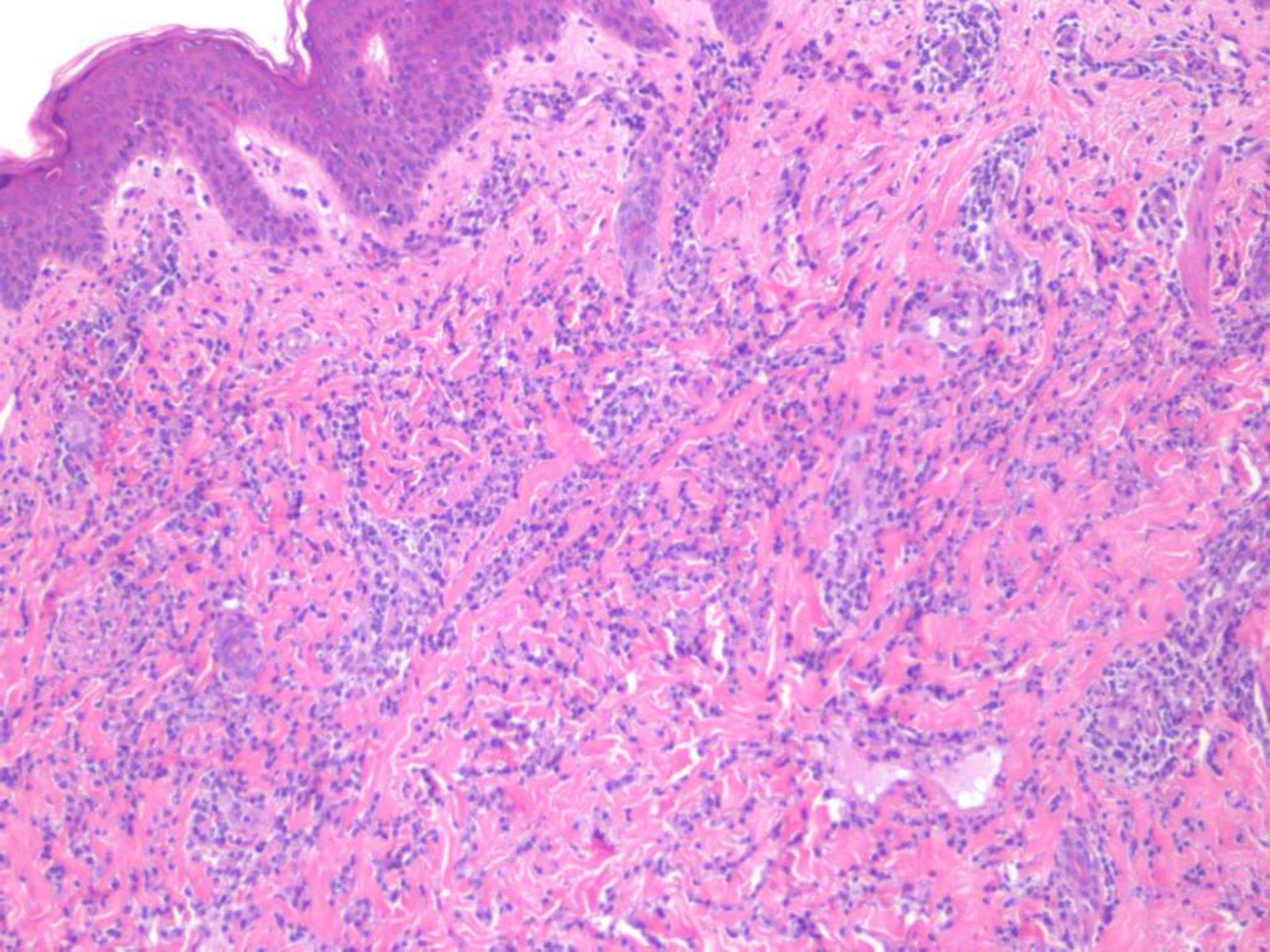

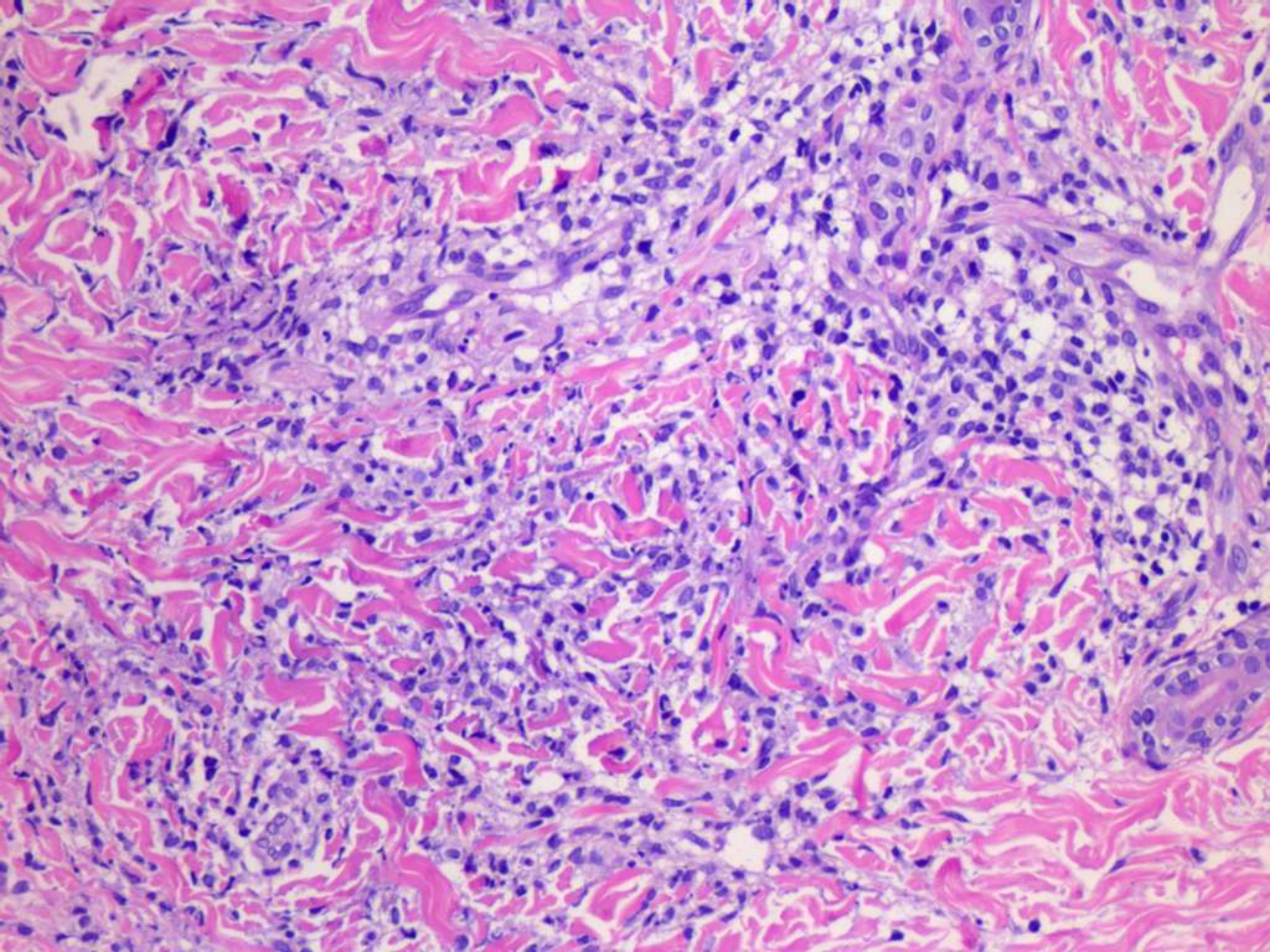

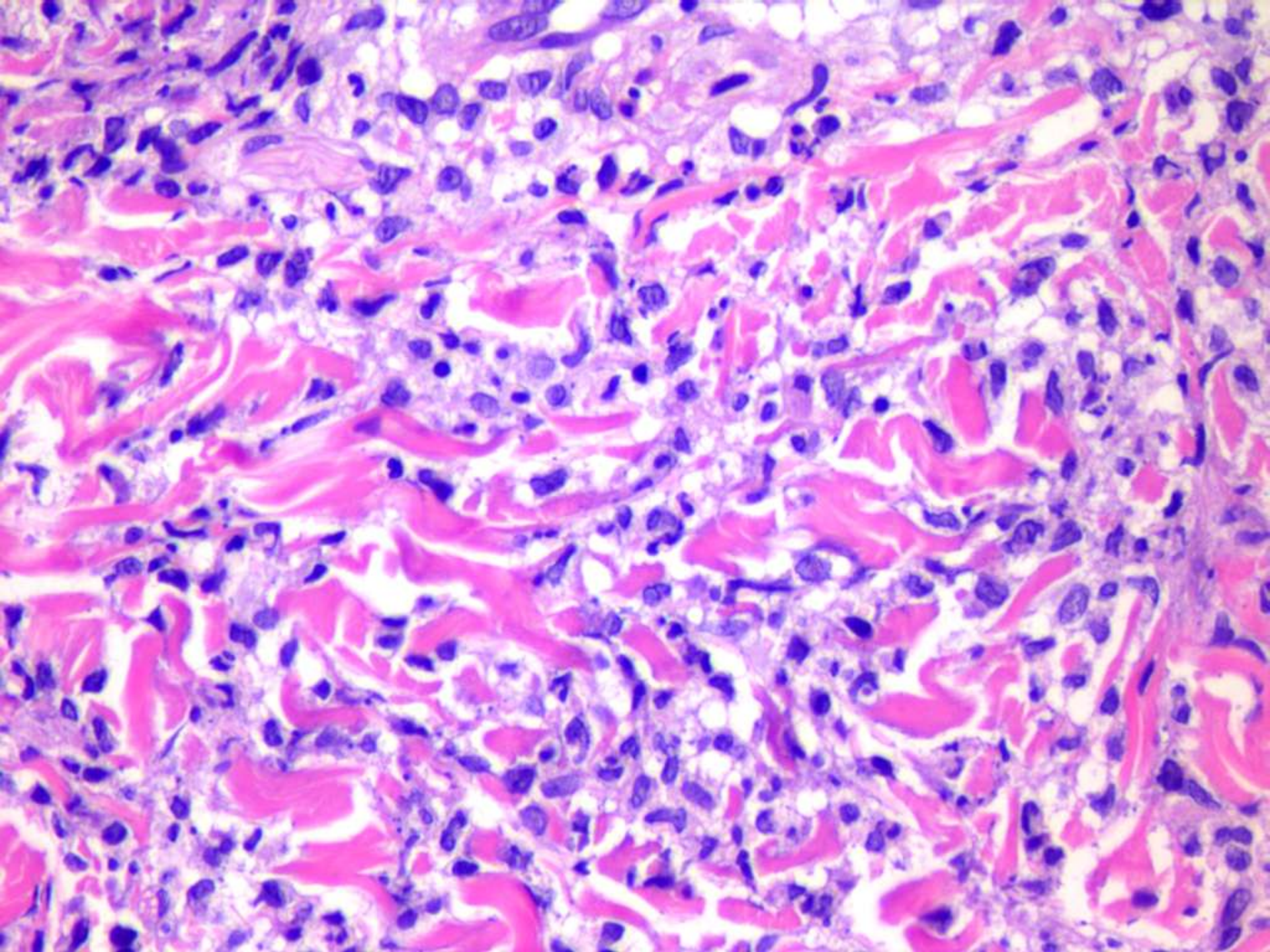

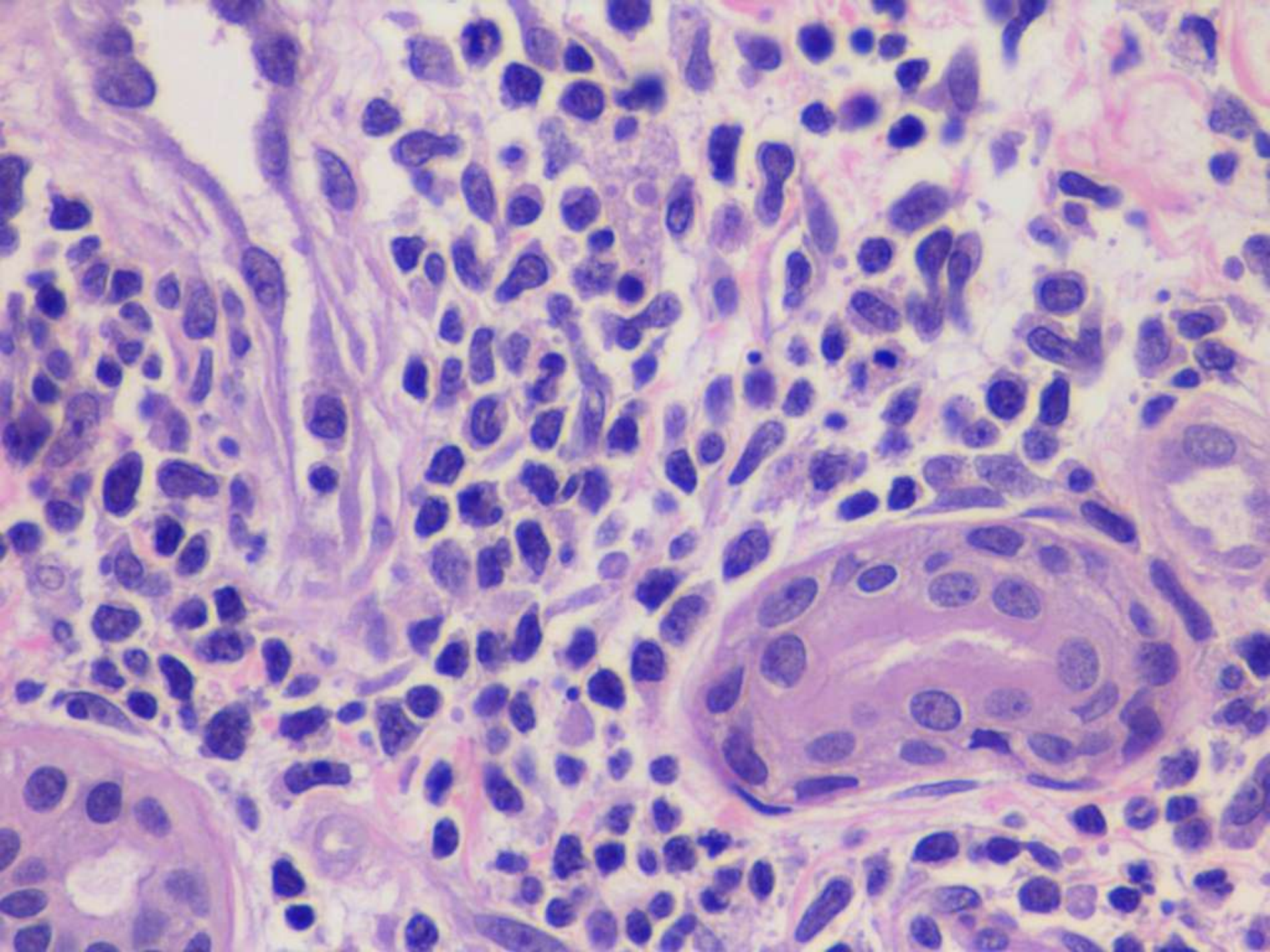

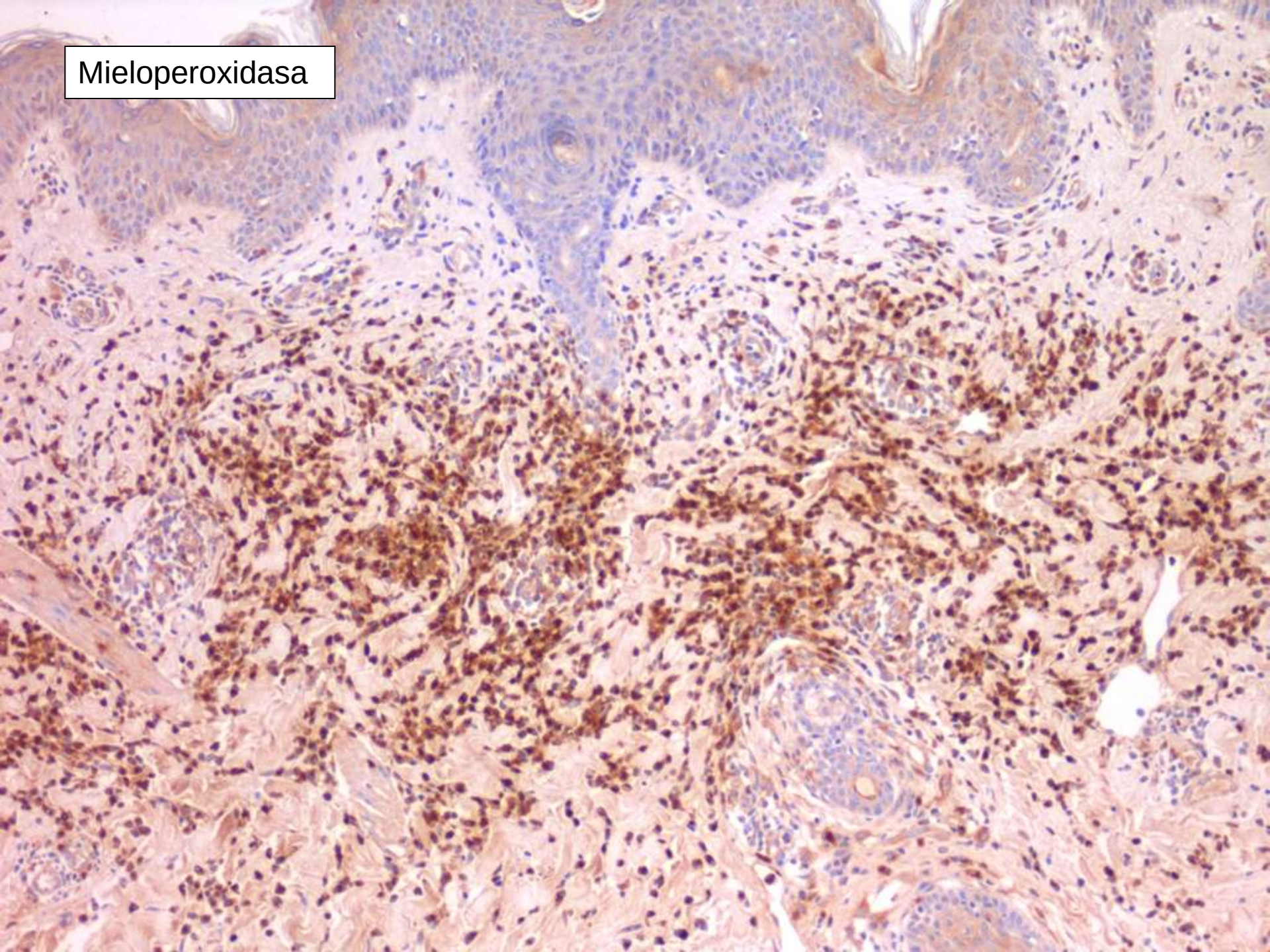
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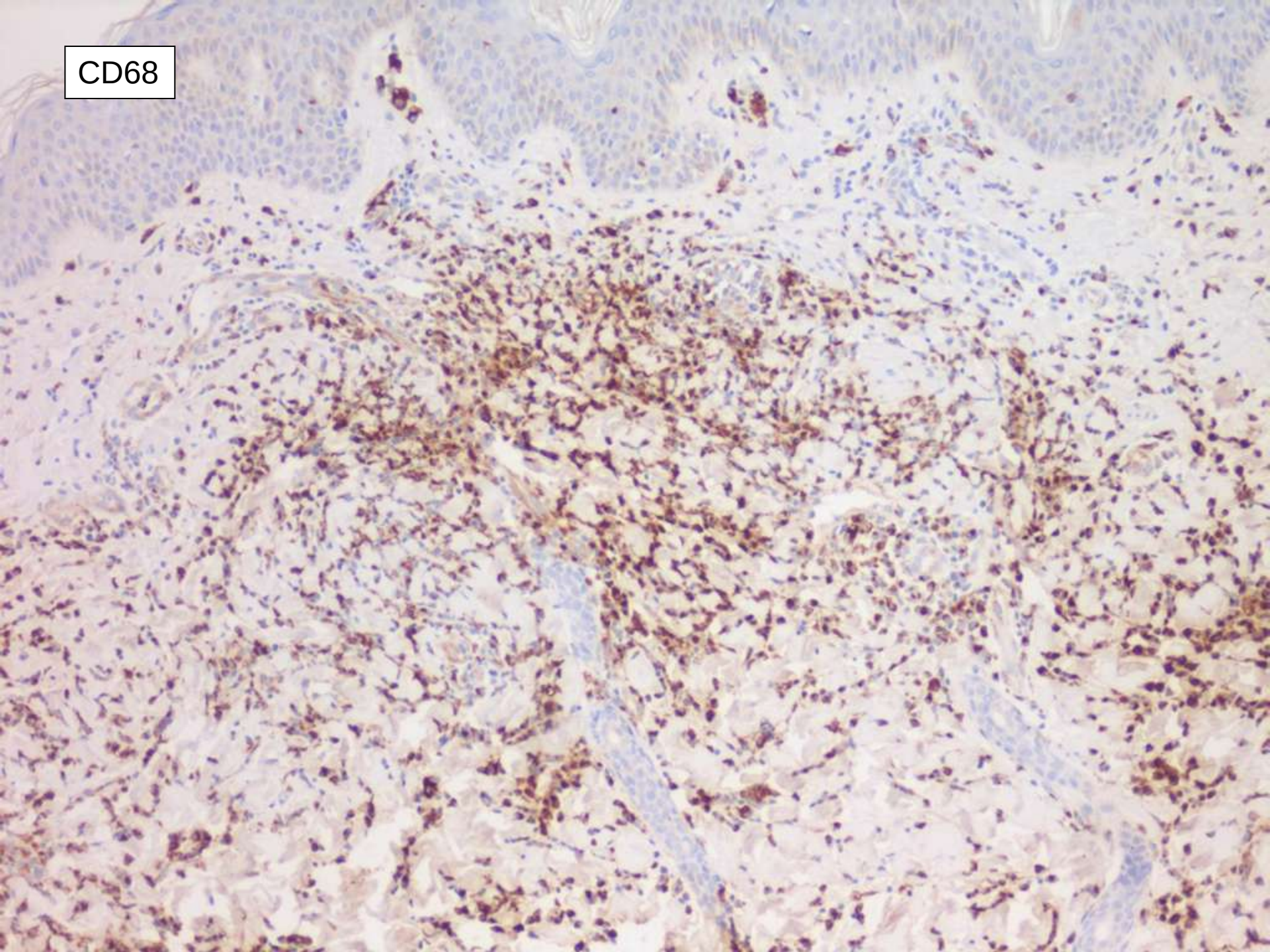
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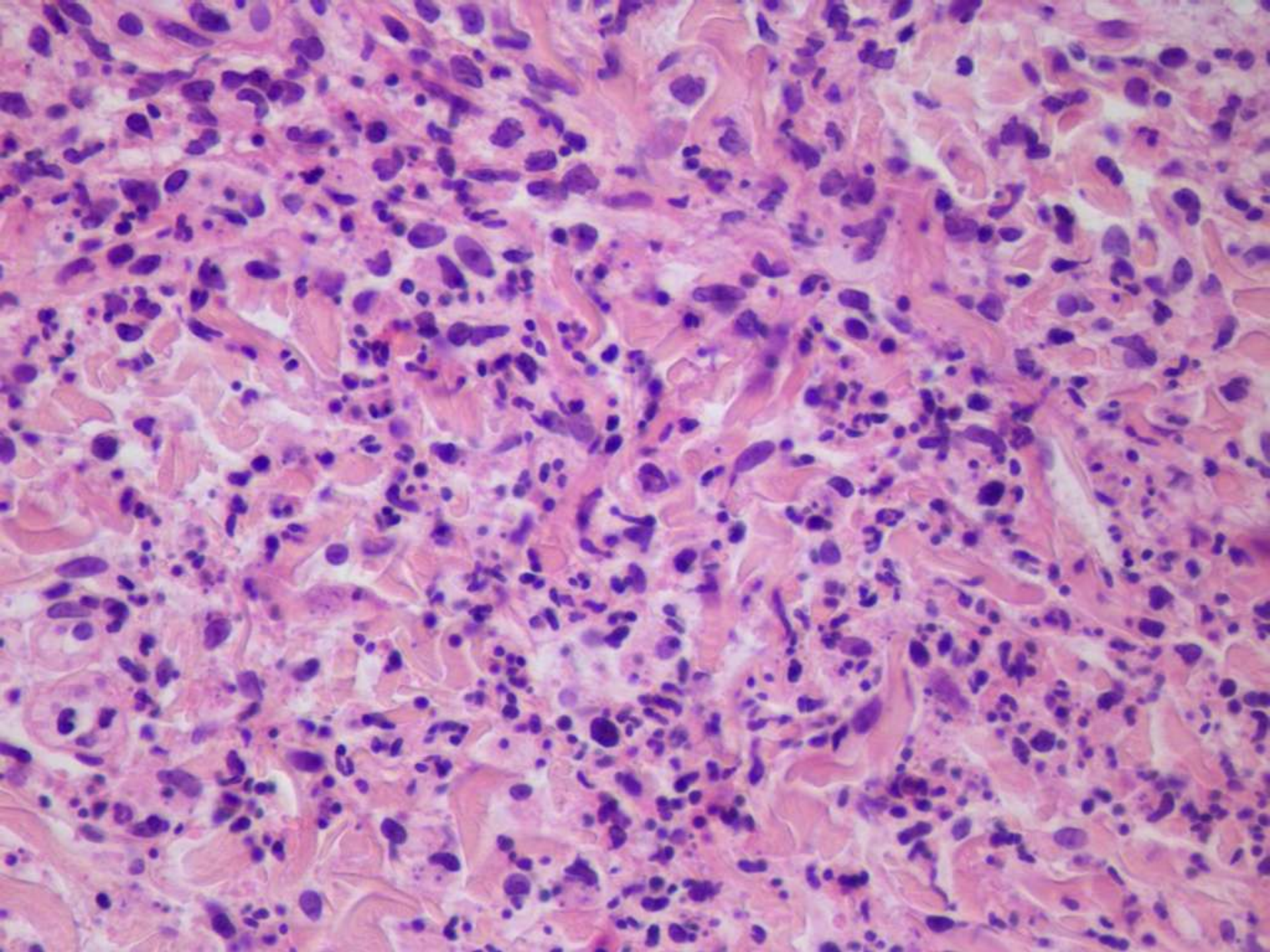
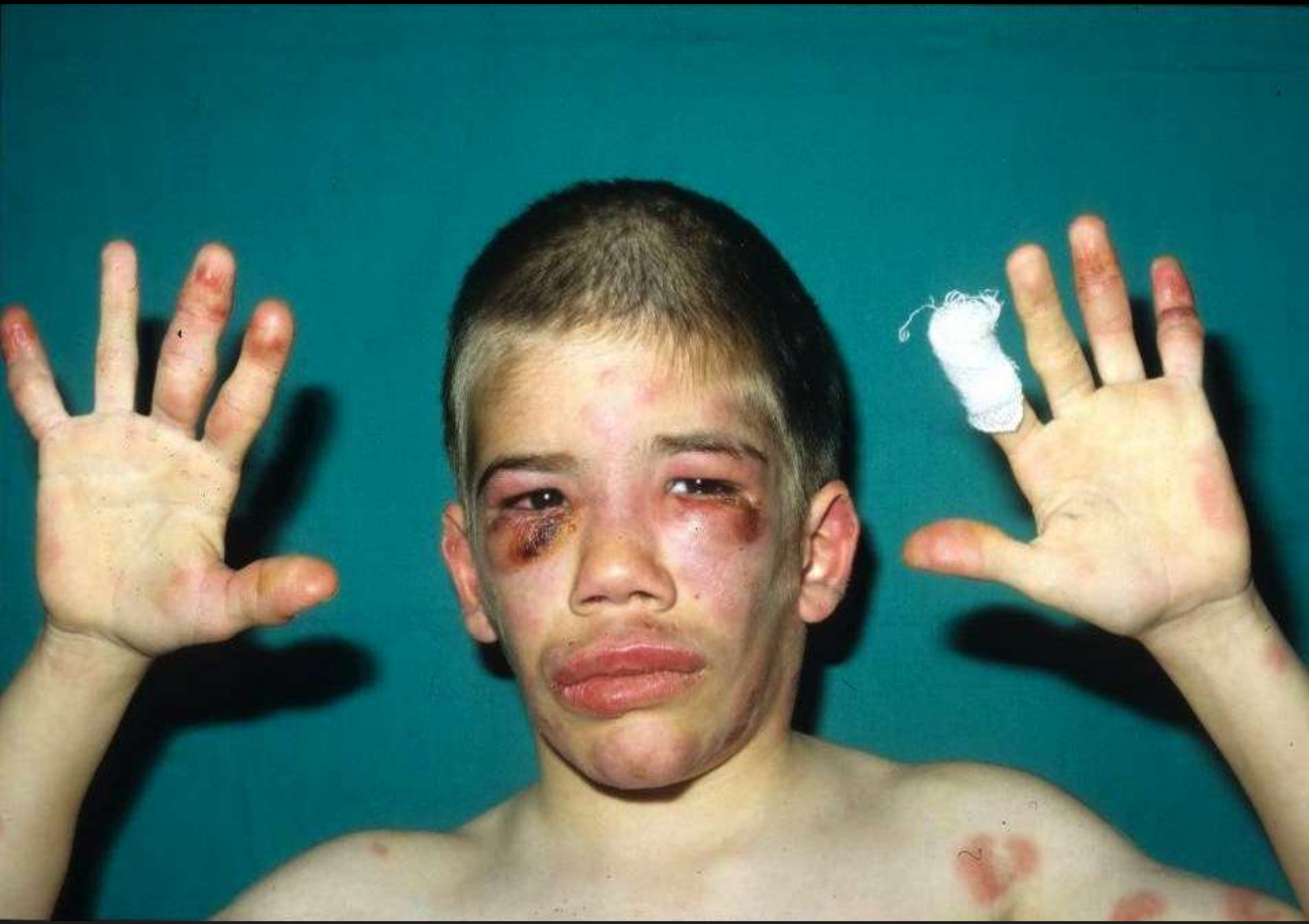
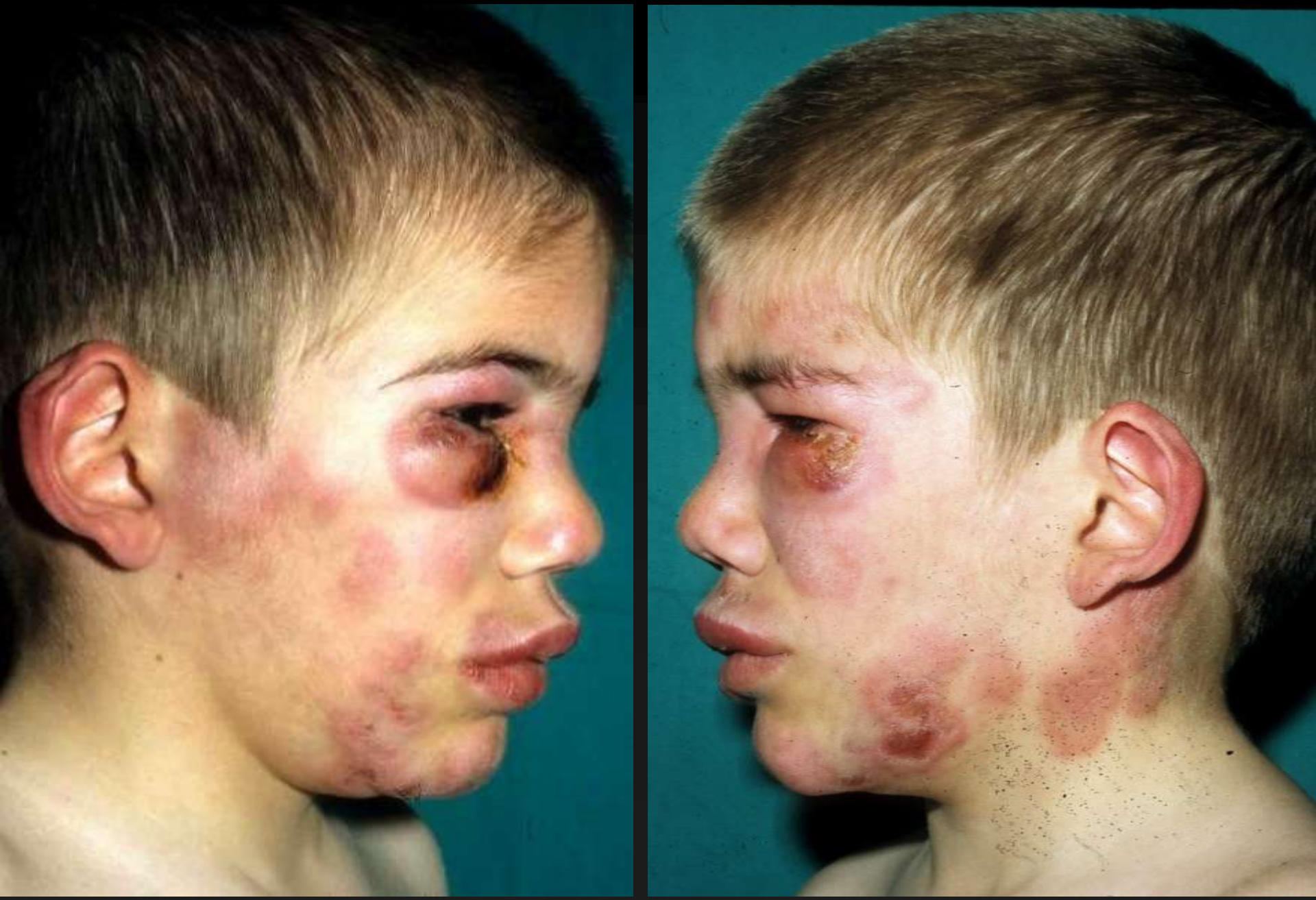


Tratamientos

- AINEs
- Colchicina
- Inmunoglobulina IV
- Corticoides orales
- Dapsona
- Metotrexato
- PUVA
- Azatioprina
- Infliximab
- Ciclosporina
- Anakinra
- Etanercept





Seguimiento del síndrome

- 2 casos previamente sin diagnóstico
- 1 nuevo caso publicado
- 3 nuevos casos aún sin publicar
- 2 entidades relacionadas

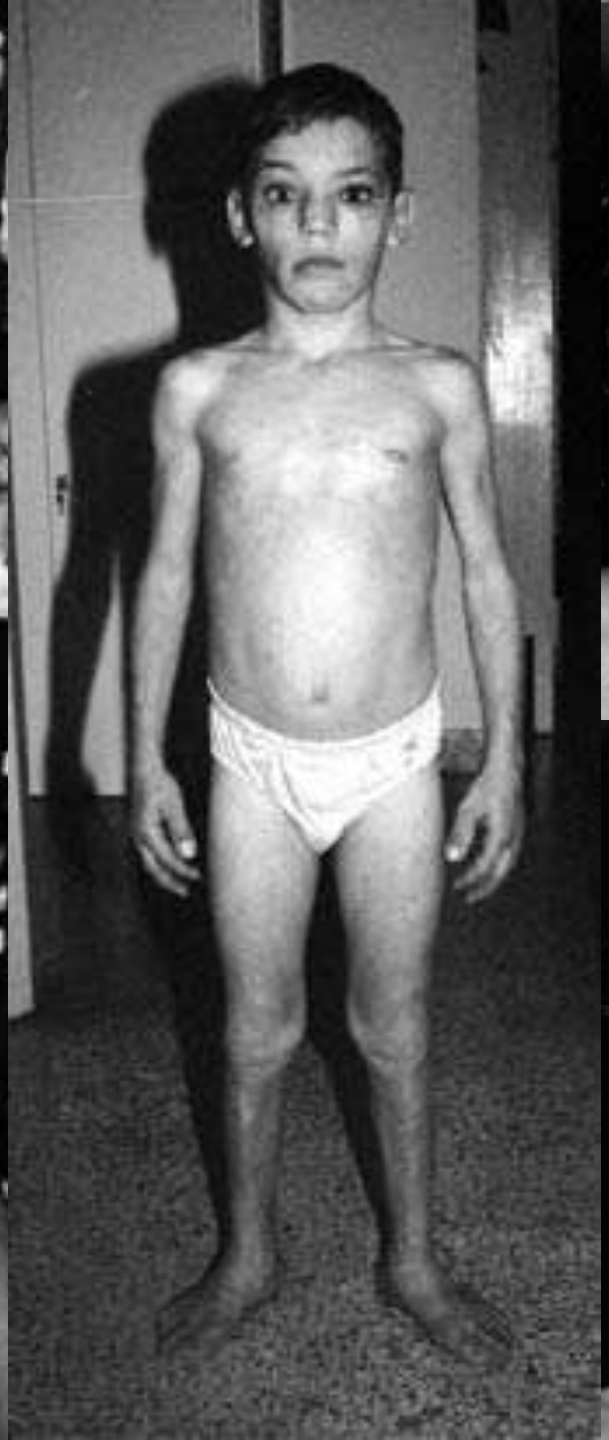
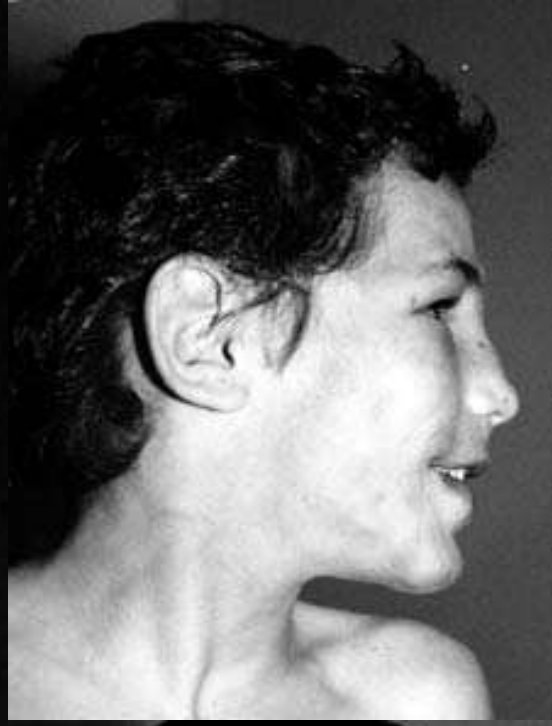
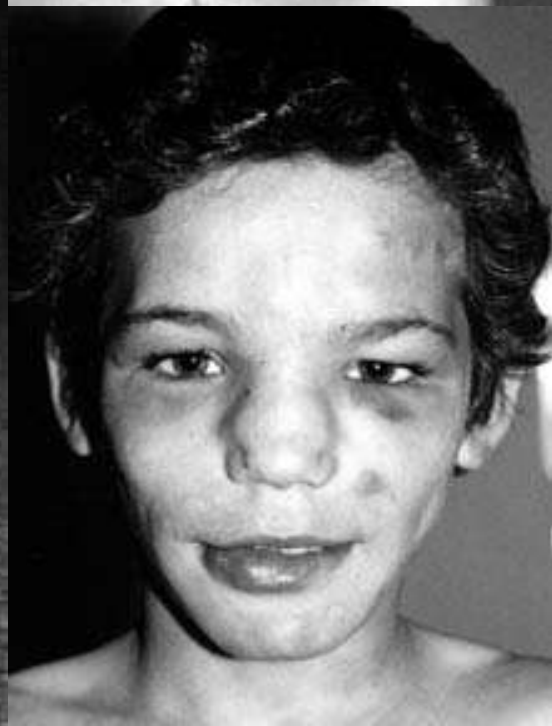
Case Report

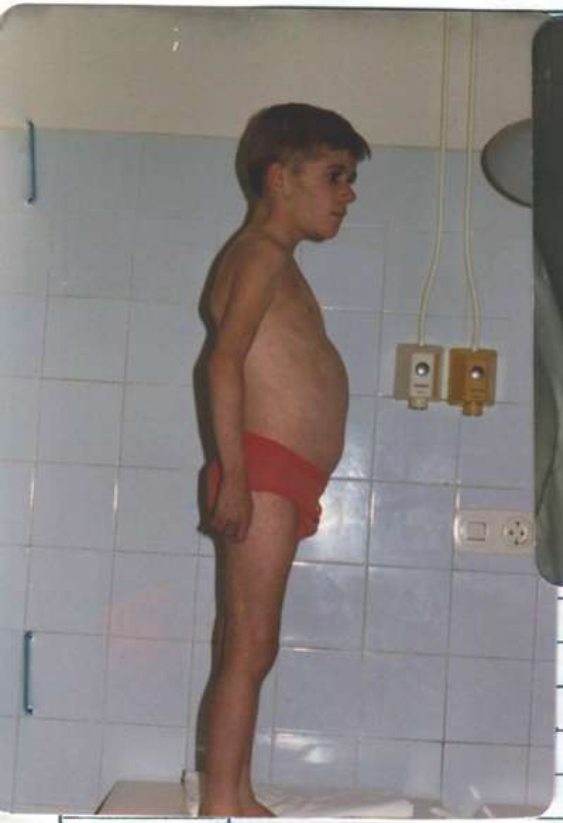
An Unknown Autoinflammatory Syndrome Associated with Short Stature and Dysmorphic Features in a Young Boy

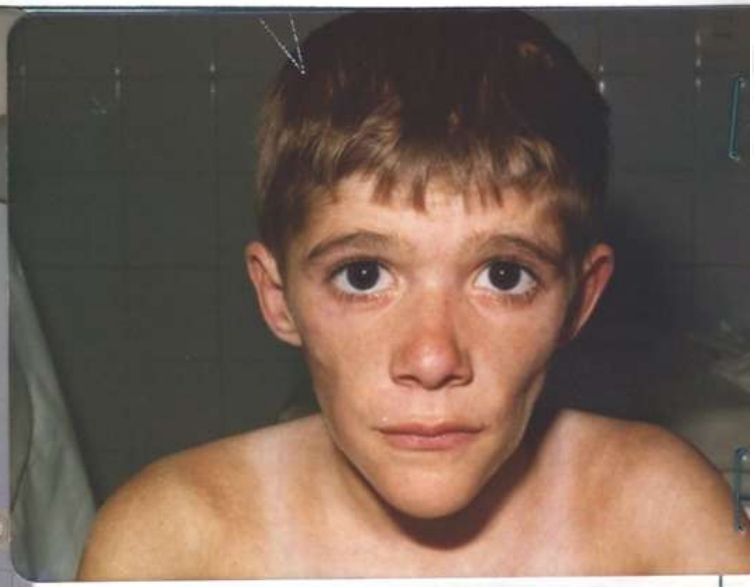
ANDRÉ MÉGARBANÉ, AGNÈS SANDERS, ELIANE CHOUERY, VALÉRIE DELAGUE, MYRNA MEDLEJ-HASHIM, and PAUL-HENRI TORBEY

ABSTRACT.

A young boy from nonconsanguineous Palestinian parents presented with short stature, motor developmental delay, wide nasal bridge, bilateral periorbital edema, everted lower lip, brachydactyly, large interphalangeal articulations, drumstick extremities of the fingers, bilateral simian crease, clinodactyly of the 5th fingers, painful joints, subcutaneous nodules all over his body and recurrent episodes of fever of unknown origin. Differential diagnoses such as the hyperimmunoglobulinemia D syndrome, tumor necrosis factor receptor associated periodic syndrome (TRAPS), the chronic infantile neurological cutaneous and articular (CINCA) syndrome, and the newly recognized nodulosis, arthropathy, and osteolysis (NAO) syndrome are discussed. This syndrome may not have been previously reported. (J Rheumatol 2002;29:1084-7)





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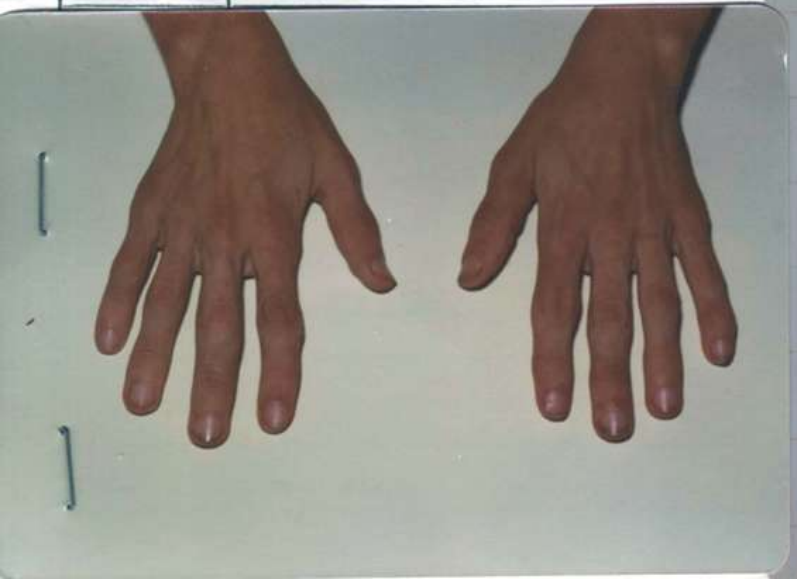
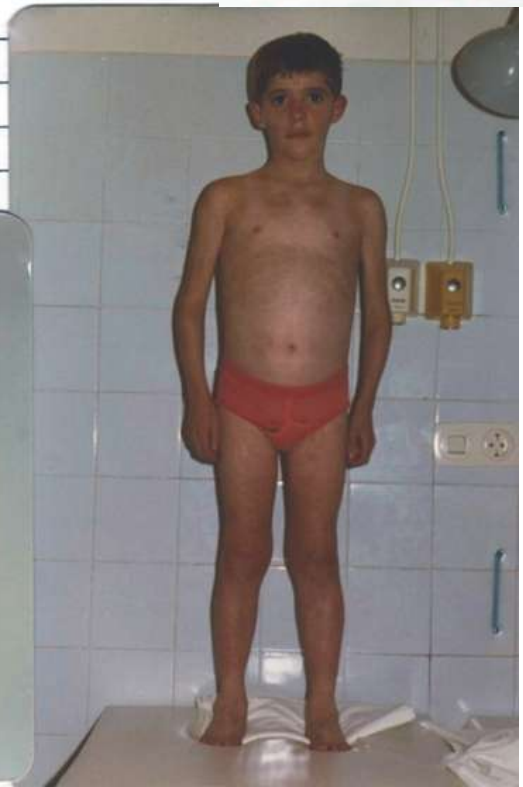
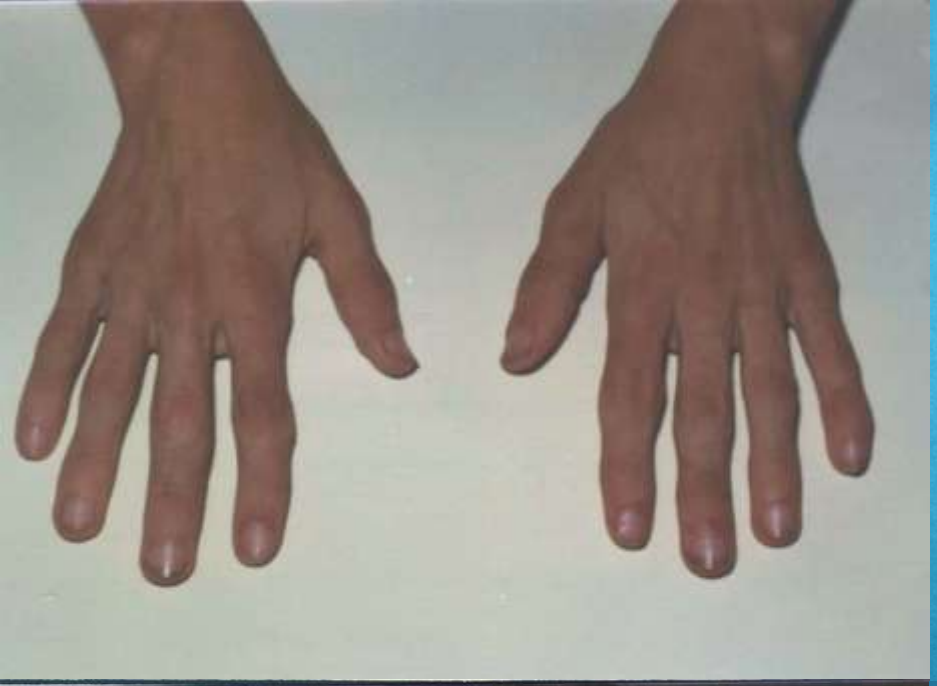
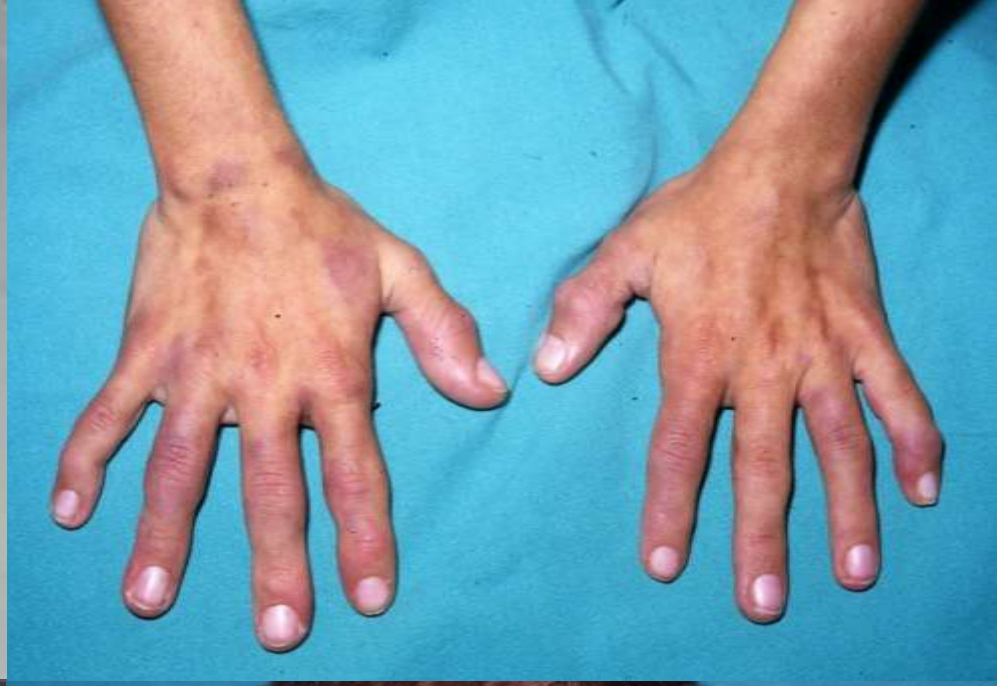
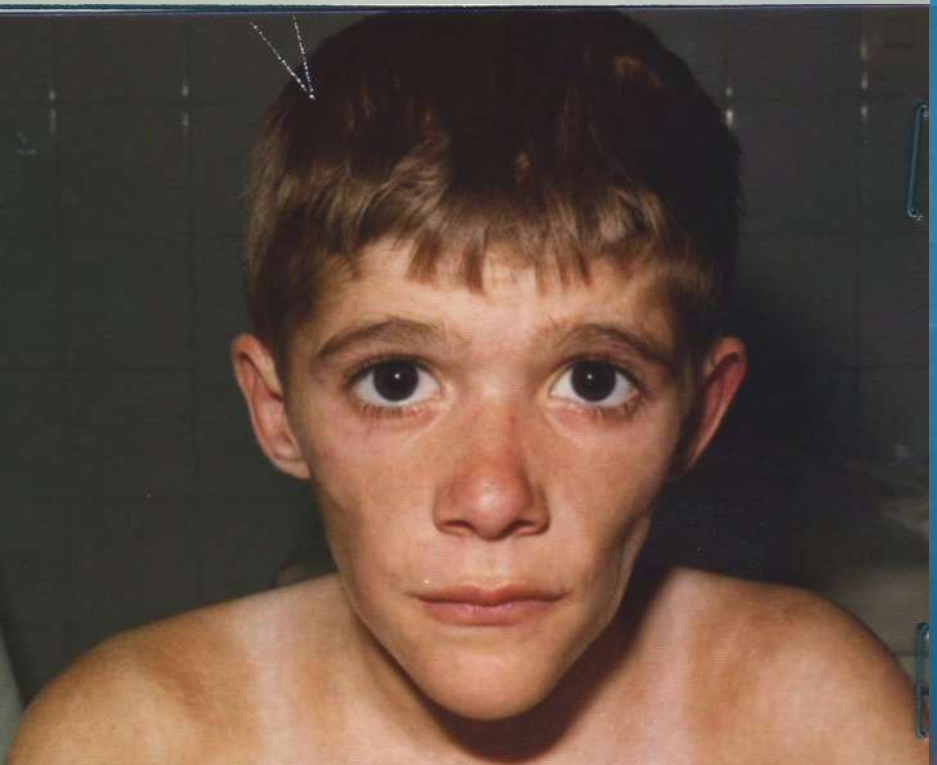
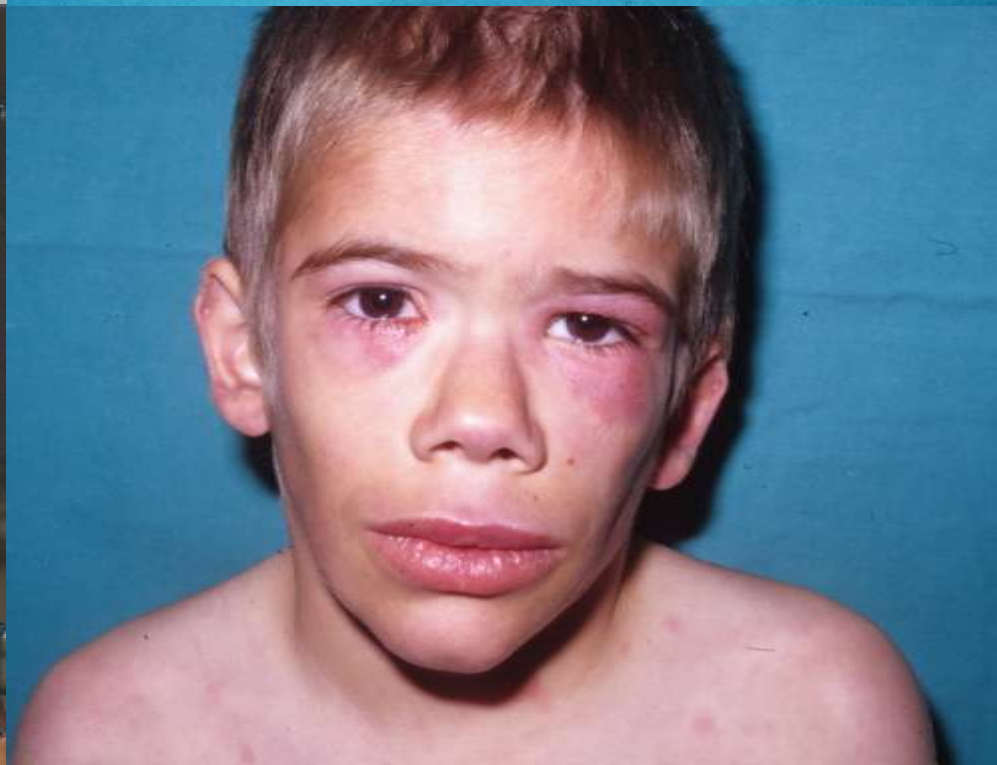
OBSERVACIONES ACERCA DEL CURSO CLINICO





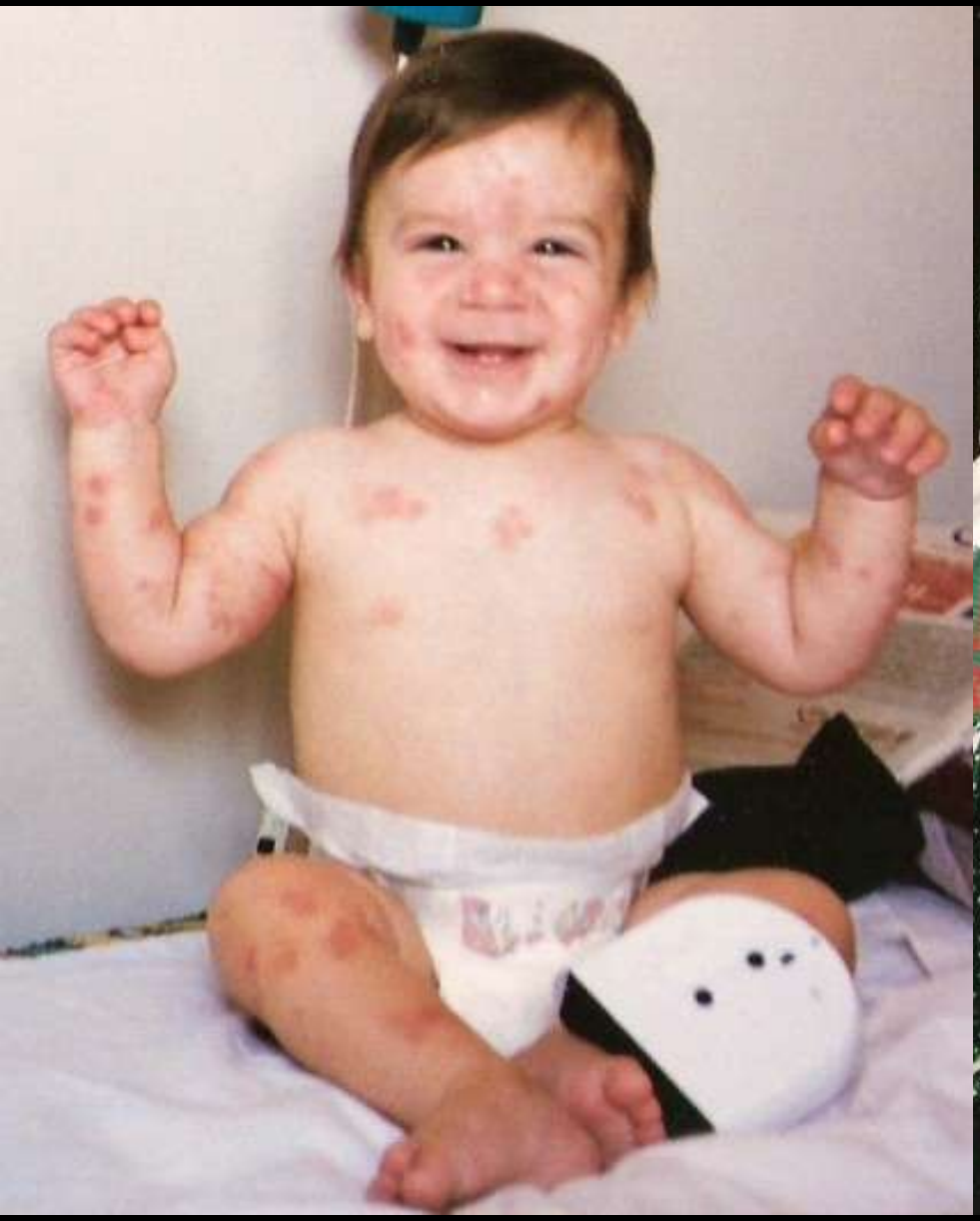
Pediatric Dermatology 1–4, 2010

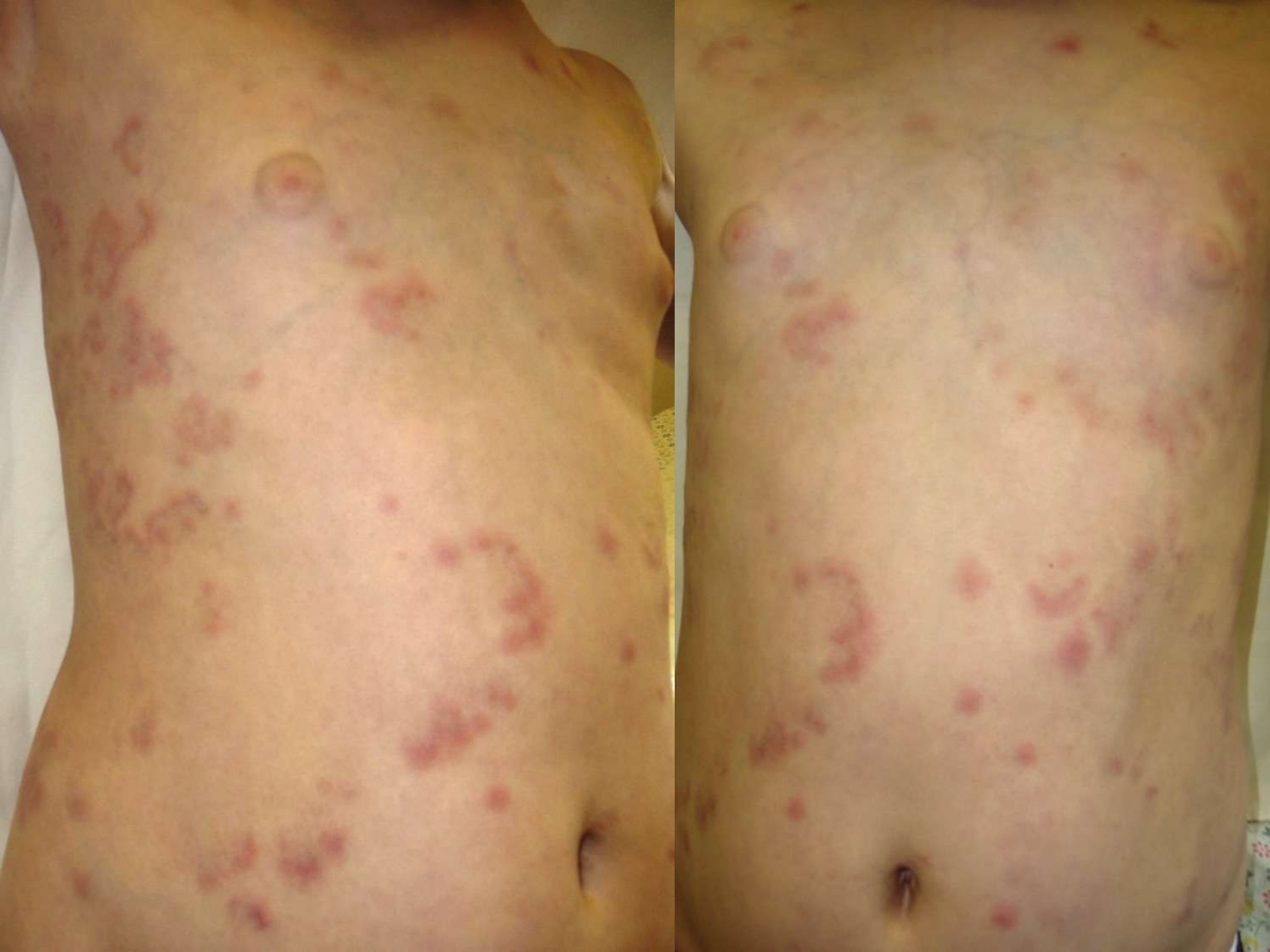
Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature Syndrome: A Case Report

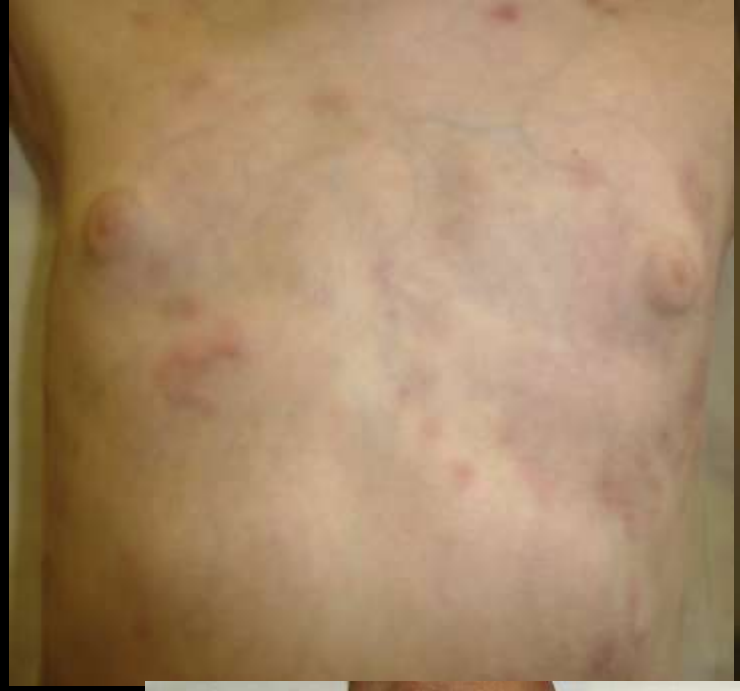
Yuval Ramot, M.Sc., M.D.,*,‡ Tali Czarnowicki, M.D.,* Alex Maly, M.D.,† Paulina Navon-Elkan, M.D.,§ and Abraham Zlotogorski, M.D.*,‡

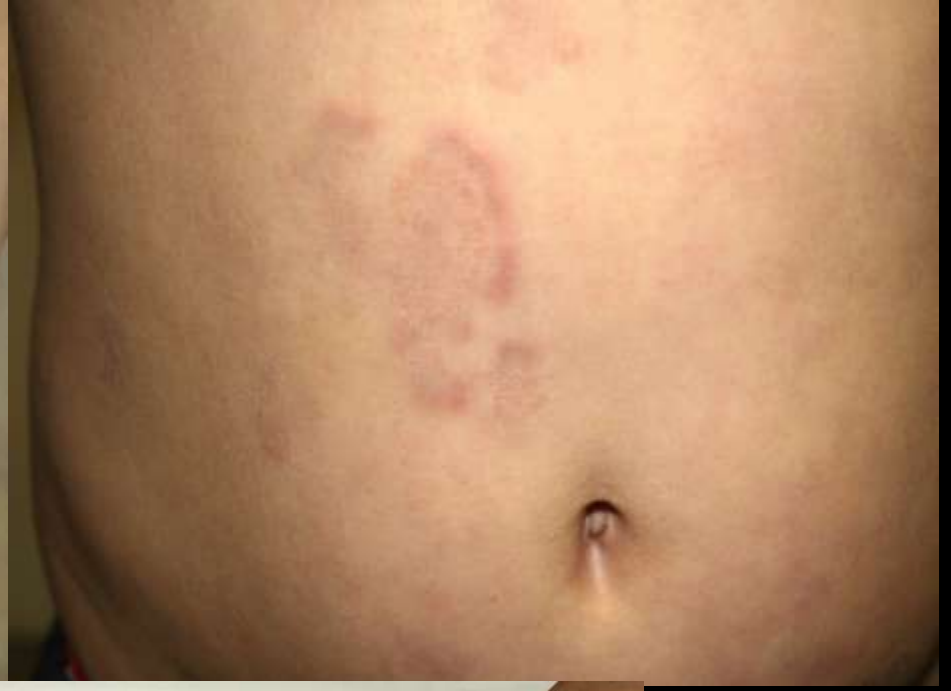
*Departments of *Dermatology and †Pathology, ‡The Center for Genetic Diseases of the Skin and Hair, Hadassah-Hebrew University Medical Center, Jerusalem, §Department of Pediatrics, Shaare-Zedek Medical Center, Jerusalem, Israel*

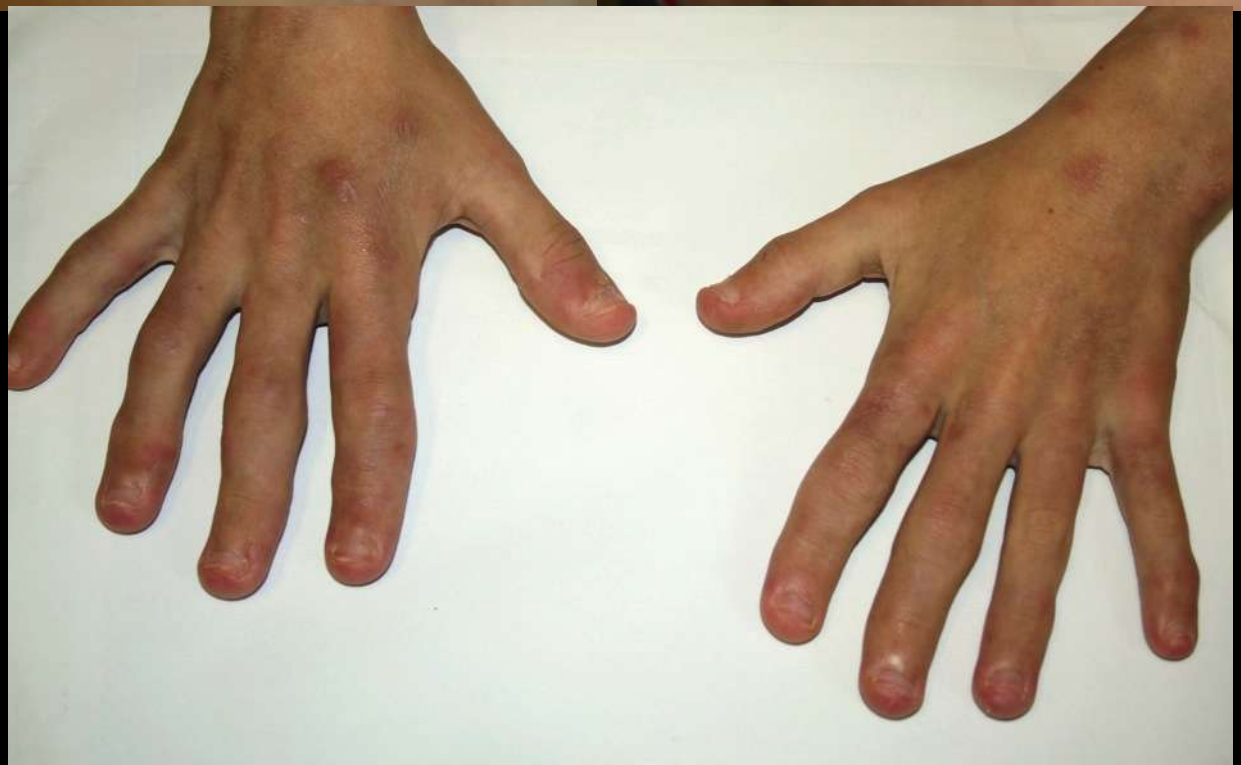
Abstract: **Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome is a recently described chronic inflammatory syndrome consisting of widespread annular violaceous skin lesions and multisystemic inflammatory manifestations. We report a 12½-year-old boy with a young-age onset of recurrent fevers, annular violaceous plaques, alopecia areata, lipodystrophy, low weight and height, deformed fingers, wide-spaced nipples, chronic anemia, and elevated acute phase reactants. An abdominal punch biopsy demonstrated dense perivascular and interstitial infiltrates in the dermis, composed mainly of mononuclear cells. This syndrome may represent a new autosomal recessive auto-inflammatory genodermatosis. Increased awareness may lead to the discovery of more cases, and clarify its pathogenesis.**

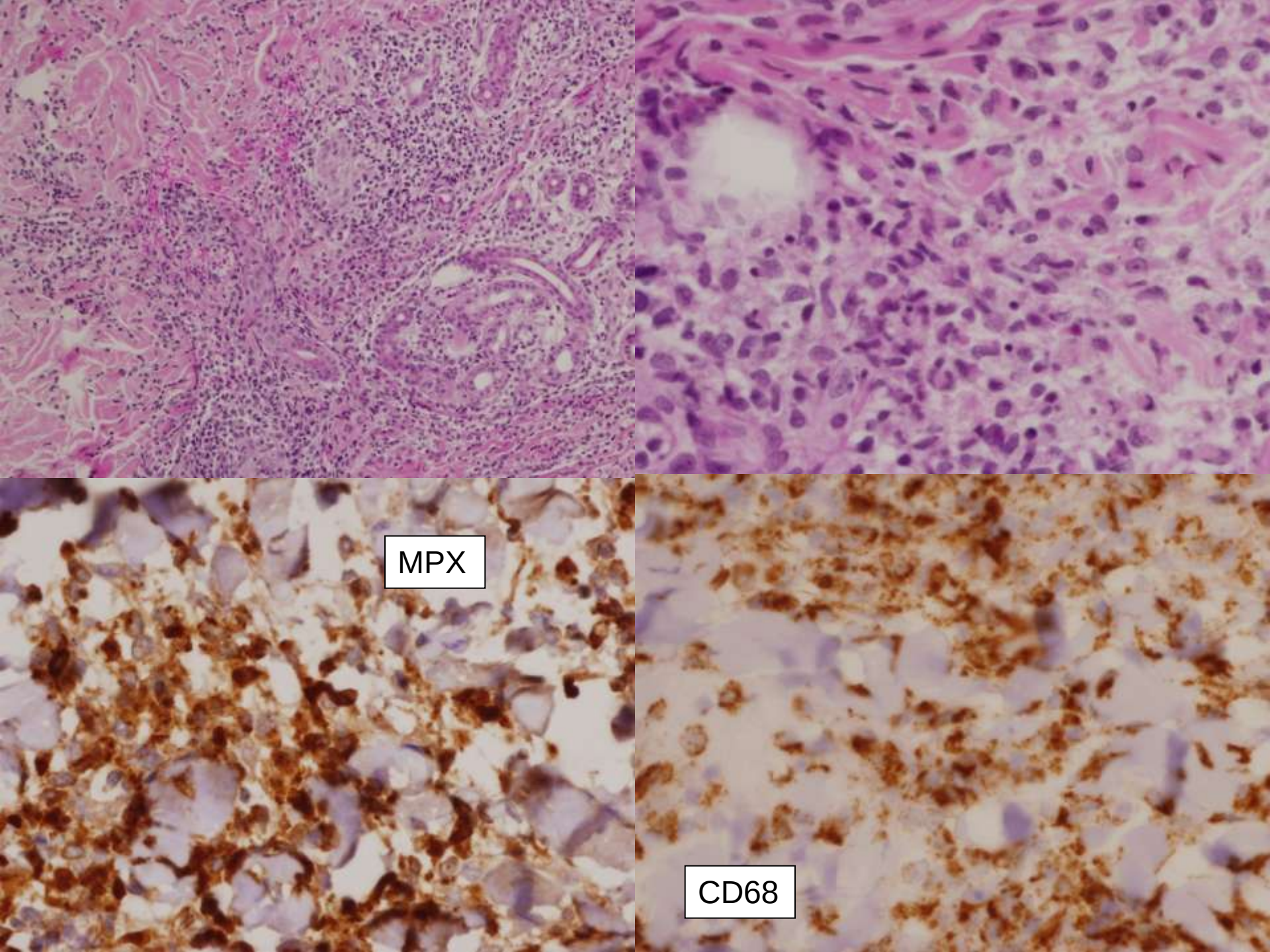








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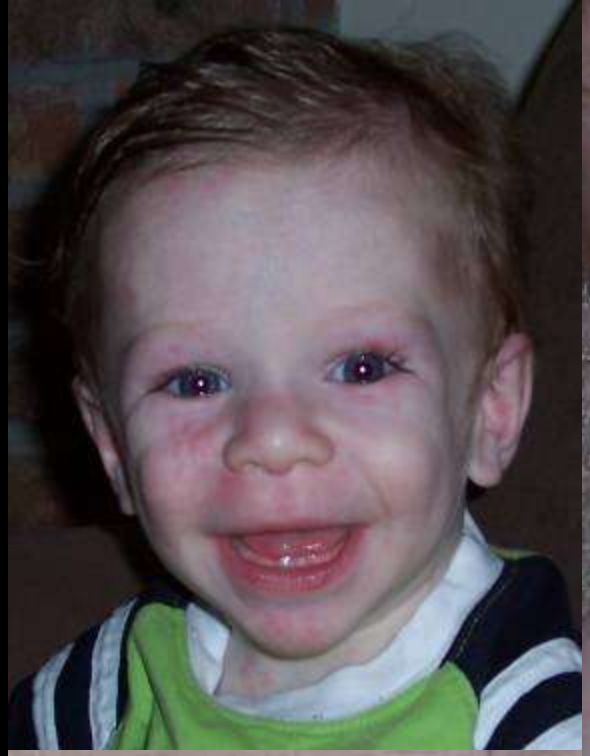

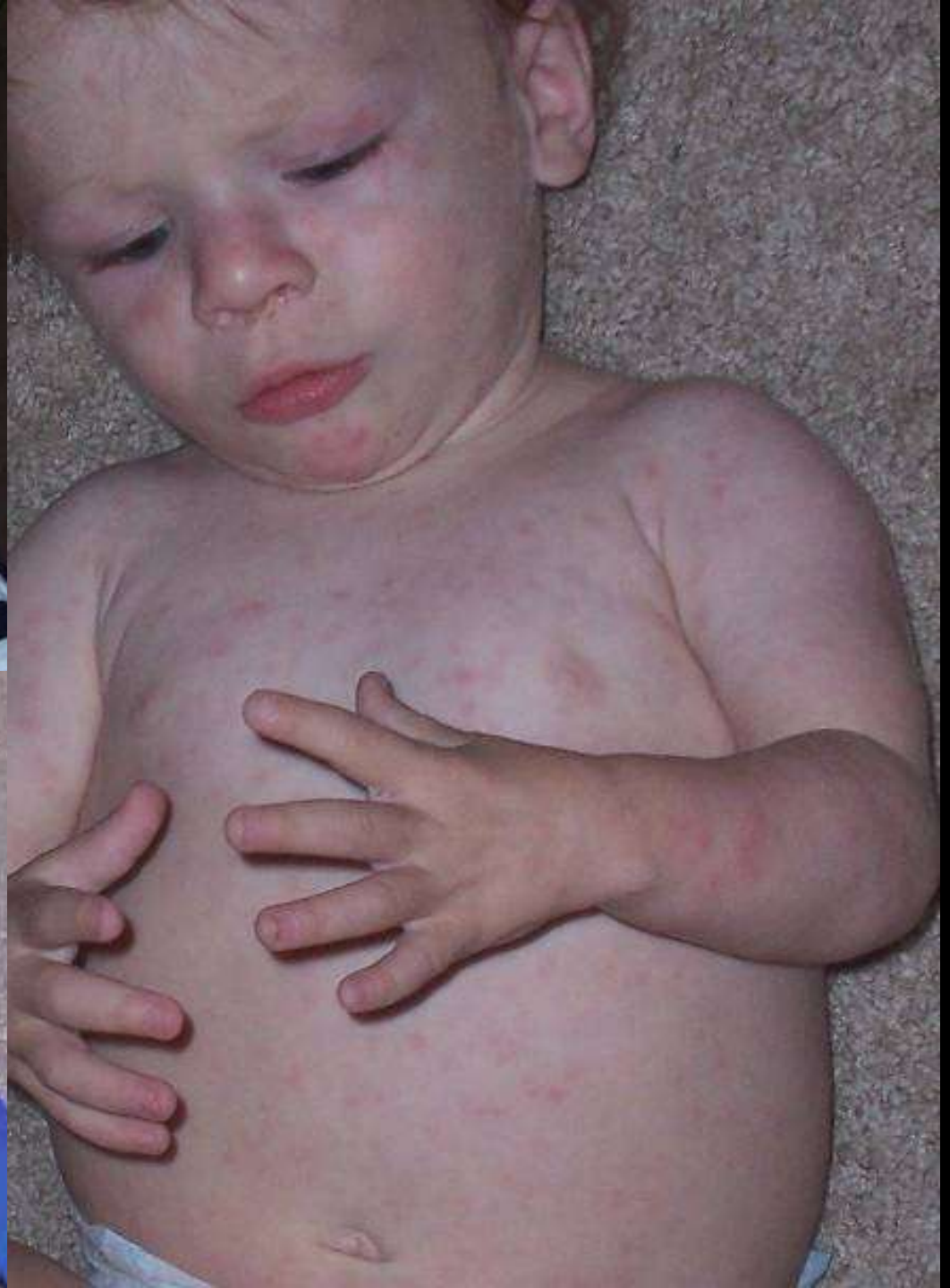

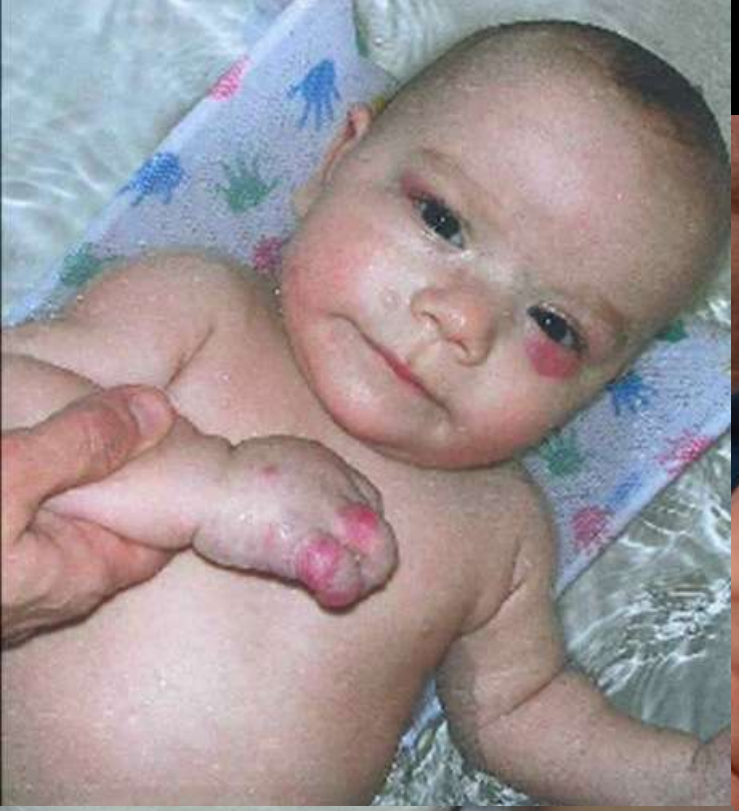

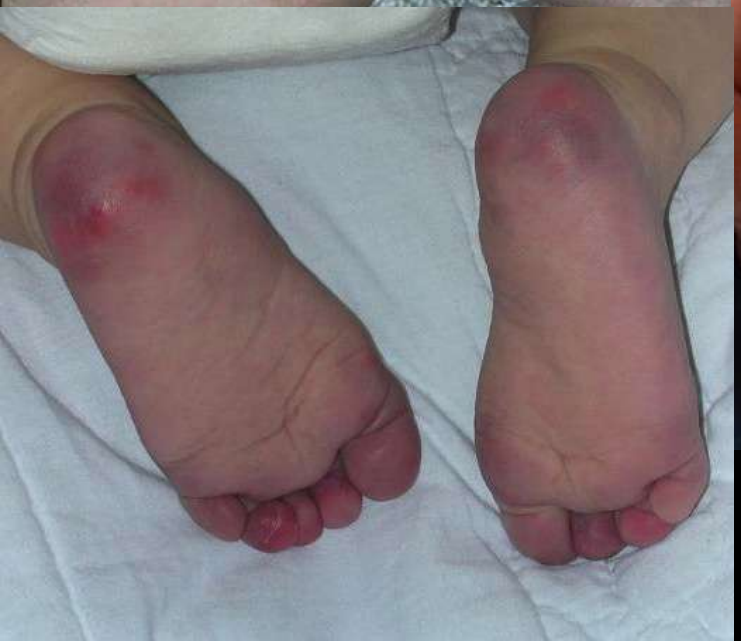

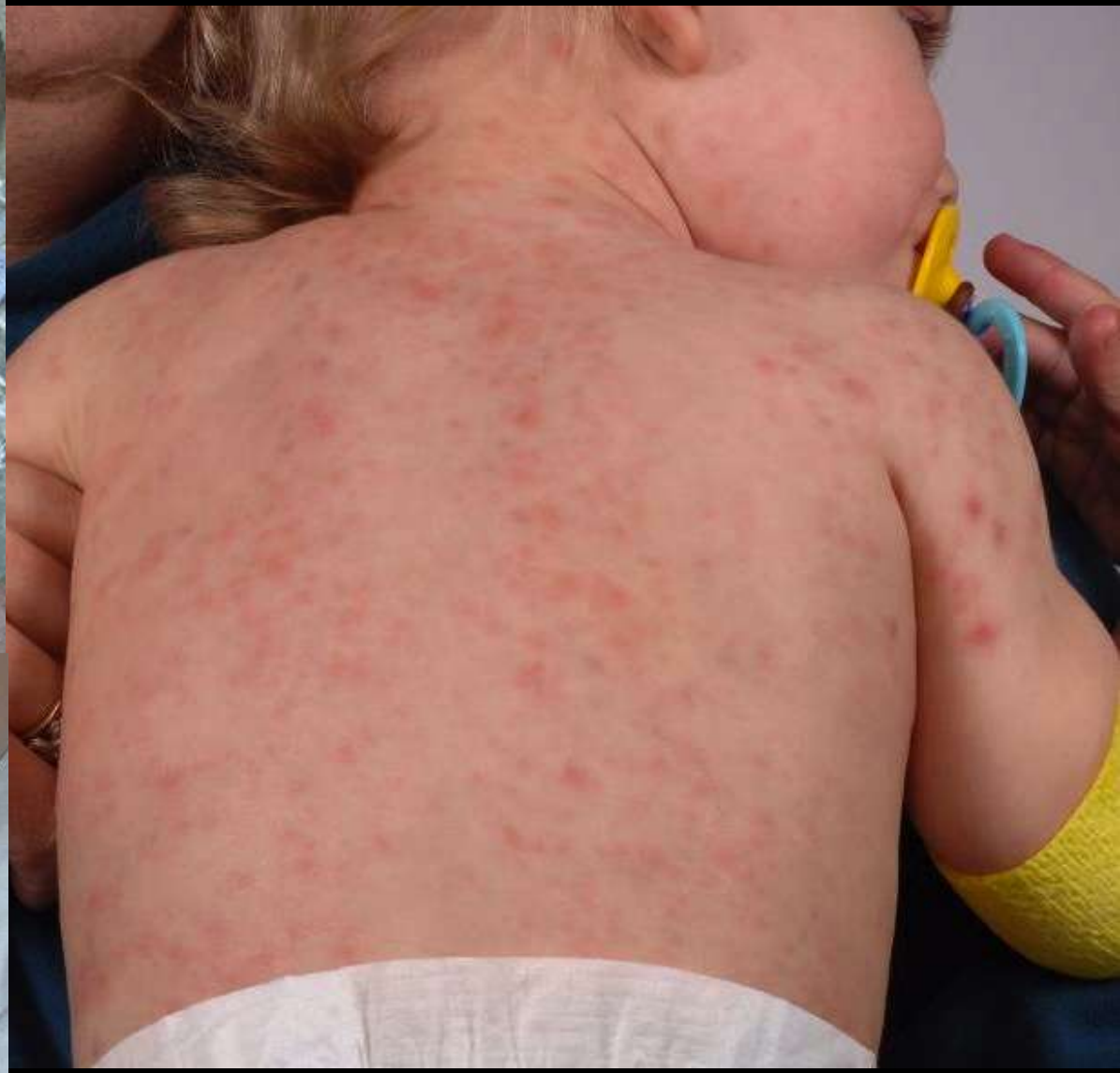

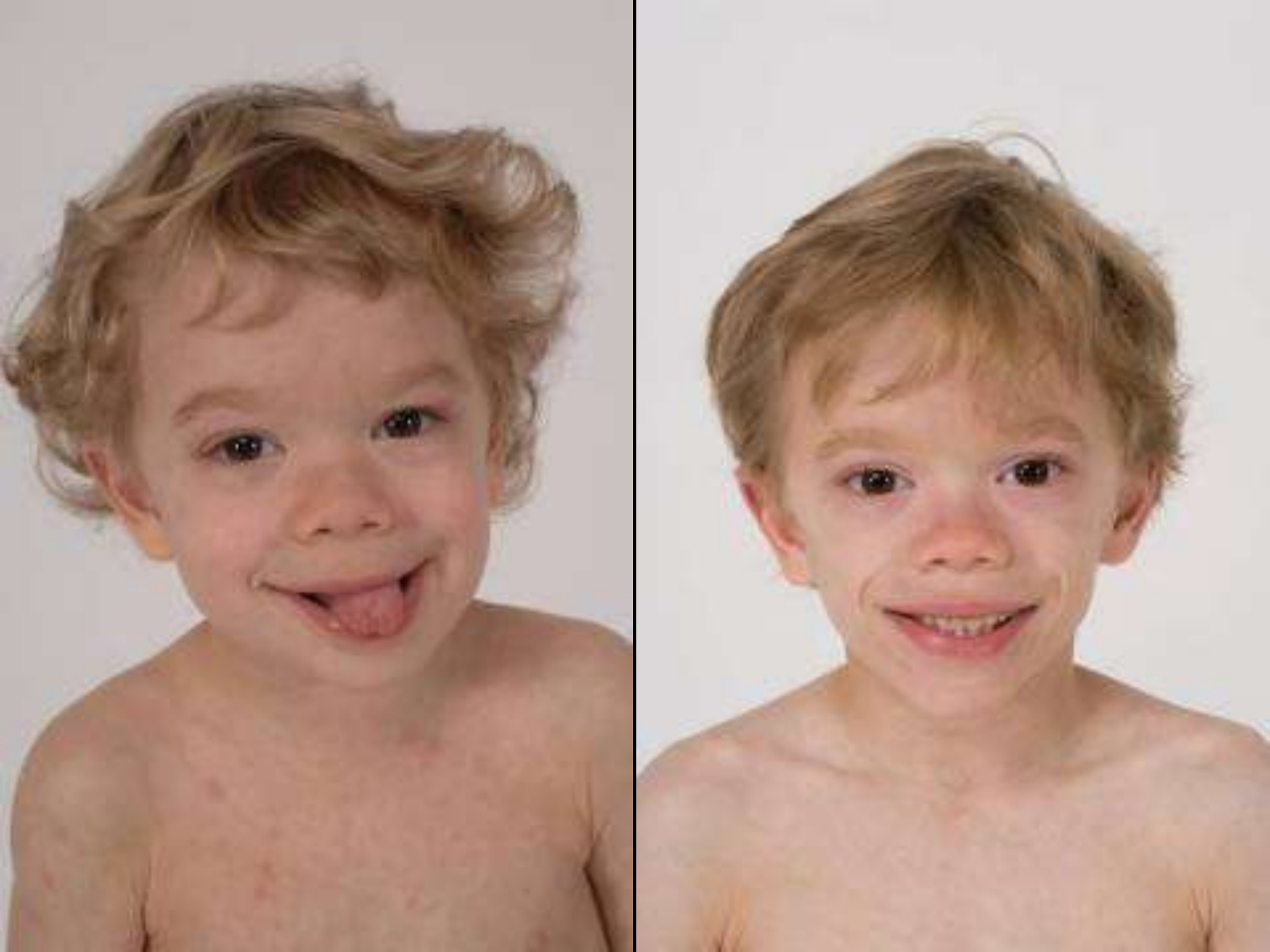

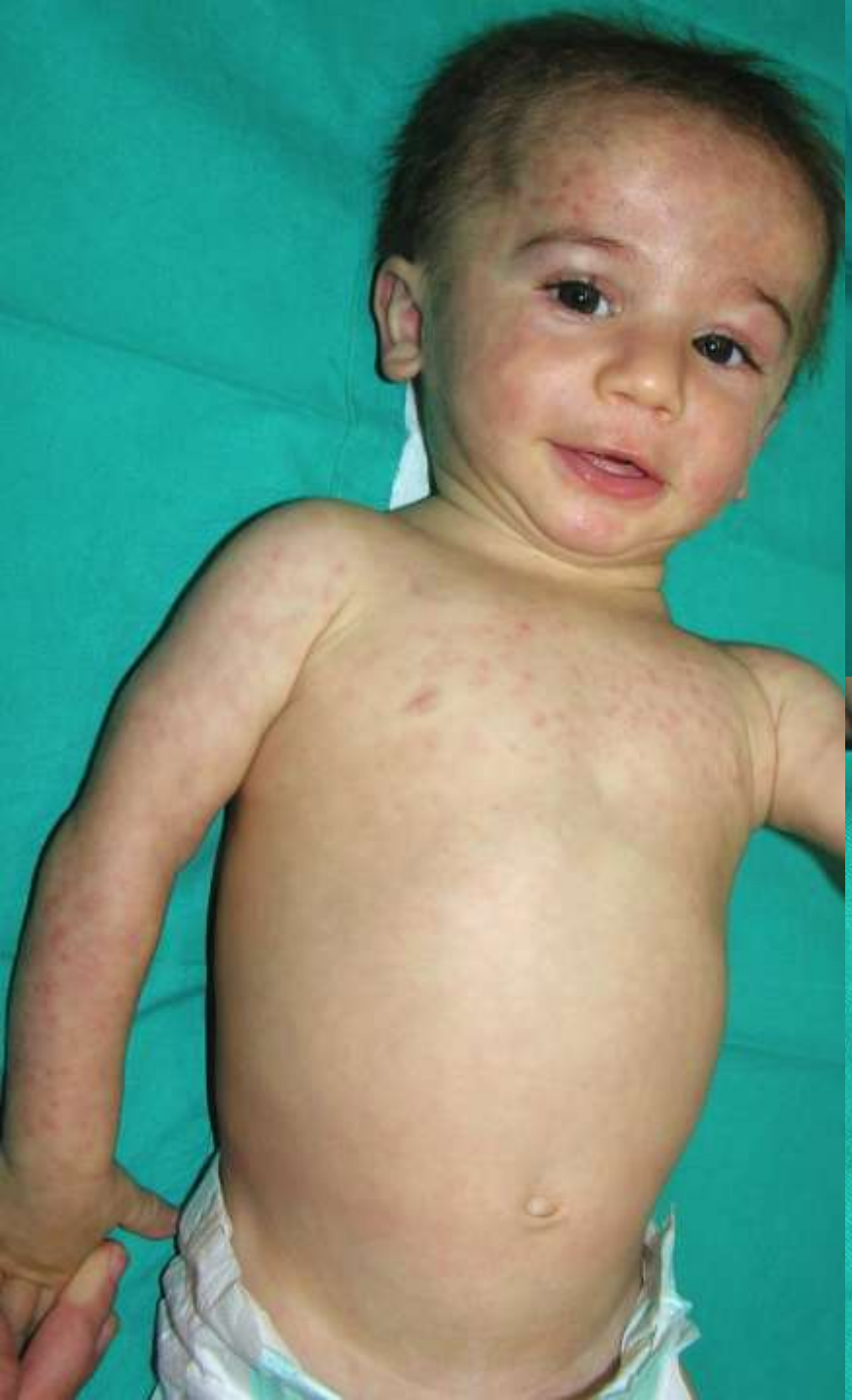
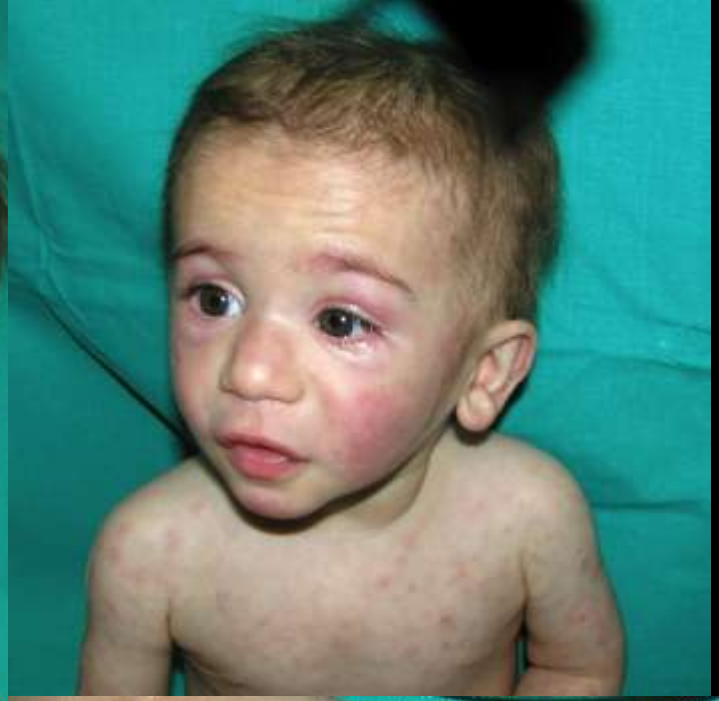


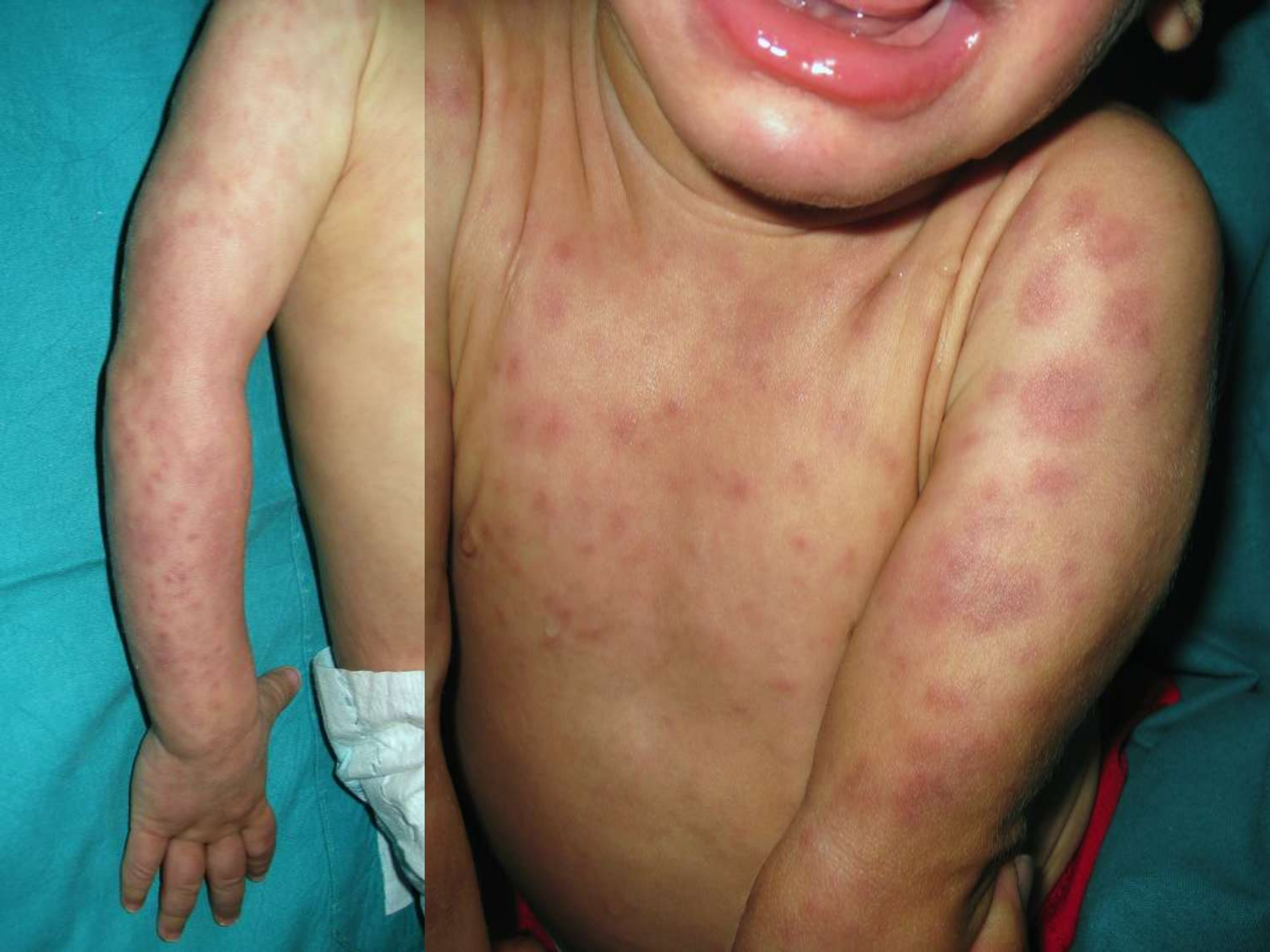

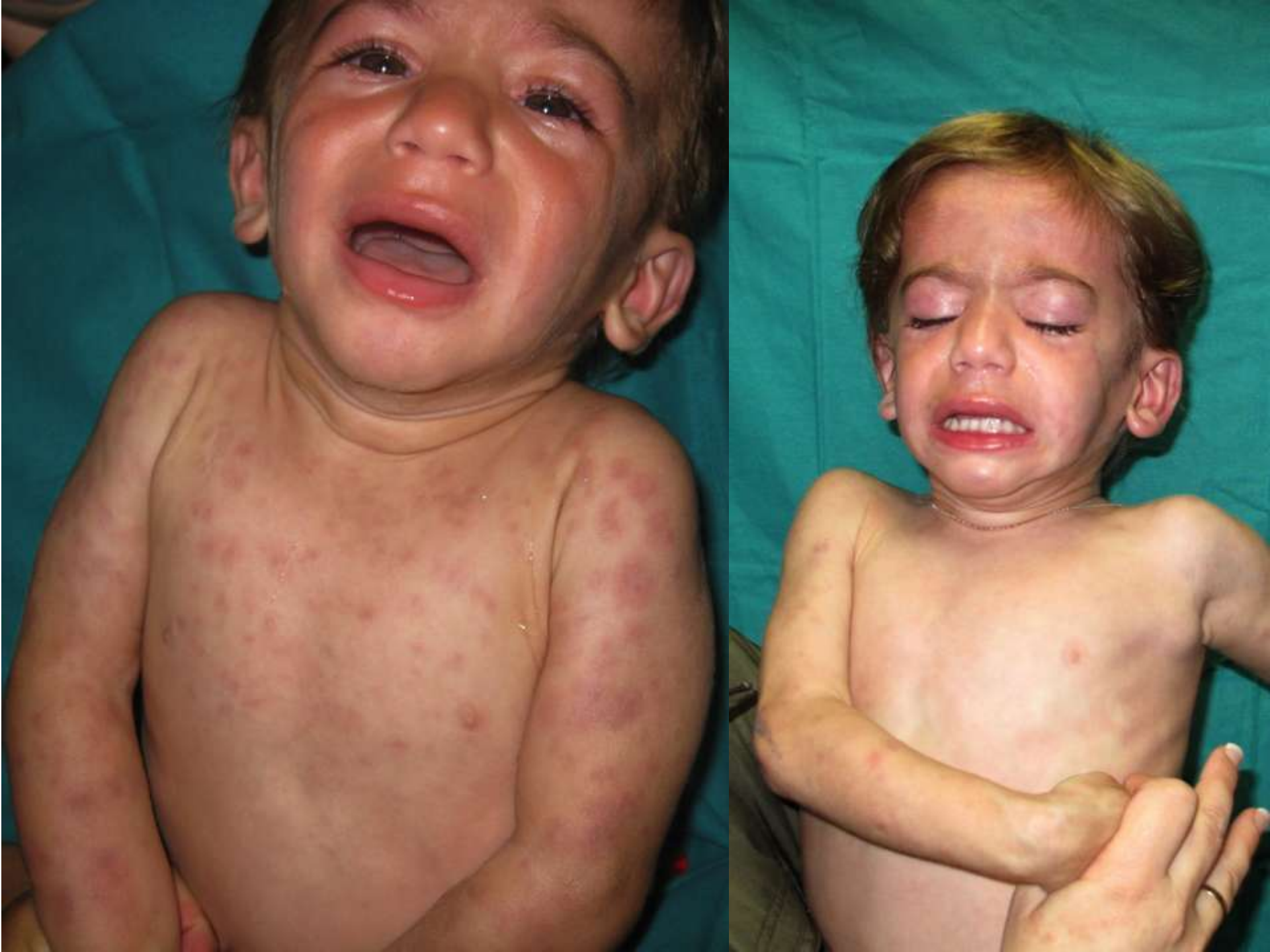

An Autosomal Recessive Syndrome of Joint Contractures, Muscular Atrophy, Microcytic Anemia, and Panniculitis-Associated Lipodystrophy

Abhimanyu Garg, Maria Dolores Hernandez, Ana Berta Sousa, Lalitha Subramanyam, Laura Martínez de Villarreal, Heloísa G. dos Santos, and Oralia Barboza

J Clin Endocrin Metab. First published ahead of print June 9, 2010

Asunto: CANDLE Syndrome
Fecha: miércoles 25 de agosto de 2010 10:51:57 p.m. España (Madrid)
De: Abhimanyu Garg
A: atorrelo@aedv.es

Dear Dr. Torrelo:
It was interesting to read about your patients with autoinflammatory syndrome and lipodystrophy. We recently published our experience. See paper attached. There seems to be some overlap between the two. We would like to know more about their pattern of lipodystrophy and whether they develop panniculitis or not. Also, we wonder whether you will like to collaborate with us to identify the genetic basis of this syndrome.
Sincerely,

Abhimanyu Garg, M.D.
Professor of Internal Medicine
Chief, Division of Nutrition and Metabolic Diseases
Endowed Chair in Human Nutrition Research
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd., K5-214
Dallas, TX 75390-8537.
(214) 648-2895 (phone)
(214) 648-0553 (Fax)

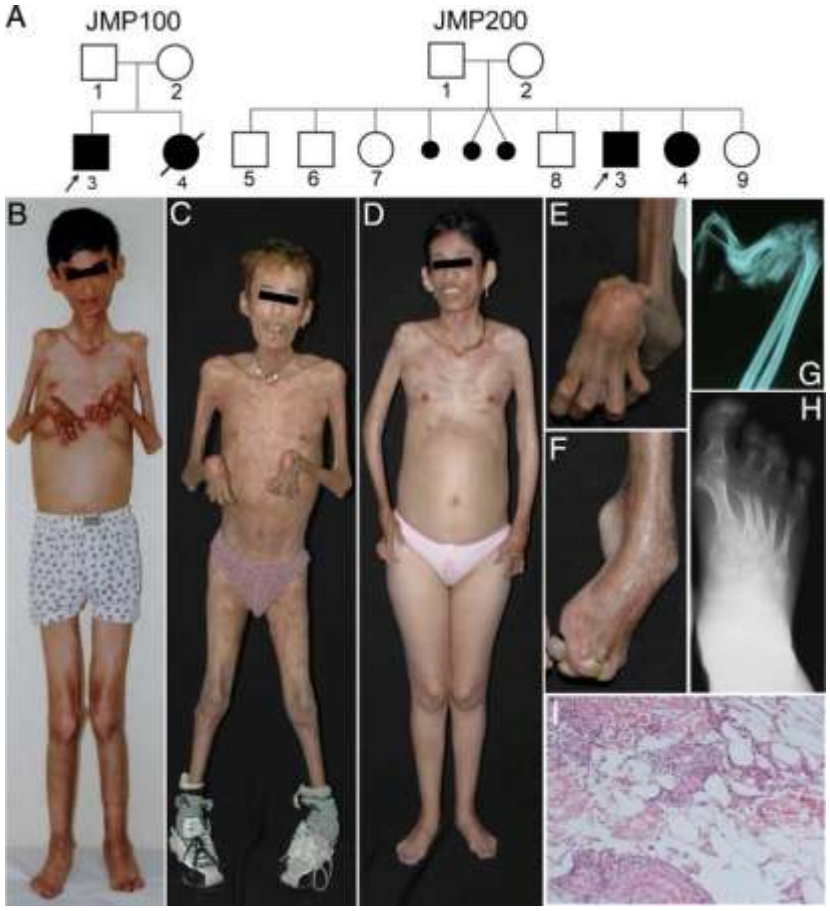

FIG. 1. Pedigrees and clinical features of our patients with JMP syndrome. A, Pedigrees of

TABLE 1. Clinical features in our patients and previously reported patients from Japan: comparison with other progeroid syndromes due to laminopathies

	JMP 100.3	JMP 200.3	JMP 200.4	Japan 1 (3)	Japan 2 (3)	Japan 3 (6)	MAD (8, 12)	HGPS (13, 14)	APS (15)
Consanguinity	No	No	No	Yes	Yes	No	+/–	No	No
Sex	M	M	F	M	F	F	M/F	M/F	M/F
Age at report (yr)	35	30	26	47[a]	51	38	1–56	1–20	5–53
Age of onset (yr)	NA	6	14	12	6	1.5	2–4	1–3	4–17
Sclerodermatous skin and erythematous lesions	+	+	+	+	+	+	+	+	+/–
Lipodystrophy	+	+	+	+	+	+	+	+	+
Joint contractures	+	+	+	+	+	+	+	+	+
Seizures	–	+	+	–	–	–	–	–	–
Mental retardation	–	–	–	+	+	+	–	–	–
Basal ganglia Calcification	NA	+	NA	–	+	+	–	–	–
Microcytic anemia	+	+	+	–	–	–[b]	–	–	–
Hypergammaglobulinemia	+	+	+	+	+	+	–	–	–
Elevated ESR	+	NA	NA	+	+	+	–	–	–
Muscle atrophy	+	+	+	+	+	–	–	–	–
Corneal opacities	+	–	–	–	–	–	–	–	–
Gynecomastia	+	–	NR	–	NR	NR	–	–	–
Short stature	+	+	+	–	+	+	+	+	+
Diabetes	–	–	–	+	IGT	–	+/–	–	+/–
Hypertriglyceridemia	–	–	–	–	–	–	+/–	–	+/–
Low HDL cholesterol	+	+	+	NA	NA	NA	+/–	+/–	+/–
Hepatomegaly	+	+	+	+	+	+	+/–	–	+/–
Splenomegaly	+	+	+	+	+	+	–	–	–
Macroglossia	–	–	–	+	+	–	–	–	–

Hypertriglyceridemia was defined as fasting serum triglycerides greater than 200 mg/dl. M, Male; F, female; –, absent; +, present; +/–, present in some and absent in others; NA, not available; NR, not relevant; IGT, impaired glucose tolerance; MAD, mandibuloacral dysplasia due to *LMNA* or *ZMPSTE24* mutations; HGPS, Hutchinson-Gilford Progeria syndrome; APS, atypical progeroid syndrome; ESR, erythrocyte sedimentation rate.

[a] Died at age 47 yr due to congestive heart failure.

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Report

PSMB8 Encoding the ! 5i Proteasome Subunit Is Mutated in Joint Contractures, Muscle Atrophy, Microcytic Anemia, and Panniculitis-Induced Lipodystrophy Syndrome

Anil K. Agarwal[1], Chao Xing[2], George N. DeMartino[3], Dario Mizrachi[4], Maria Dolores Hernandez[5], Ana Berta Sousa[6], Laura Martínez de Villarreal[5], Heloísa G. dos Santos[6] and Abhimanyu Garg[1],

[1] The Division of Nutrition and Metabolic Diseases, Department of Internal Medicine and the Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA

[2] Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA

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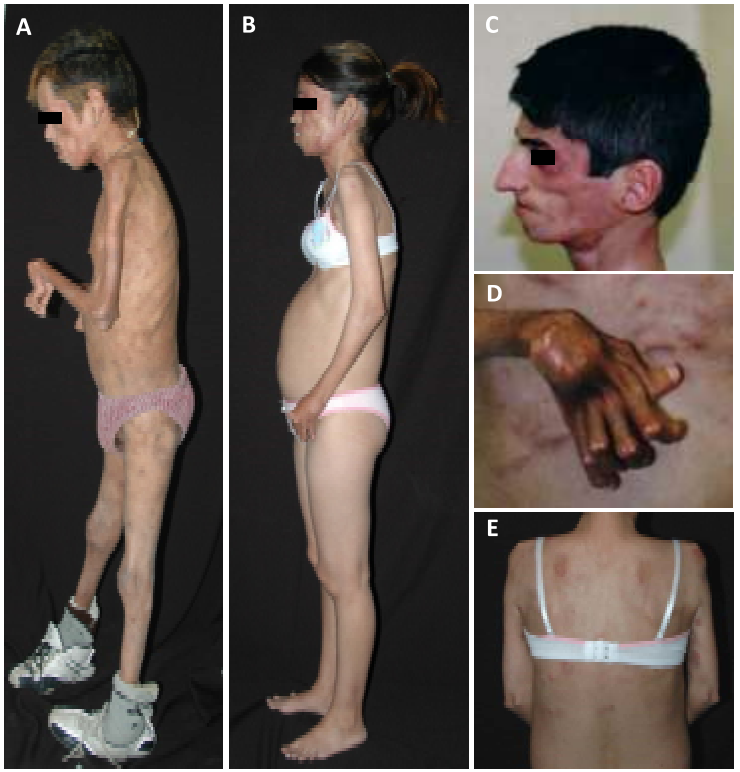
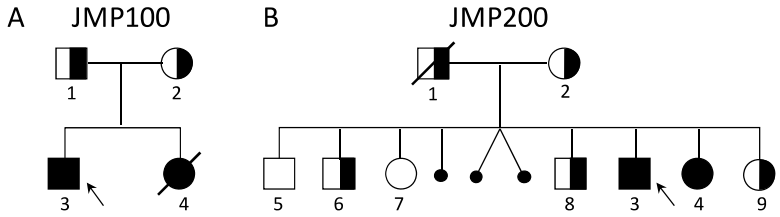
[5] Departamento de Genética, Facultad de Medicina, Universidad Autonoma de Nuevo Leon, Monterrey, Nuevo León, 66603, México

[6] Serviço de Genética Médica, Hospital de Santa Maria, 1649-035 Lisbon, Portugal

Received 2 September 2010; revised 18 October 2010; accepted 25 October 2010. Published online: December 2, 2010. Available online 2 December 2010.

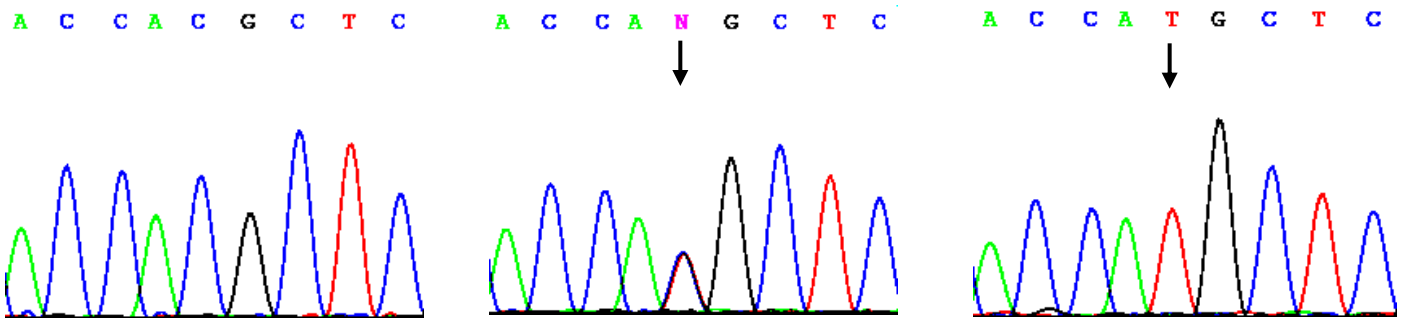
We performed homozygosity mapping in two recently reported pedigrees from Portugal and Mexico with an autosomal-recessive autoinflammatory syndrome characterized by joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy (JMP). This revealed only one homozygous region spanning 2.4 Mb (5818 SNPs) on chromosome 6p21 shared by all three affected individuals from both families. We directly sequenced genes involved in immune response located in this critical region, excluding the HLA complex genes. We found a homozygous missense mutation c.224C>T (p.Thr75Met) in the proteasome subunit, beta-type, 8 (*PSMB8*) gene in affected patients from both pedigrees. The mutation segregated in an autosomal-recessive fashion and was not detected in 275 unrelated ethnically matched healthy subjects. *PSMB8* encodes a catalytic subunit of the 20S immunoproteasomes called ! 5i. Immunoproteasome-mediated proteolysis generates immunogenic epitopes presented by major histocompatibility complex (MHC) class I molecules. Threonine at position 75 is highly conserved and its substitution with methionine disrupts the tertiary structure of PSMB8. As compared to normal lymphoblasts, those from an affected patient showed significantly reduced chymotrypsin-like proteolytic activity mediated by immunoproteasomes. We conclude that mutations in *PSMB8* cause JMP syndrome, most probably by affecting MHC class I antigen processing.





Sequencing of *PSMB8*

Original Spanish families (3 families- 2 Spain, 1 USA)



Wildtype

Heterozygote (c.224C>T)

Homozygote (c.224C>T)

Asunto: CANDLE syndrome
Fecha: martes 11 de enero de 2011 04:31:52 p.m. España (Madrid)
De: 金澤 伸雄
A: atorrelo@aedv.es
CC: Hiroaki Ida

Dear Dr. Antonio Torrelo,

I am a Dermatologist working in Wakayama, Japan.

I have read your paper with great interest "Chronnic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome" published in the last year's JAAD, because I am following a series of very similar cases in Japan.
In Japan, the disease has been called Nakajo-Nishimura syndrome, which was originally reported by Nakajo in 1939 and Nishimura in 1950 as "secondary hypertrophic osteoperiostosis with pernio". The designation "Nakajo syndrome" or "Nakajo-Nishimura syndrome" was already registered in OMIM256040 and ORPHA1953 or ORPHA2615, respectively. As you reported, many of the cases show early-onset periodic fever and therefore the disease is considered a new autoinflammatory disease.
Actually, I and colleagues have reported the disease in the International Congress on FMF and Systemic Autoinflammatory Diseases since 2008. And last year, we have successfully reported the identification of its responsible genetic mutation at the latest Congress.

Therefore, we would like to ask you to let us investigate the mutation in your reported 4 patients. Furthermore, if available, the patients-oriented cells such as primary fibroblasts or immortalized B cells, would be also useful for functional assay.

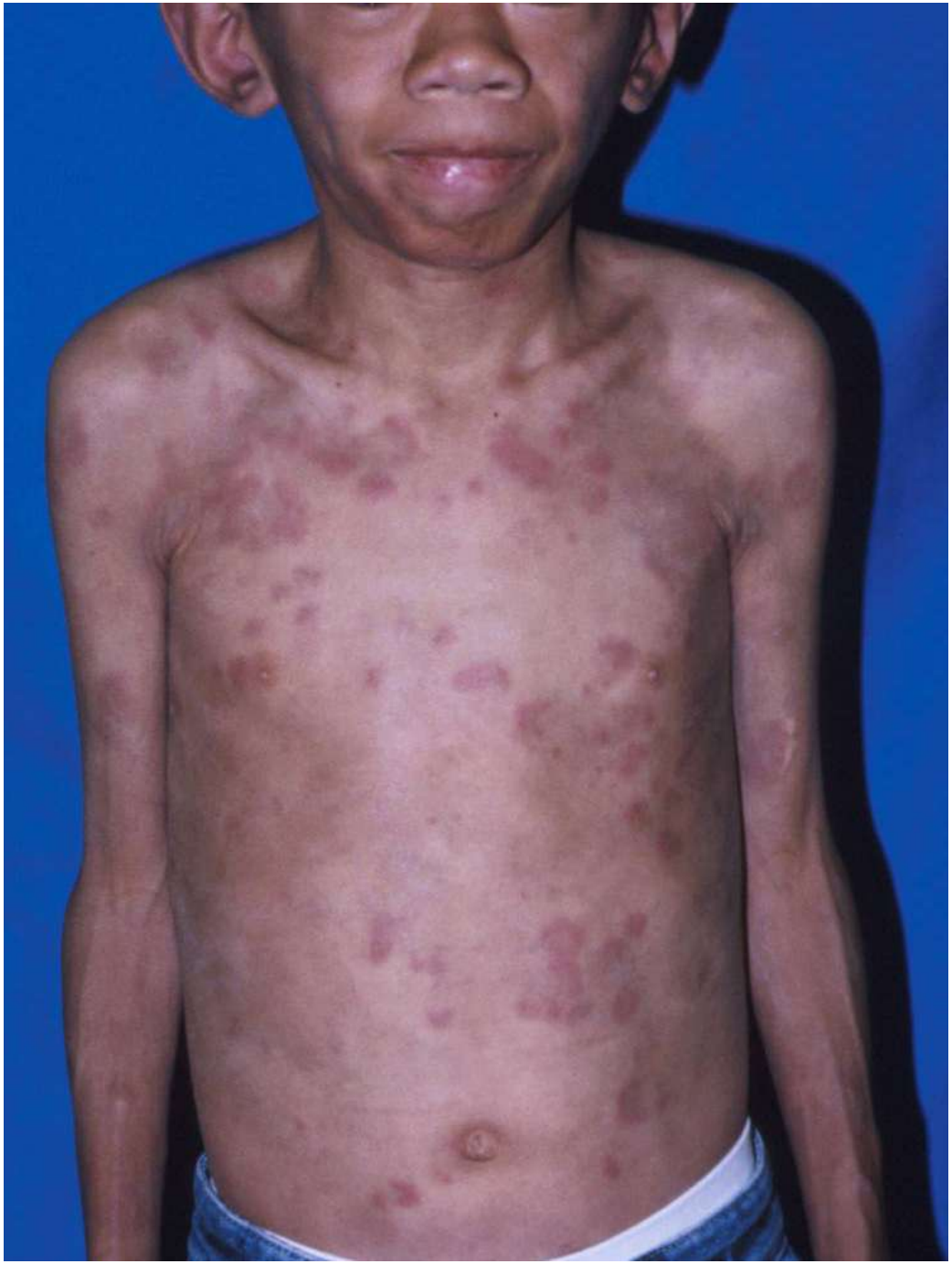
I am looking forward to hearing from you soon.
Thank you in advance,

(One representative photo of our patients is attached.)

Yours sincerely,

Nobuo Kanazawa, MD, PhD

Assistant Professor of
Department of Dermatology, Wakayama Medical University
811-1 Kimiidera, Wakayama 641-0012, Japan
Tel: +81-73-441-0661
Fax: +81-73-448-1908
E-mail: nkanazaw@wakayama-med.ac.jp



in 1939

皮膚科泌尿器科雜誌

第45巻 第2號 昭和14年(1939)2月

凍瘡ヲ合併セル續發性肥大性骨骨膜症

A. Nakazyô: Über zwei Fälle von Osteoperiostopathia hypertrophiant secundaria mit Perniones.

東北帝國大學醫學部皮膚科泌尿器科教室(主任 伊藤教授)

助手 中條敦

緒言

血族結婚ニ際ヲ發スル先天性疾患、機能障碍ノ症例ハ枚擧ニ遑ナキ處ナルモ、最近余ハ血族結婚ノ兩親ノ產レタル同胞中2名ニ於テ、一見肢端肥大症樣症狀ヲ呈セル者ガ臨牀檢査ノ結果之ト病因ヲ全ク異ニシ、脳腫瘍、先天性心臟瘤膜症、氣管枝擴張症、諸種、化膿性、腐敗性疾患等ノ患者ニ續發的ニ見ラル、鼓槌狀指趾、四肢末端部ノ不均等肥大、管狀骨骨膜肥厚ヲ呈スルMarie氏ノ所謂肺性肥大性骨關節症ナル事ヲ確メ、且ツ凍瘡ヲ合併シ、剩ヘ人工的ニ容易ニ凍瘡樣症狀ヲ形成シ得ラレ、是等徵候群ノ基因トシテ先天性心臟障碍ヲ推定セラル、興味アル症例ヲ經驗シタルヲ以テ玆ニ報告セントス。

症例(病因ニ缺文ニ括弧)

第1例

福野某、男、10歲、初診昭和13年3月17日。

家族歷

兩親父母ハ孰ニモ死亡シ病名不詳ナリ。兩親ハ從兄妹同志ノ結婚ニシテ共ニ健在、WaR. 陰性ナリ。同胞7人中、第3子早產ニシテ、患者ハ第4子ニ當リ、末子ニ當ル2歲ノ妹第2例モ患者同樣ノ主訴ヲ有セリ。餘レル3同胞4名ハ現在ハ健全ナリ。

既往歷並ニ現病歷 2歲ノ時百日咳罹患後急激ニ腹部ヲ來リ、全身各部ノ先端突起部ニ不均等肥大ヲ認メ、同年10月始メノ凍傷ヲ生ジ、之ガ漸年增惡シ、同時ニ先端部ノ腫脹、長大症ヲ顯著トナリ、遂ニ本年3月當科ヲ訪ルニ至レリ。

現症 體格、榮養極メテ不良、身長108.5cm、體重15.8kgナリ。顏貌全ク無感覺的ニシテ、智能ハ稍惡ニ等シク10ヲ算スルヲ得ズ、姿勢ハ前屈シ腰部ハ脊柱後屈見ラレ、第肉組織ハ全身的ニ極度ニ退化萎縮シテ脆上甚ダ遲鈍ナリ。皮膚ハ一般ニ思われる疾患は全く認められない所謂原發性のもので色々な點で興味あると思われるので報告し諸賢の御批判を仰ぎたい。

症例 第1症例：患者朱澤某、18歲未婚の女子。初診昭和24年8月24日。家族歷：父母は從兄妹同志の結婚である。同胞9人。中3人死亡。長兄は5—6歲頃より患者と全く同樣な皮疹と上半身が非常に高度し、關西の病院で診察を受けたが診斷不明のまゝ打過して15歲の時腦炎にて死亡した。他2人は肺炎、ザフテルにて死亡、他は健在にて患者は第8番目である。既往歷：特記すべきものはない。月經は未だ來潮しない。現病歷：生後發育狀態は普通で健康であつたが5歲頃に顏面、耳介部、胸部、上肢、手等に略ゝ左右對側性に散在性に淡紅色の小豆大より兩豆大の結節が發生し此等の結節は漸次扁平となり色素沈着を殘して治癒するが絶えず新生して治癒せず皮疹は自覺症狀は殆んどなく時に僅かに瘙痒感があつた。6歲頃より發育狀態が停止された狀態で特に顏面、上肢の高度が著明となり、小學校2~3年頃より下半身に比し上半身の高度が著明となり特異な顏貌及び高度狀態となつた。發疹の生じ始めた頃より疲労し易く現在では勞働不能狀態で倦怠、少食、寒がりで興奮し易く小學校時代の成績は普通であつた。現症：體格は非常に小、顏面、頭部、上肢は非常に高度し、兩側手指は特異な形態を示して長大、各指節關節部は腫大して典型的な鼓槌狀指を呈し暗紫色、爪には殆んど變化を認めない。顏面は暗紫色高度して特異な容貌を呈し無感覺である。足趾、下腿は略ゝ正常、皮膚所見：皮膚は一般に乾燥し顏面、上肢、前膊、手、耳介部、膝蓋部の高度部に一致して略ゝ左右對側性に表在血管の走行に一致して散

in 1950

2家族に發生した凍瘡樣皮膚病變を併發した續發性肥大性骨骨膜症

和歌山縣立醫科大學皮膚科泌尿器科教室(主任: 西村助教授)

西村長臣

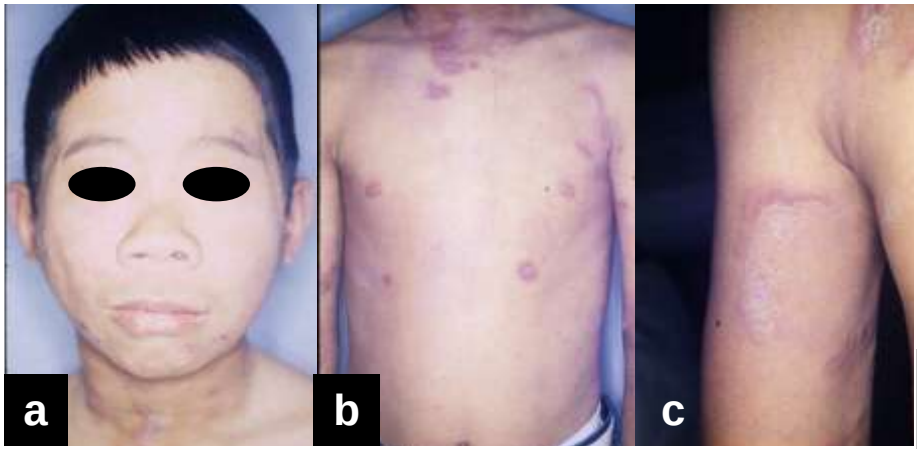
出來利夫

加藤正一郎

N. Nishimura, T. Deki and S. Kato: Hypertrophic Pulmonary Osteo-Arthropathy with Pernio-like Eruption in the Two Families. (Report of the Three Cases)

續發生肥大性骨骨膜症は1890年 Bamberger, Marie によつて初めて記載された疾患で肥大性肺性骨關節症(Marie), 續發性增殖性骨炎(Arnold), 汎發性化骨性骨性骨膜炎(Shlangenhaufer)等諸種の名稱で呼ばれている疾患であつて汎發性, 對側性の鼓槌狀指(趾)と手足の管狀骨の肥大及び前膊, 下腿管狀骨の有痛性肥厚を伴い此等の病變は主として肺, 心臟等の慢性疾患即ち氣管枝擴張症, 肺結核, 膿胸, 肺膿瘍, 肺及び縱隔膿の惡性腫瘍, 肺氣腫, 心臟瘤症, 先天性梅毒, 慢性腸炎等に續發するが稀には原病の全く認められない所謂原發性のものが報告されている。Locke によれば144例中呼吸器疾患112例, 循環器疾患6例, 消化器疾患13例, その他の疾患及び原因不明13例, 又高橋氏によれば221例中慢性化膿性腐敗性疾患95例, 惡性腫瘍45例, 膿汁性肝硬變症12例, 特殊例18例, 心臟障碍15例, 原病不明14例, その他22例であつて何れの統計に於ても原發性疾患として呼吸器疾患が壓倒的に多い。本疾患に皮膚病變を併發した症例は內外共に非常に稀有で本邦に於ては, 中條氏の凍瘡を併發した報告が存するのみである。我々は2家族に發生し而も著明な凍瘡樣皮疹を伴つた本疾患と思われる症例を經驗し, 兩親は何れも從兄妹同志の結婚であり, 幼時より先づ皮膚病變に氣付き遲れて四肢末端特に手指及び顏面に本症に特異な臨牀所見を發見し, その他諸種の檢査成績が一致し且つ本症の原發病と

症例 第1症例：患者朱澤某, 18歲未婚の女子。初診昭和24年8月24日。家族歷：父母は從兄妹同志の結婚である。同胞9人。中3人死亡。長兄は5—6歲頃より患者と全く同樣な皮疹と上半身が非常に高度し, 關西の病院で診察を受けたが診斷不明のまゝ打過して15歲の時腦炎にて死亡した。他2人は肺炎, ザフテルにて死亡, 他は健在にて患者は第8番目である。既往歷：特記すべきものはない。月經は未だ來潮しない。現病歷：生後發育狀態は普通で健康であつたが5歲頃に顏面, 耳介部, 胸部, 上肢, 手等に略ゝ左右對側性に散在性に淡紅色の小豆大より兩豆大の結節が發生し此等の結節は漸次扁平となり色素沈着を殘して治癒するが絶えず新生して治癒せず皮疹は自覺症狀は殆んどなく時に僅かに瘙痒感があつた。6歲頃より發育狀態が停止された狀態で特に顏面, 上肢の高度が著明となり, 小學校2~3年頃より下半身に比し上半身の高度が著明となり特異な顏貌及び高度狀態となつた。發疹の生じ始めた頃より疲労し易く現在では勞働不能狀態で倦怠, 少食, 寒がりで興奮し易く小學校時代の成績は普通であつた。現症：體格は非常に小, 顏面, 頭部, 上肢は非常に高度し, 兩側手指は特異な形態を示して長大, 各指節關節部は腫大して典型的な鼓槌狀指を呈し暗紫色, 爪には殆んど變化を認めない。顏面は暗紫色高度して特異な容貌を呈し無感覺である。足趾, 下腿は略ゝ正常。皮膚所見：皮膚は一般に乾燥し顏面, 上肢, 前膊, 手, 耳介部, 膝蓋部の高度部に一致して略ゝ左右對側性に表在血管の走行に一致して散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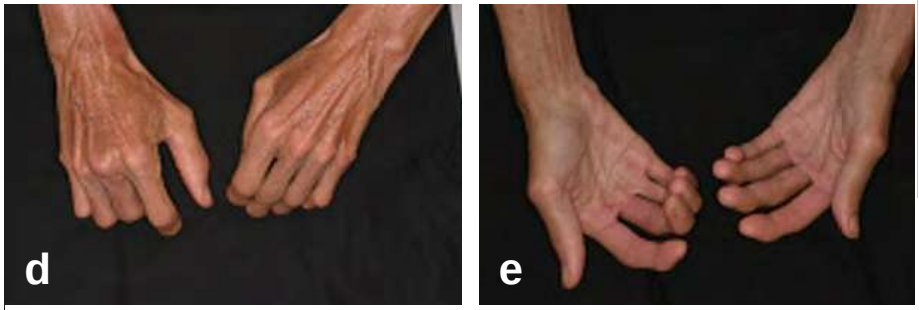
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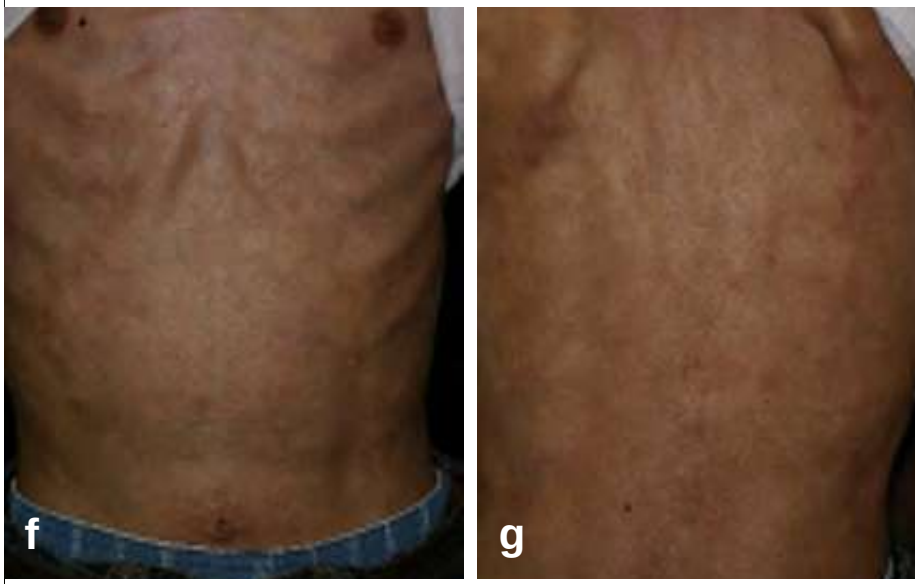
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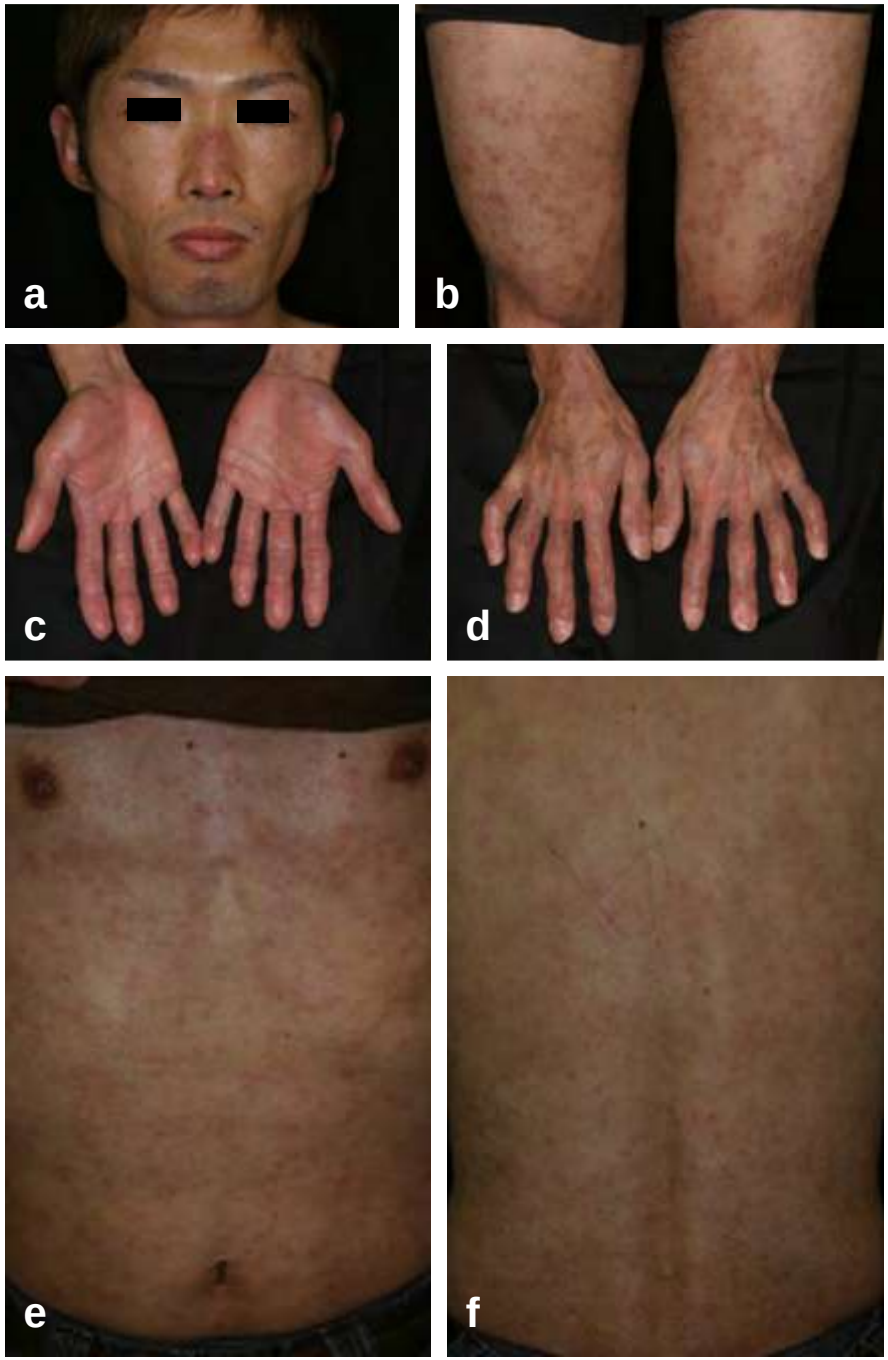
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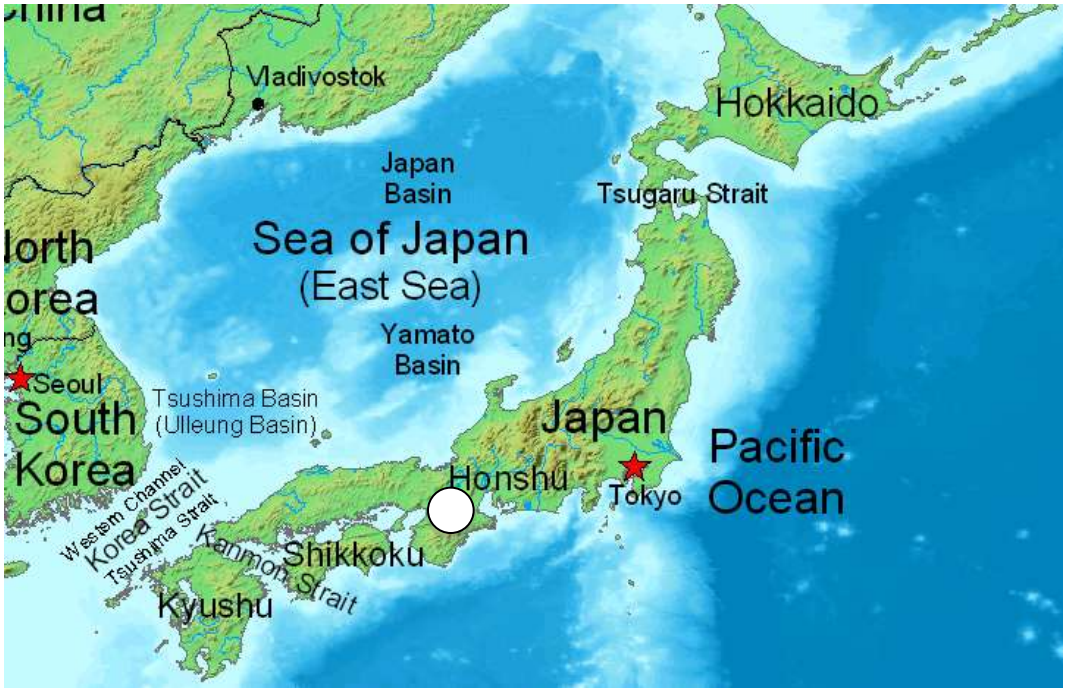

CANDLE

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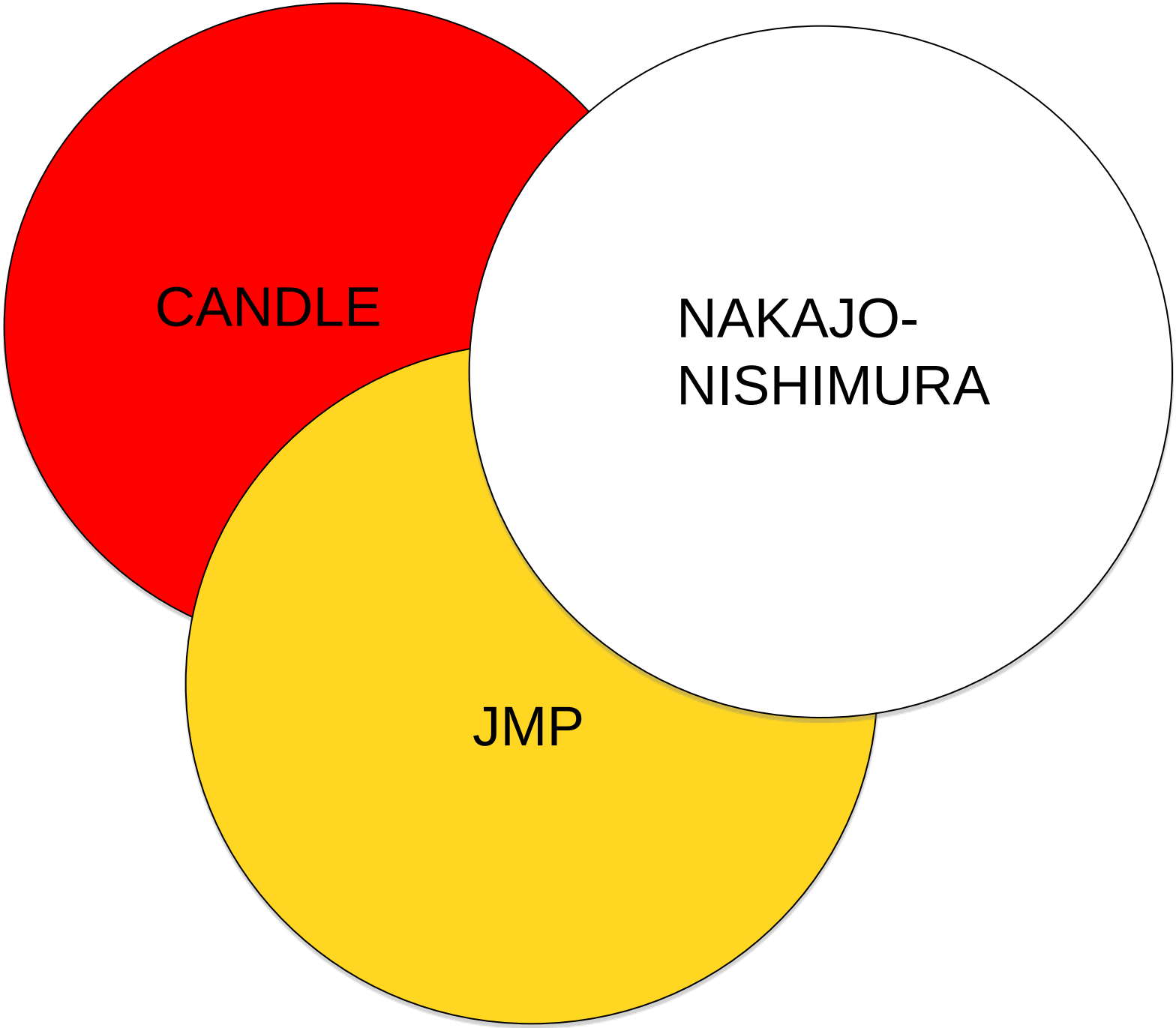
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Papular epidermal nevus with "skyline" basal cell layer (PENS)

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Madrid, Spain; Stony Brook, New York; and Regensburg and Marburg, Germany

Background: Several types of epidermal keratinocytic nevus are recognized.

Objective: We sought to describe a previously unreported keratinocytic nevus with distinctive clinical and histopathologic features in 5 patients.

Methods: We performed a clinical and photographic review, and obtained skin biopsy samples for histopathologic examination from each patient. Genetic analysis to screen for fibroblast growth factor receptor 3 and phosphatidylinositol 3-kinase, catalytic, alpha hotspot mutations was performed on lesional skin from two patients.

Results: Five infants (2 male, 3 female) had from 1 to 11 lesions present since birth. These consisted of 1- to 7-mm hyperkeratotic papules with a rough, flat surface and a round, commalike, rectangular, or polygonal shape. Histopathologic examination showed acanthosis with broad and rectangular rete ridges, and strikingly arranged basal cells with palisaded nuclei. Genetic testing on paraffin-embedded specimens from two patients ruled out hotspot mutations in the fibroblast growth factor receptor 3 and phosphatidylinositol 3-kinase, catalytic, alpha genes.

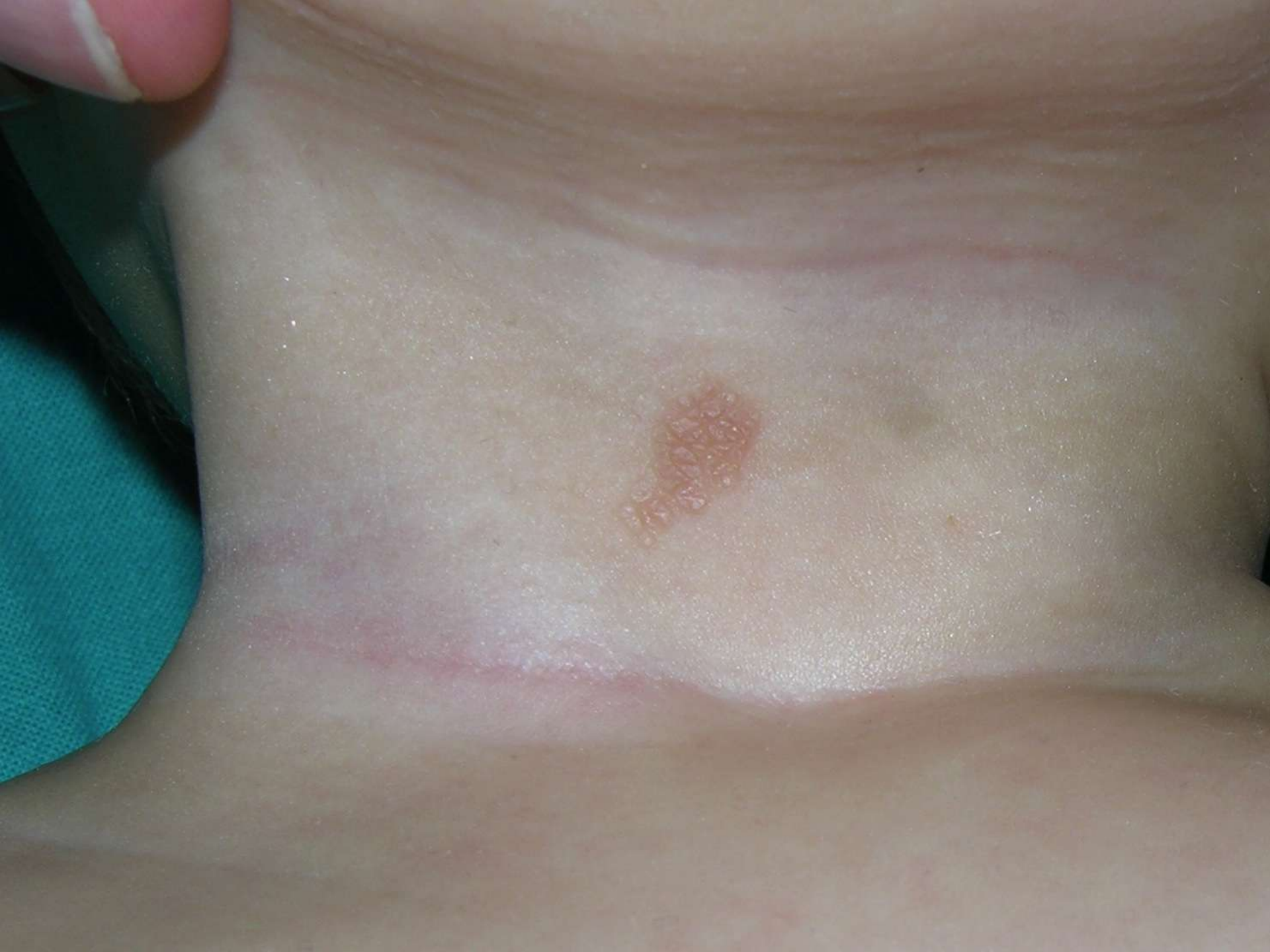
Limitations: A small number of patients are presented.

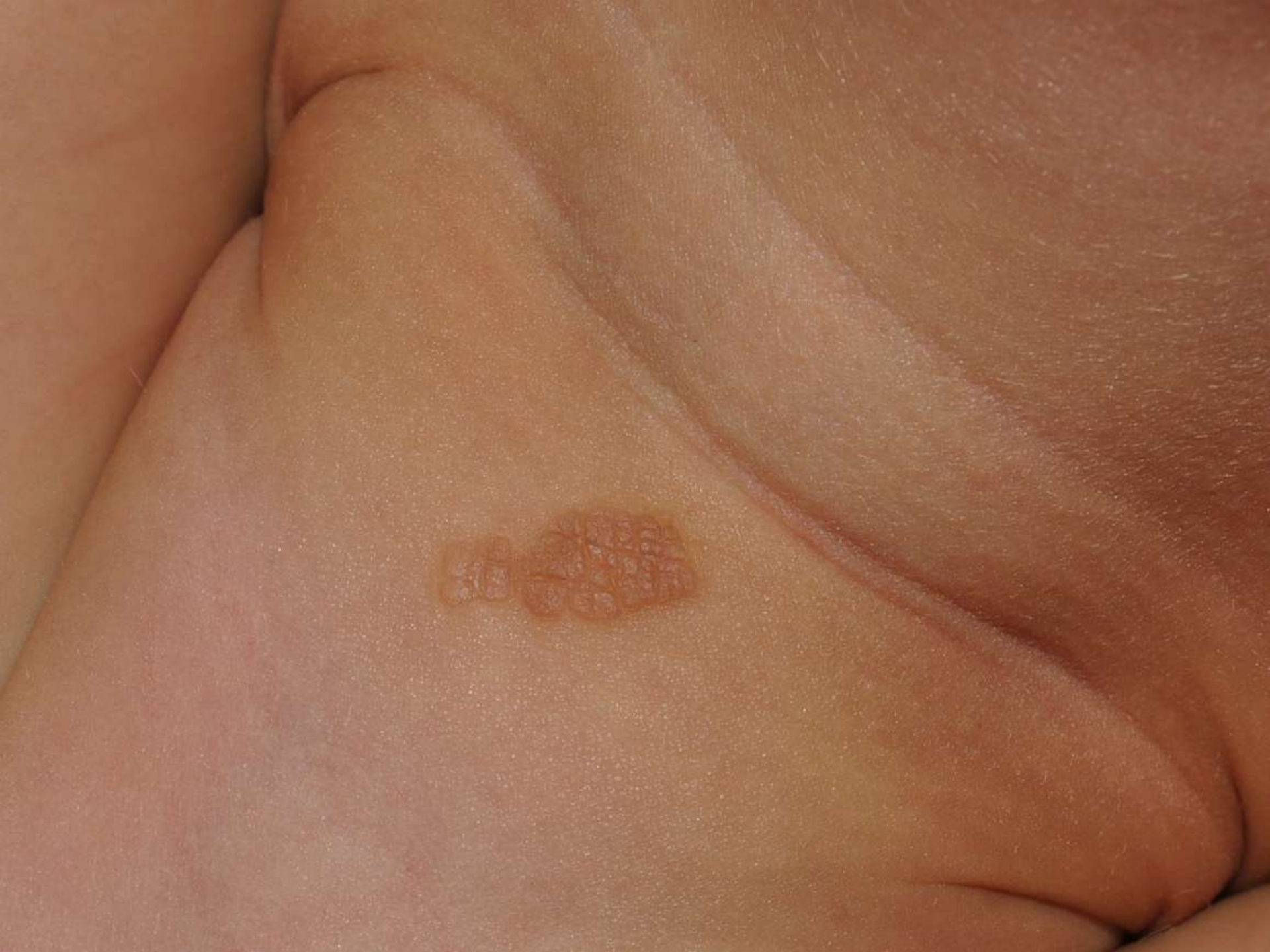
Conclusion: We propose the name "papular epidermal nevus with 'skyline' basal cell layer" (PENS) for this newly recognized condition. (J Am Acad Dermatol 10.1016/j.jaad.2010.02.054.)

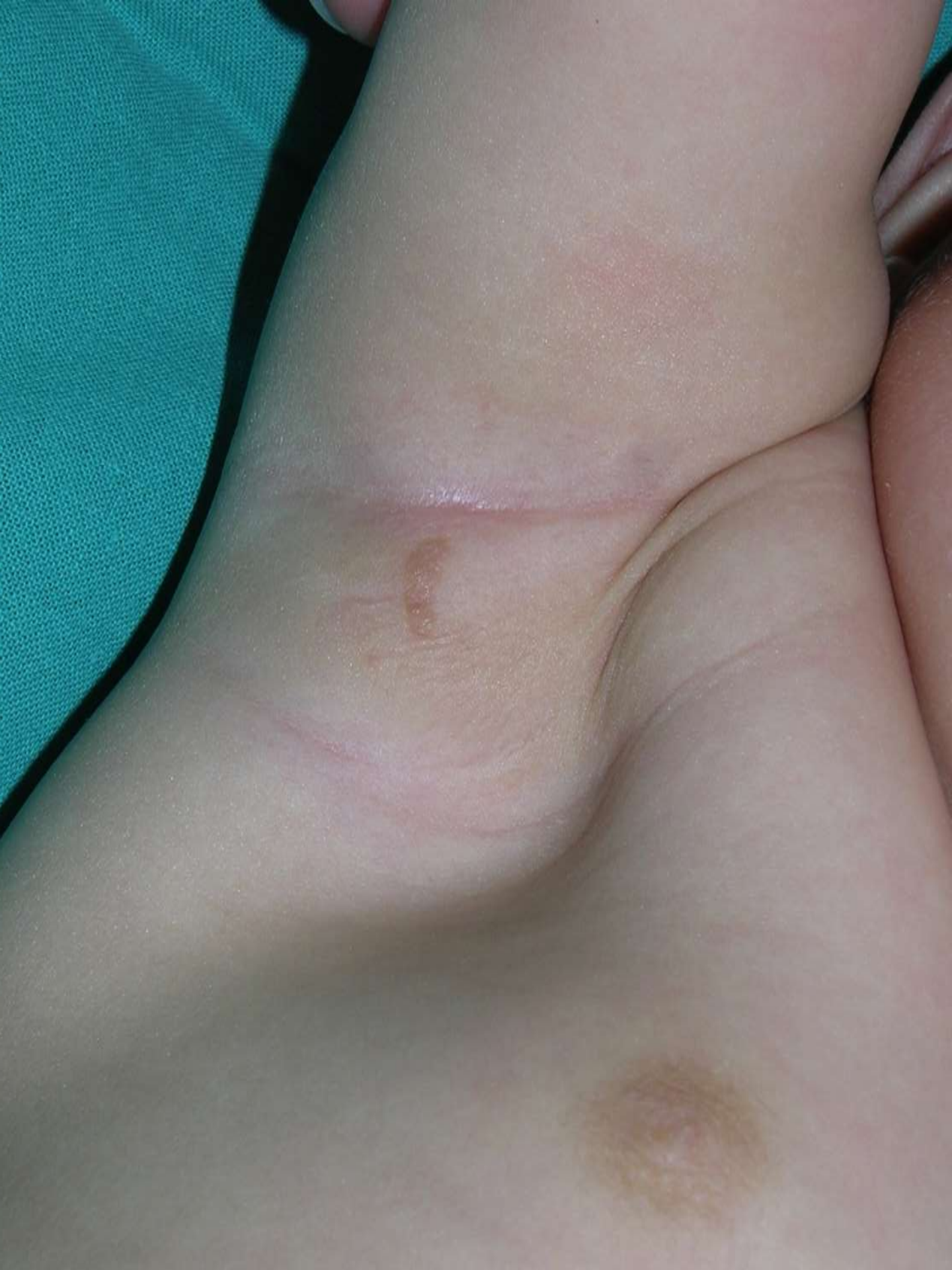
Key words: congenital nevus; epidermal nevus; keratinocytic nevus; nevus; newborn; skin hamartoma.

Primer caso

- Niña, RN, embarazo y parto normales
- Desde el nacimiento: 11 pápulas (cuello. axila, tronco, muslo, piernas y brazos)
- No otros síntomas o signos







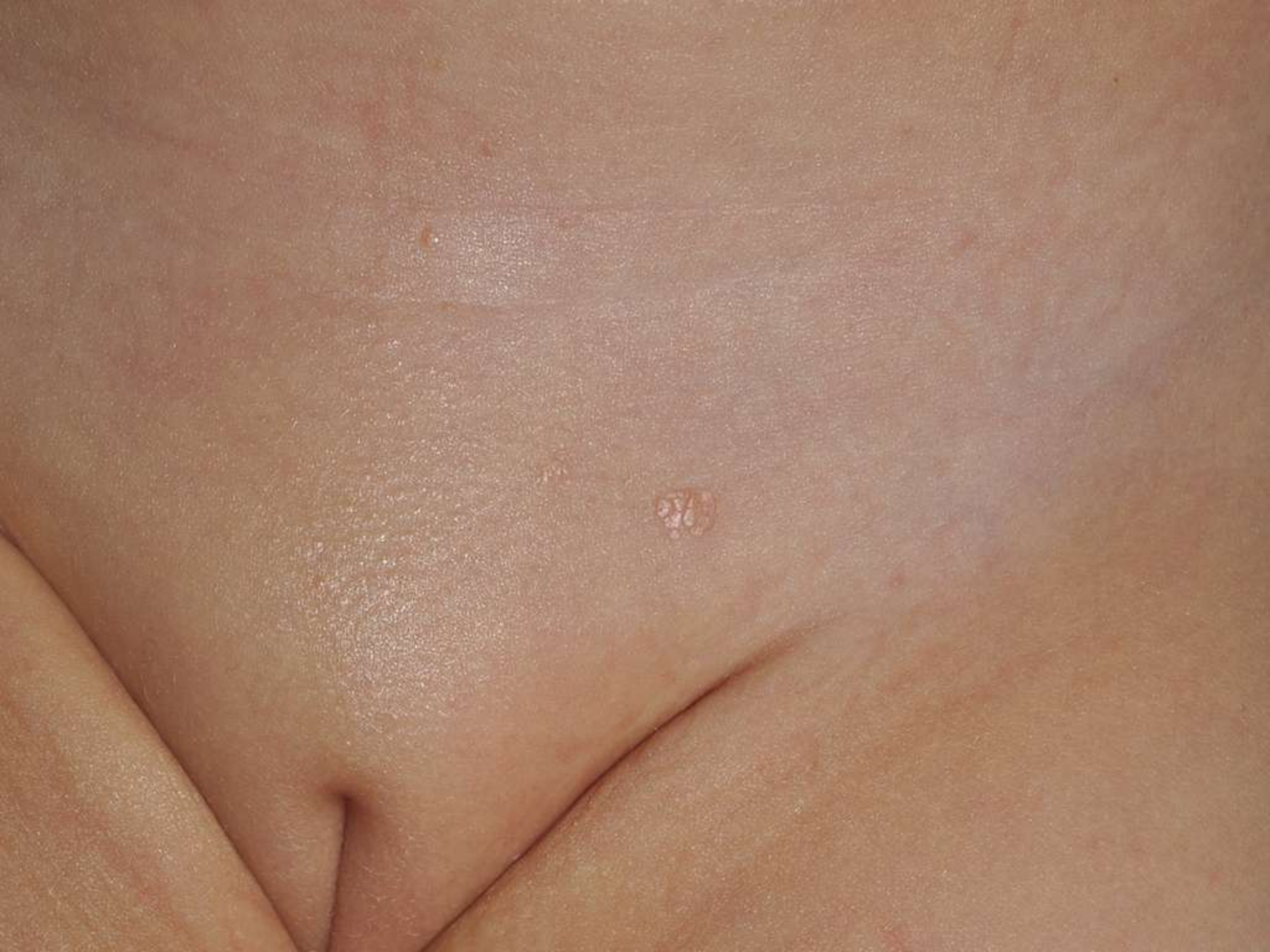
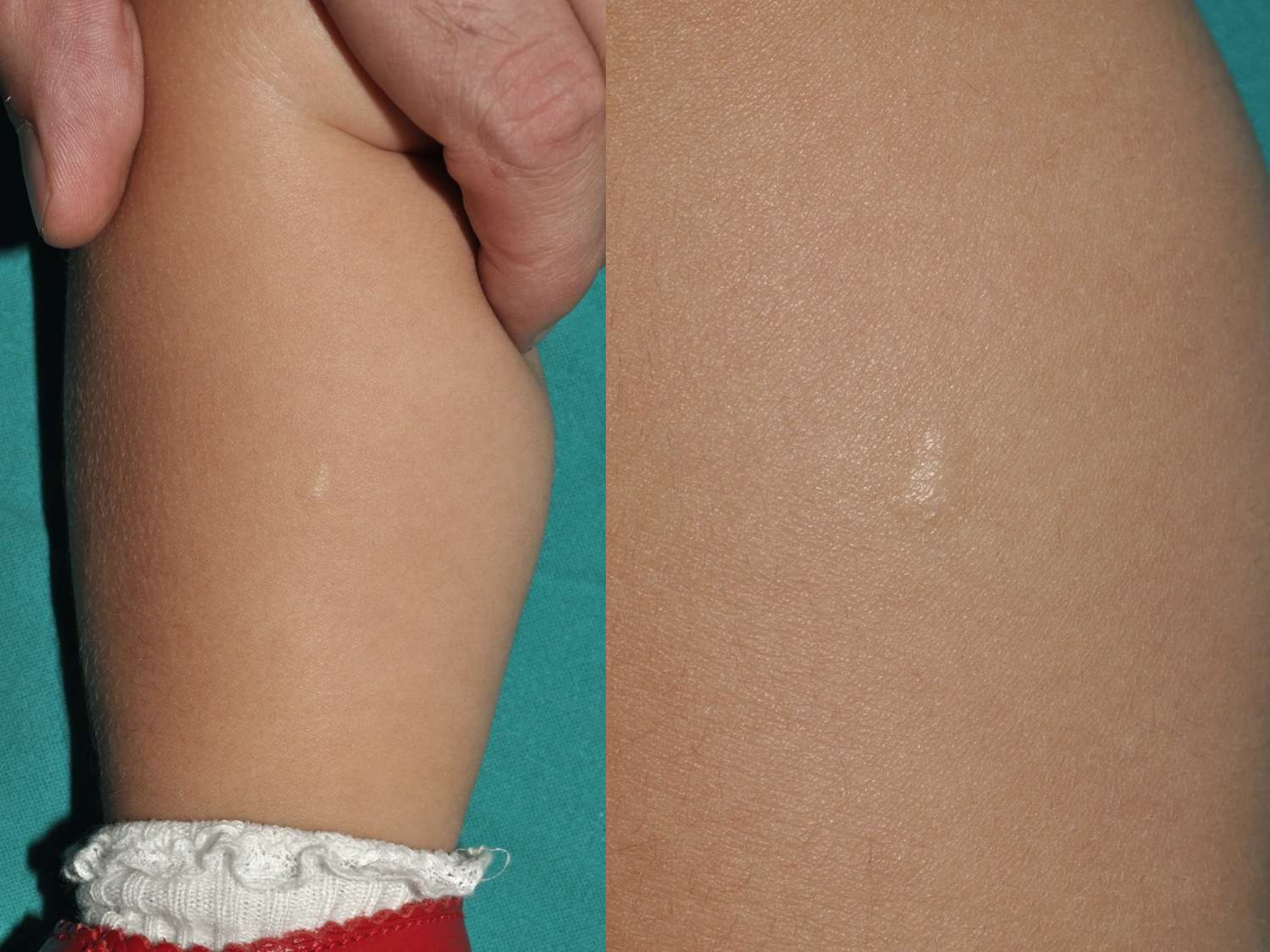
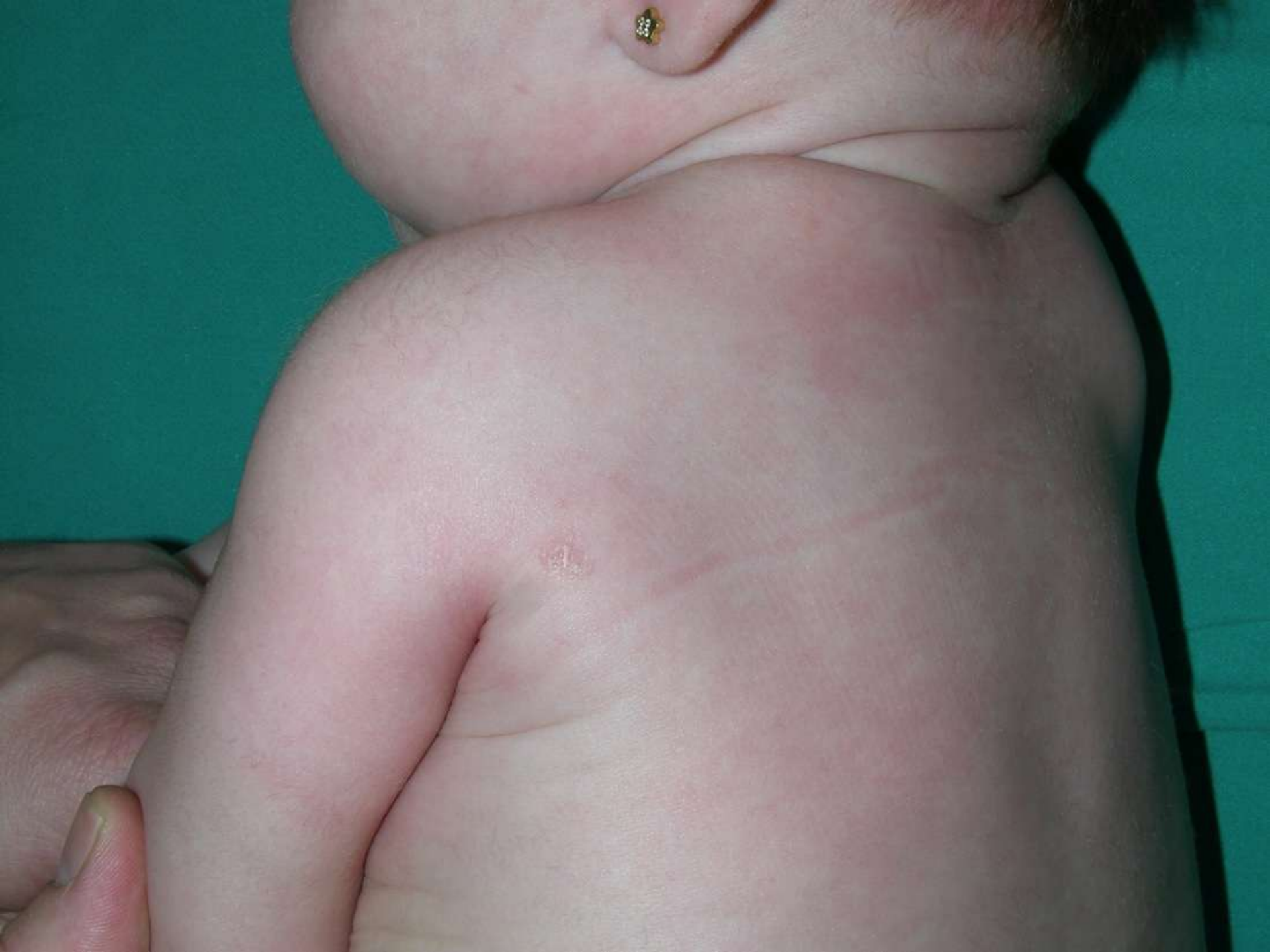


TABLE. Summary of patients

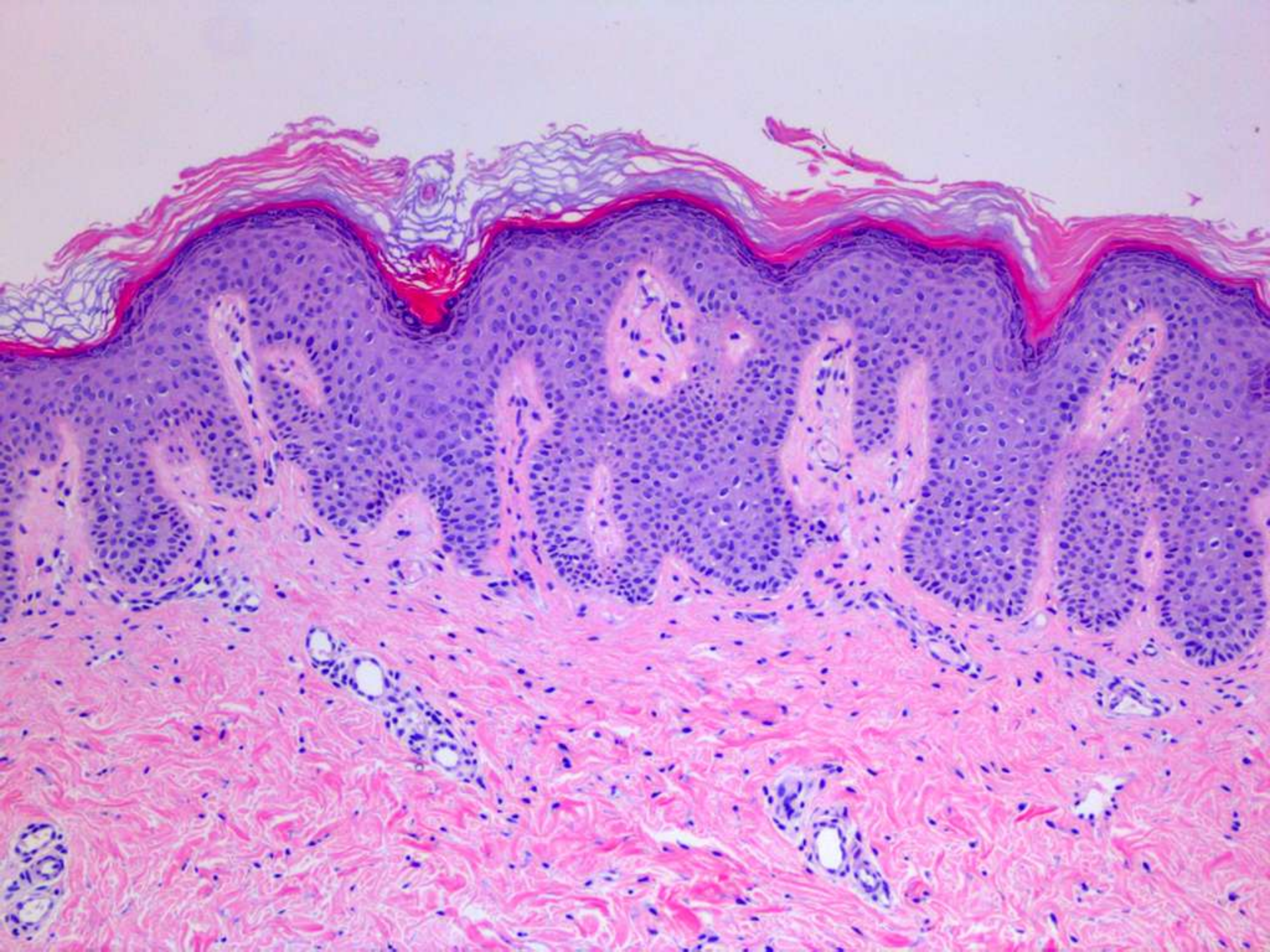
Patient	Age of onset	Sex	No of lesions	Distribution
1	Birth	M	1	Right leg
2	Birth	F	3	Neck, left thigh, left buttock
3	Birth	M	6	Right neck, left neck, right thigh, left thigh, right leg and right shoulder
4	Birth	F	7	Left cheek (2), neck, left shoulder, right arm, right thigh, and left ankle
5	Birth	F	11	Neck, abdomen (3), right axilla, right forearm (2), right thigh, left thigh, and left leg (2)

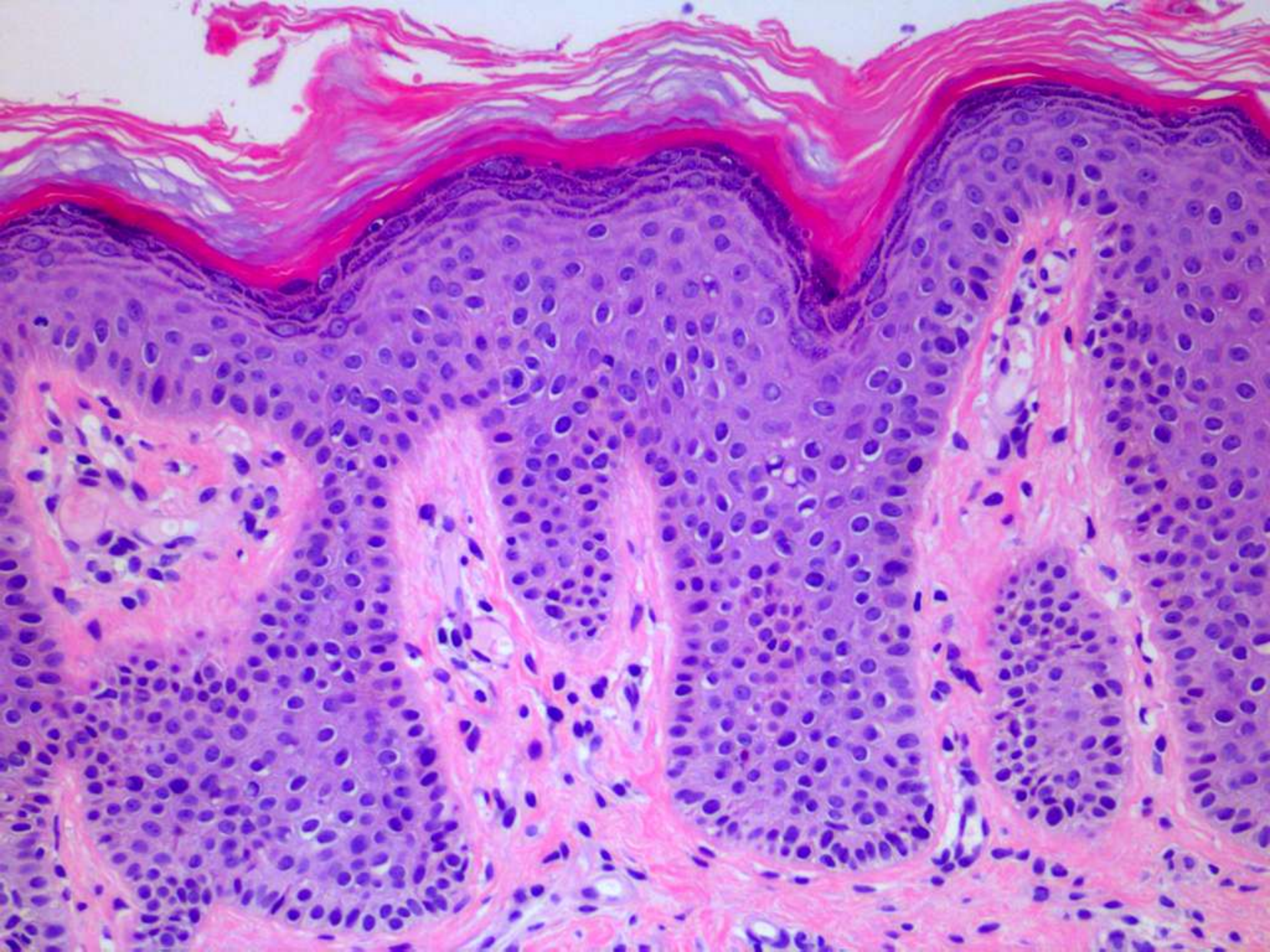


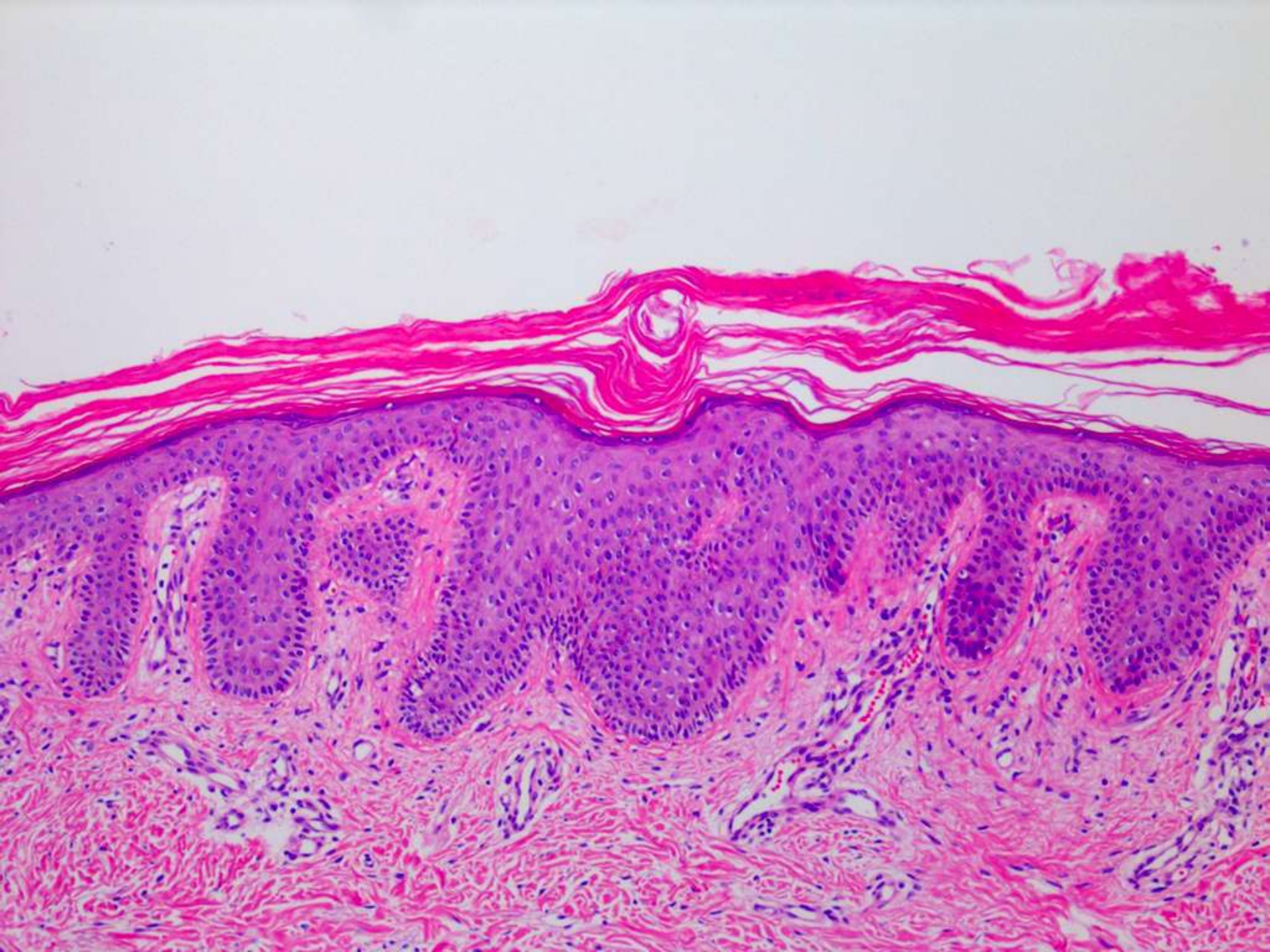


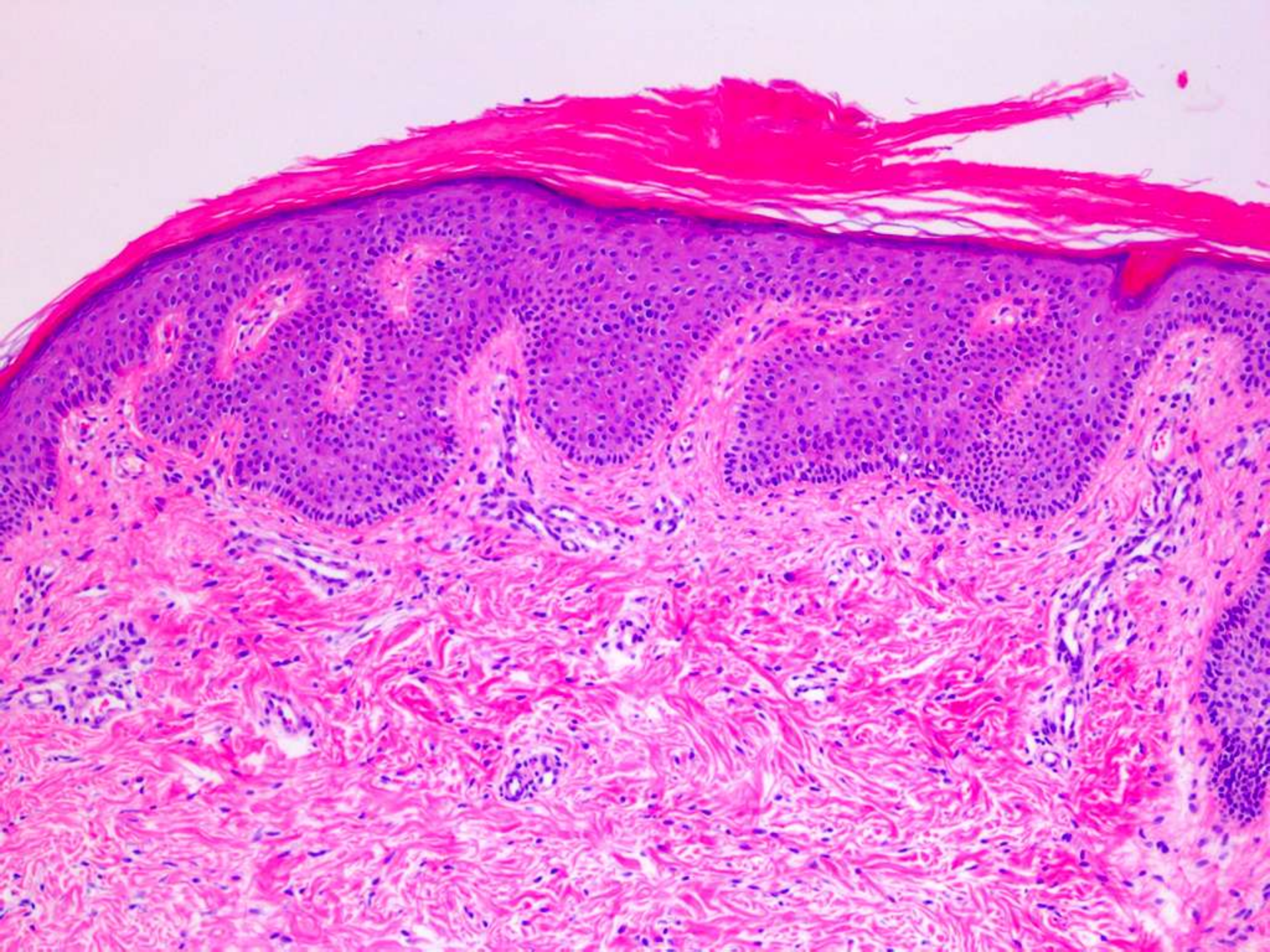
Histopatología

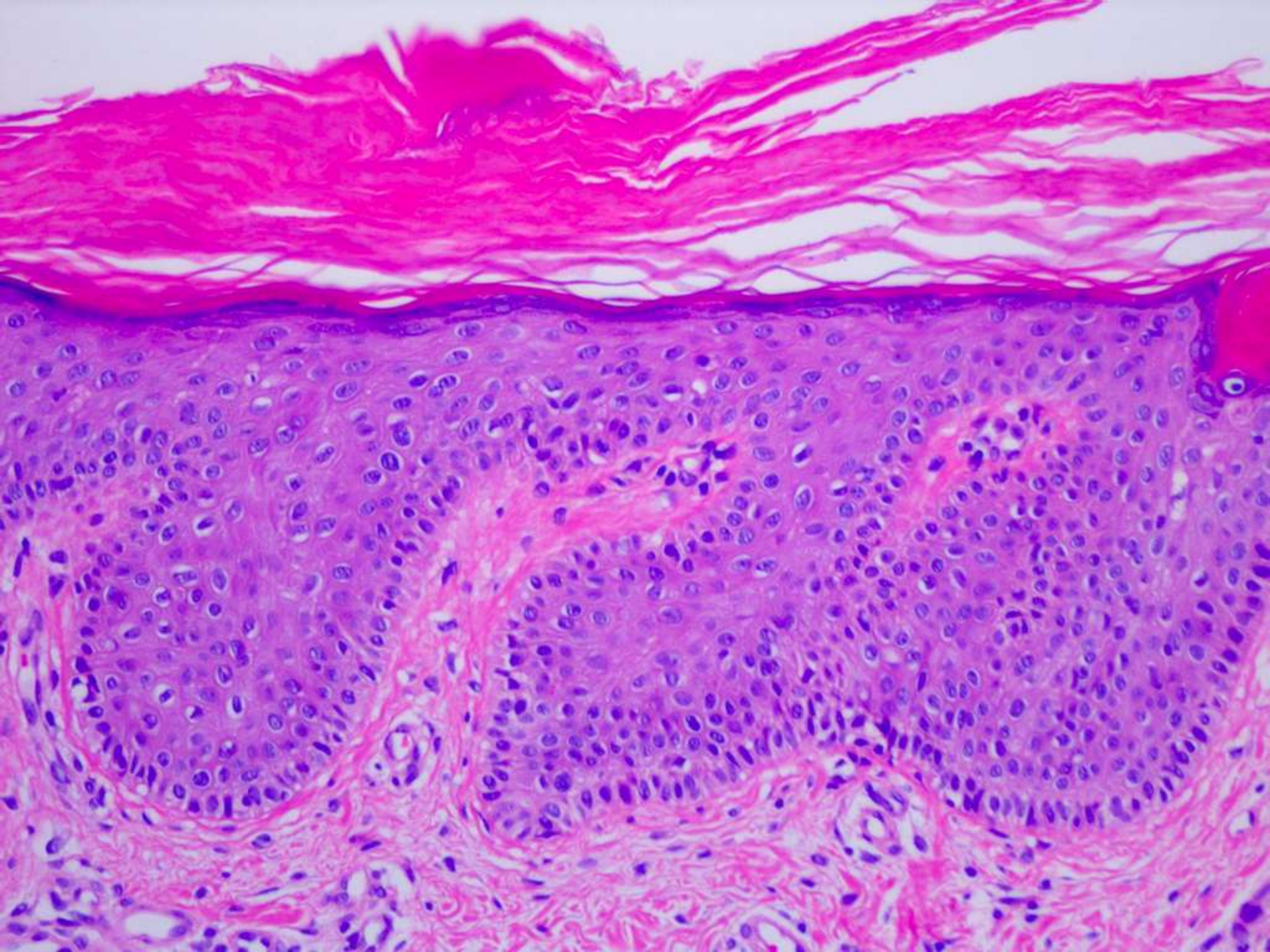
- Hiperqueratosis ortoqueratósica compacta, acantosis.
- Crestas interpapilares anchas y rectangulares
- Capa basal con llamativa empalizada de los núcleos
- Simula el patrón en horizonte ‘‘skyline’’ o en lápiz de ojos ‘‘eyeliner’’ descrito en la enfermedad de Bowen
- No cambios en la dermis

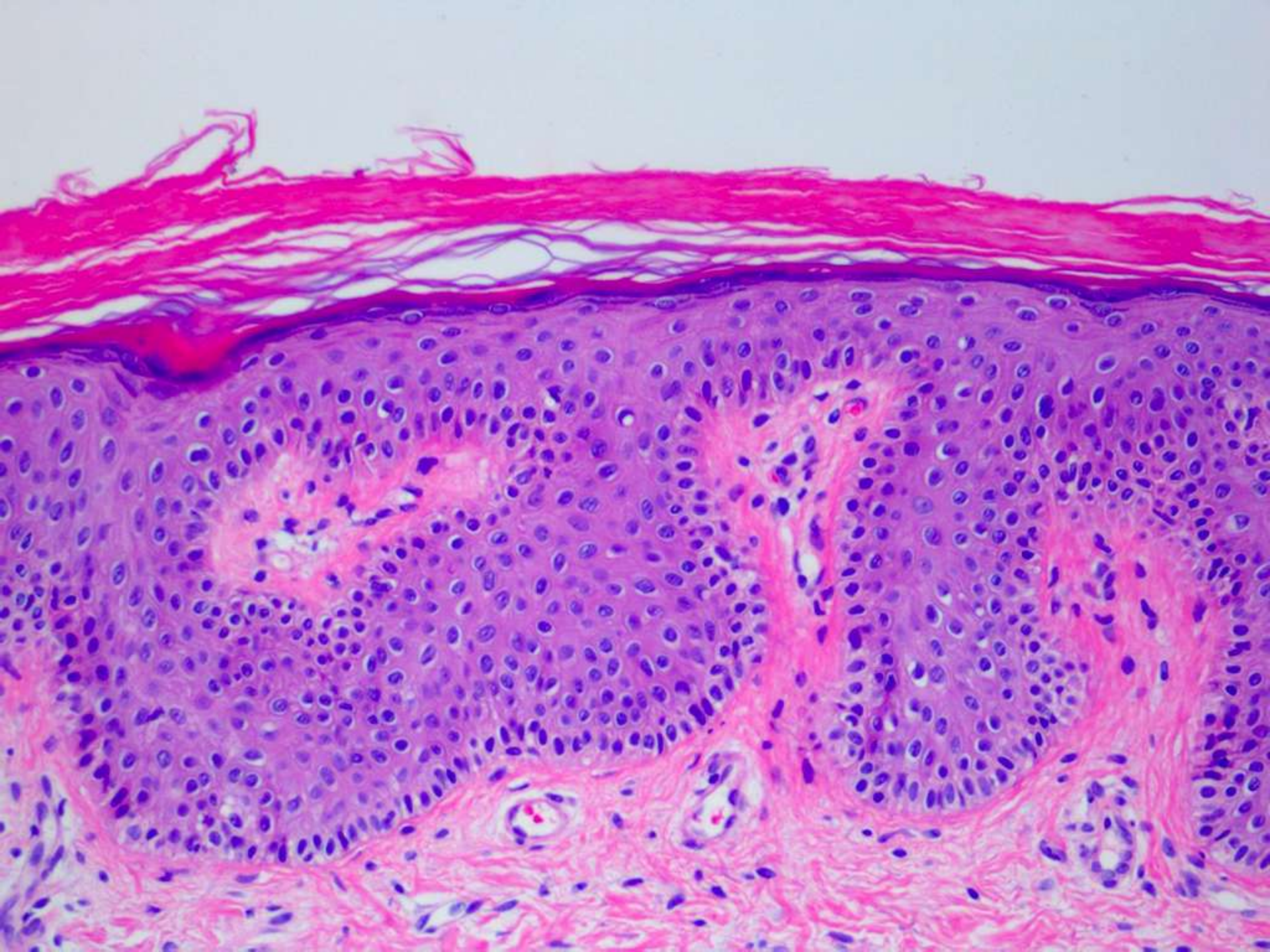












Estudios complementarios

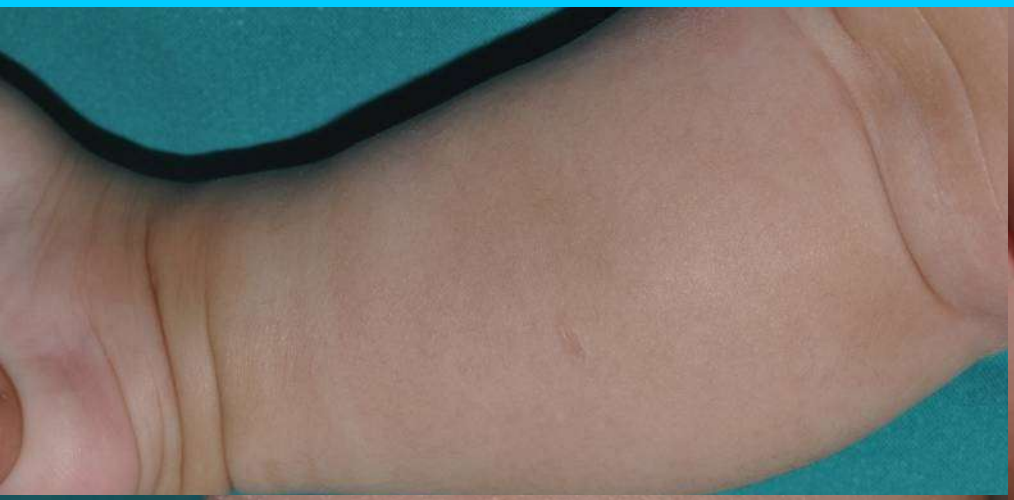
Mutaciones analizadas:

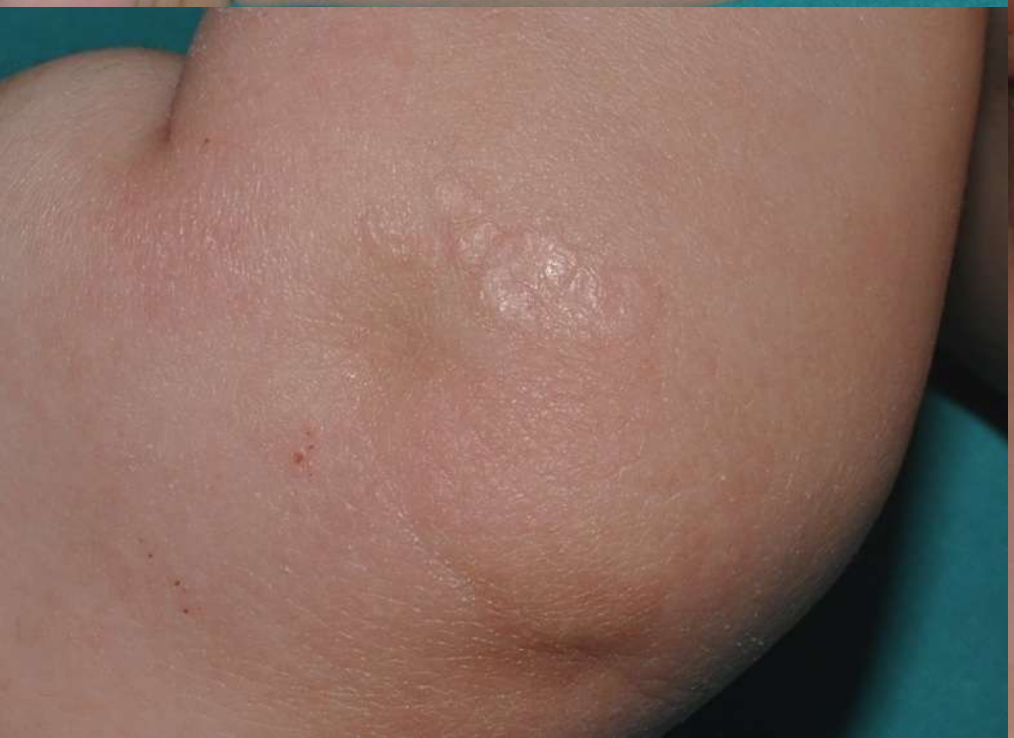
- FGFR3 hotspots mutations (R248C, S249C, G372C, S373C, Y375C, G382R, A393E, K652E, K652M, K652Q, K652T)
- PIK3CA hotspots mutations (E542K, E545G, E545K, E545Q, H1047L, H1047R)

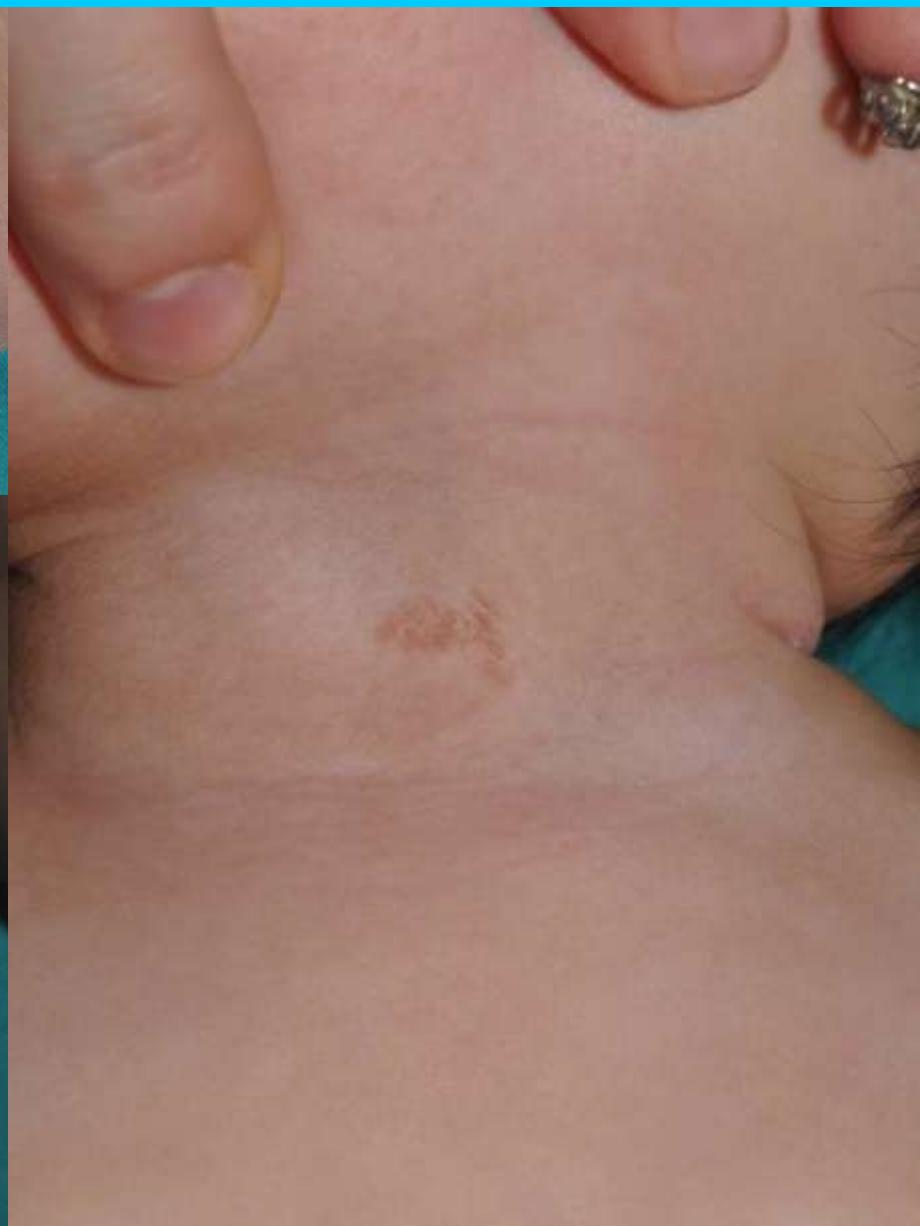
Se descartan todas las mutaciones en FGFR3 y PIK3CA que originan nevus epidérmicos

PENS es una nueva entidad

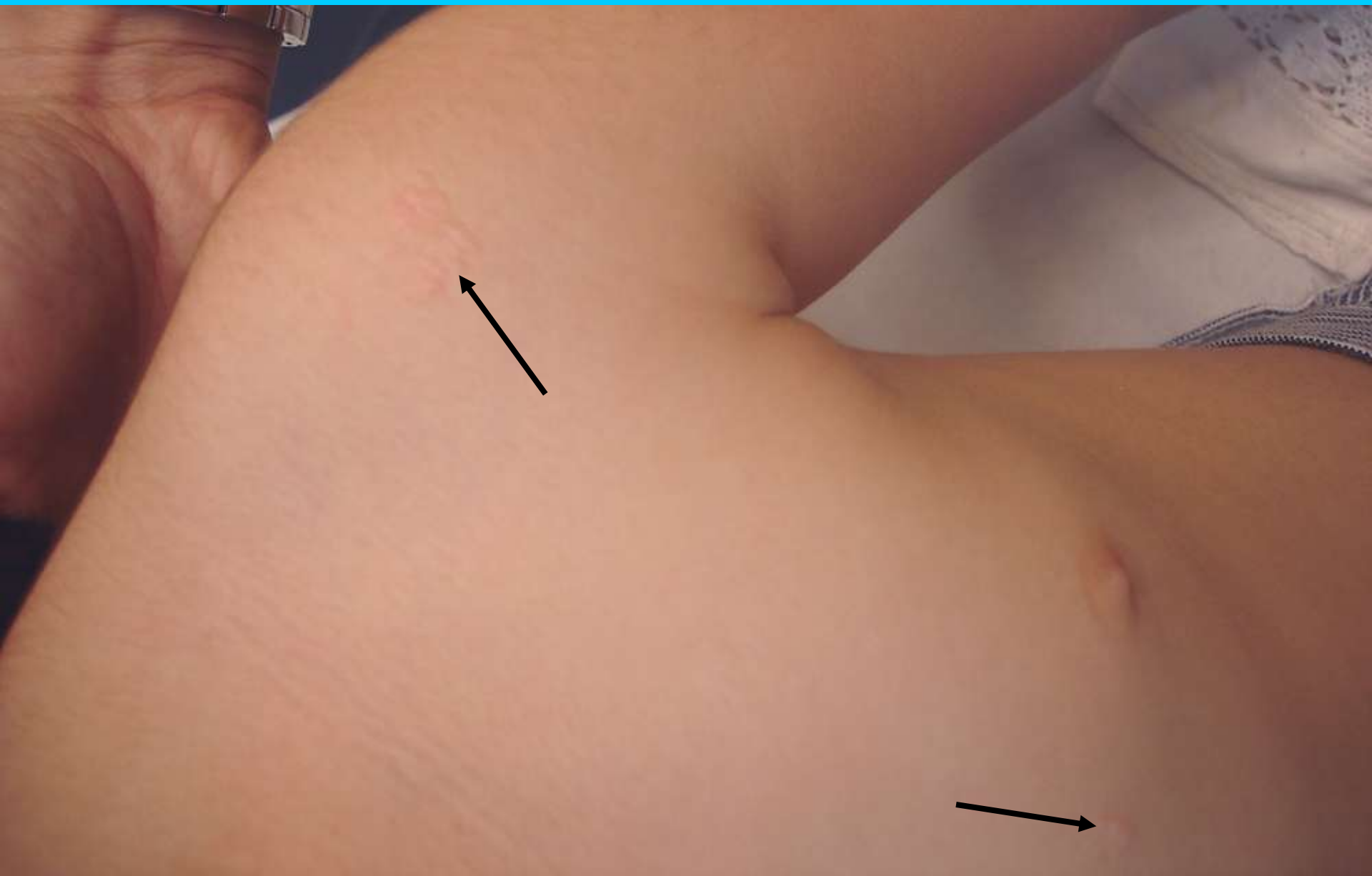
Seguimiento del síndrome

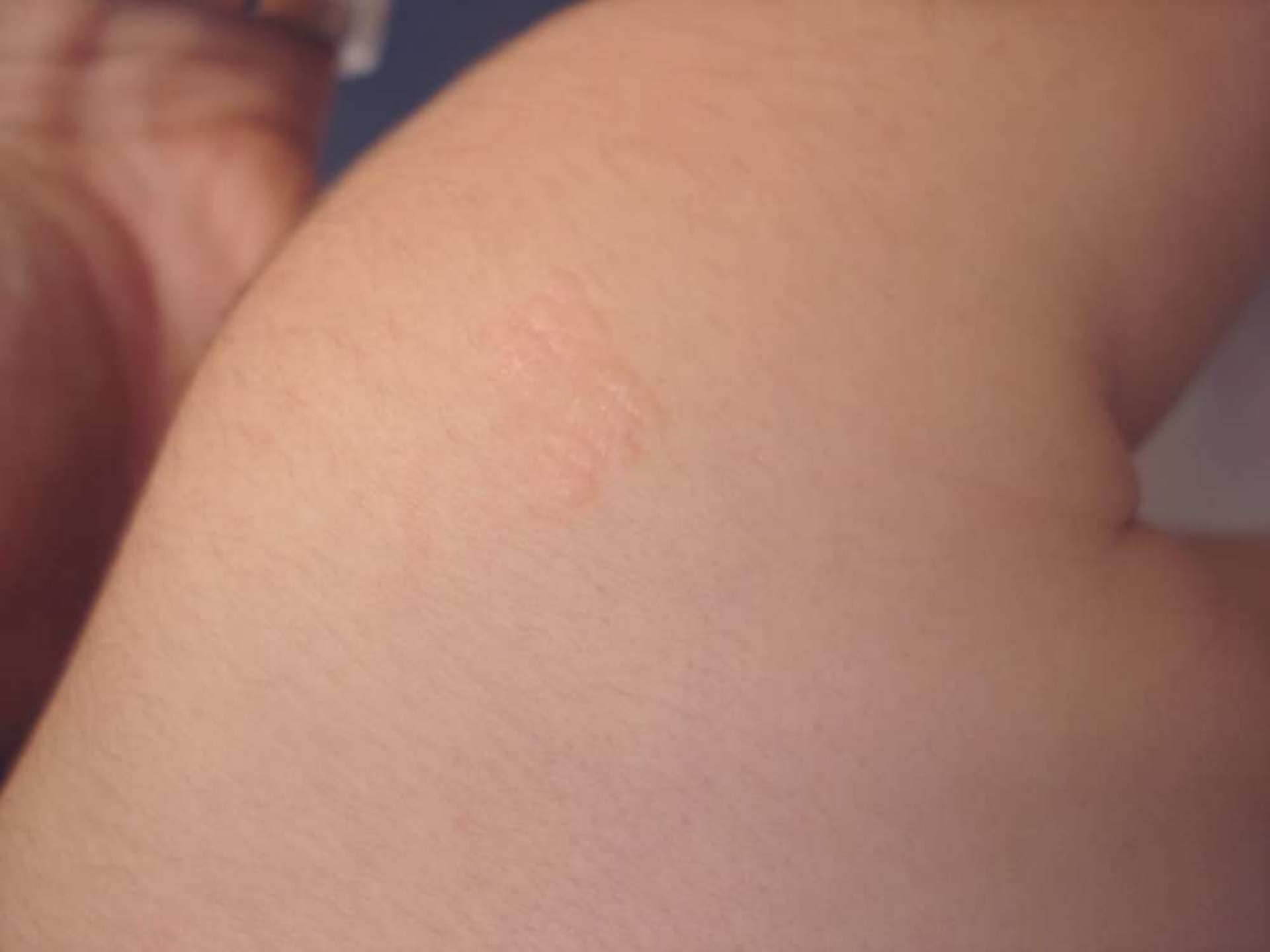


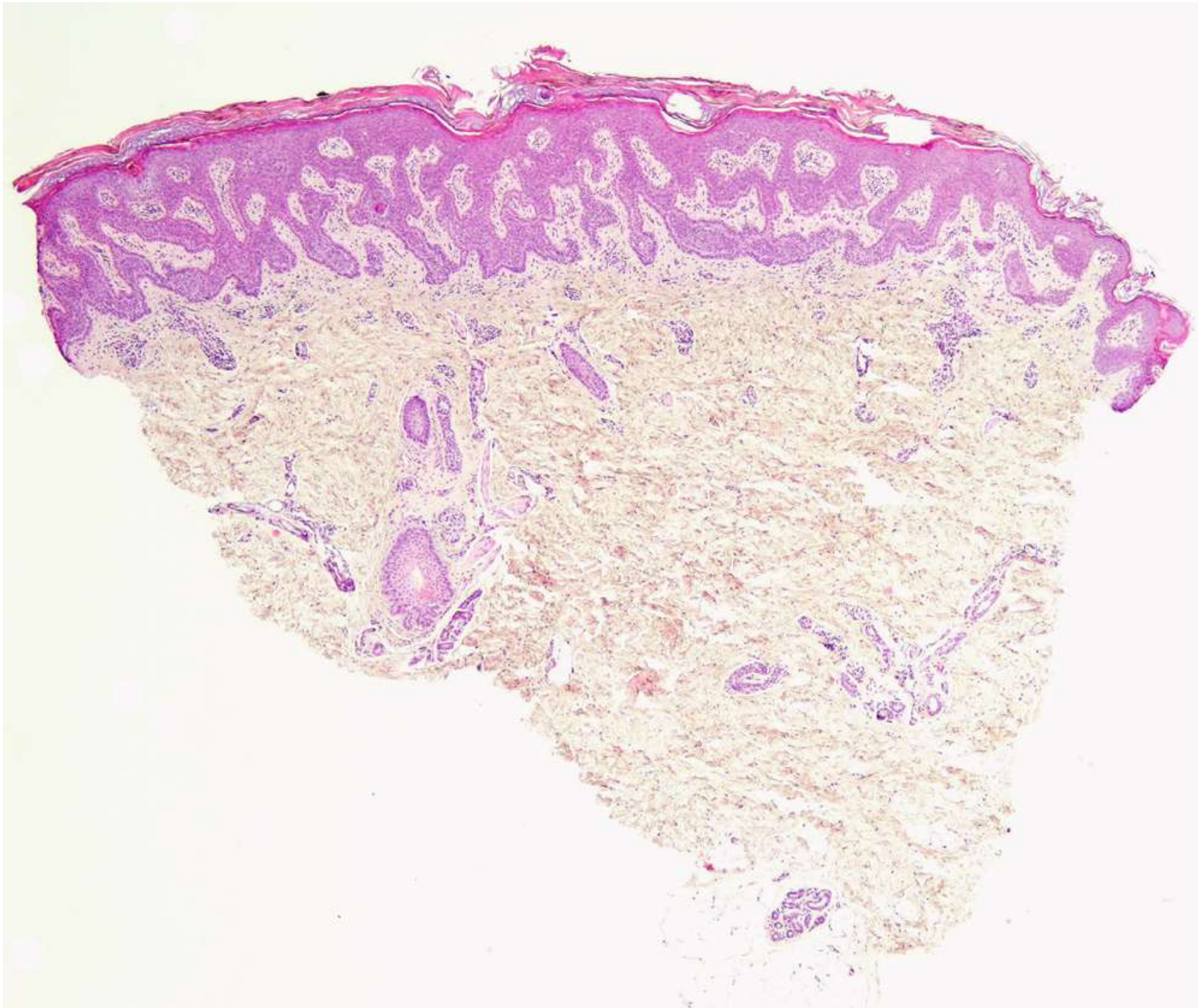


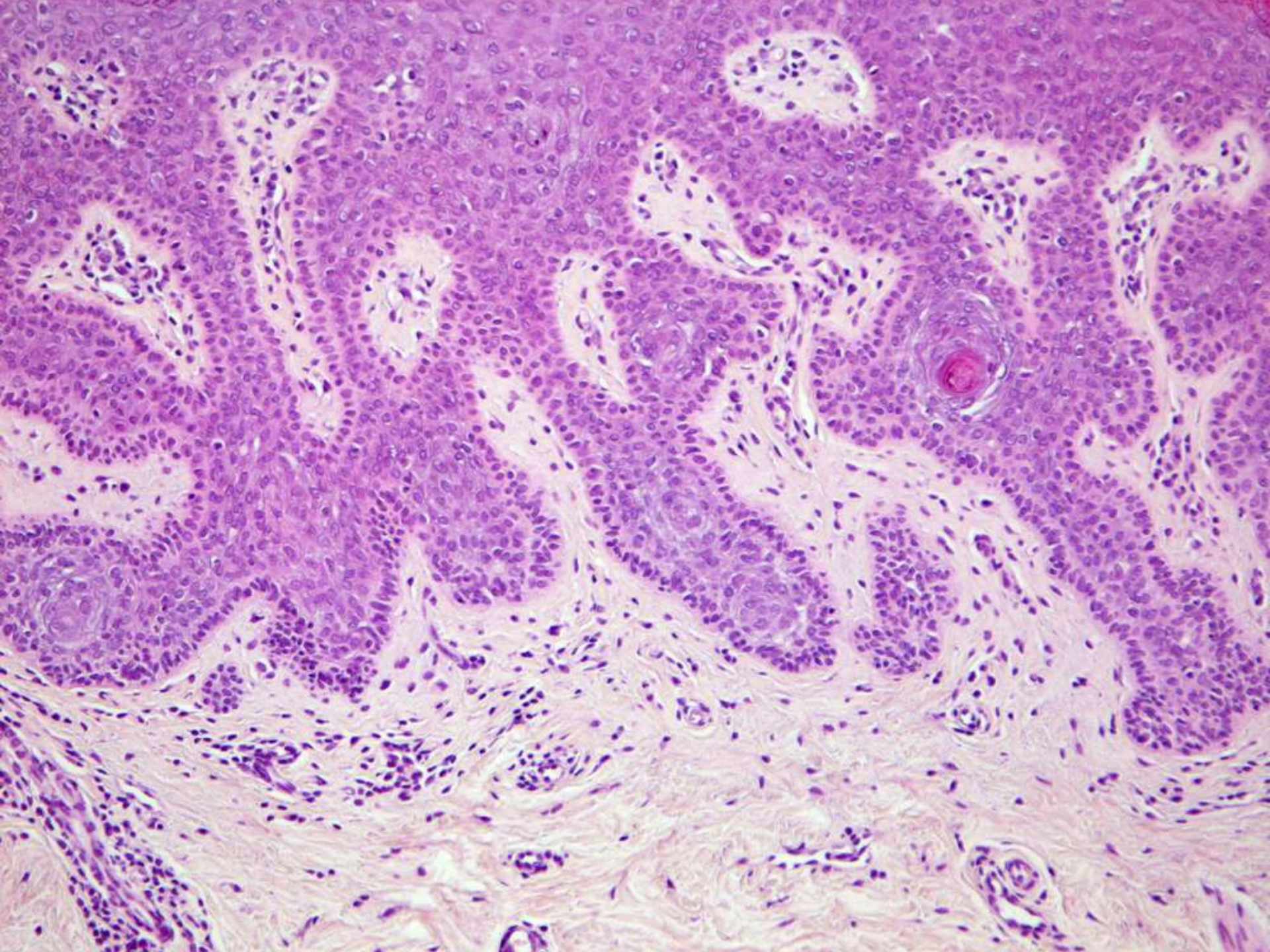


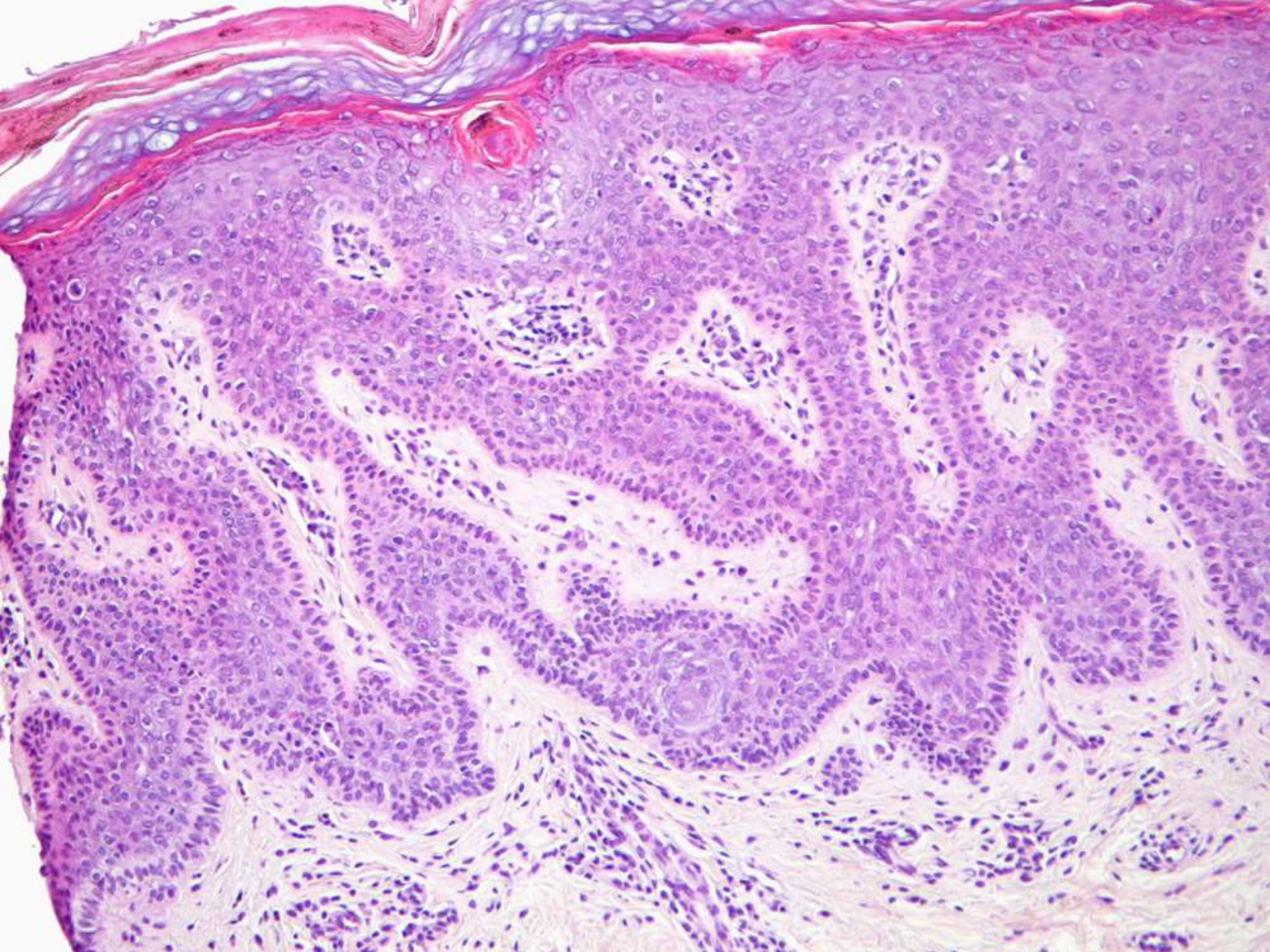
Dr. Sergio González (Chile)

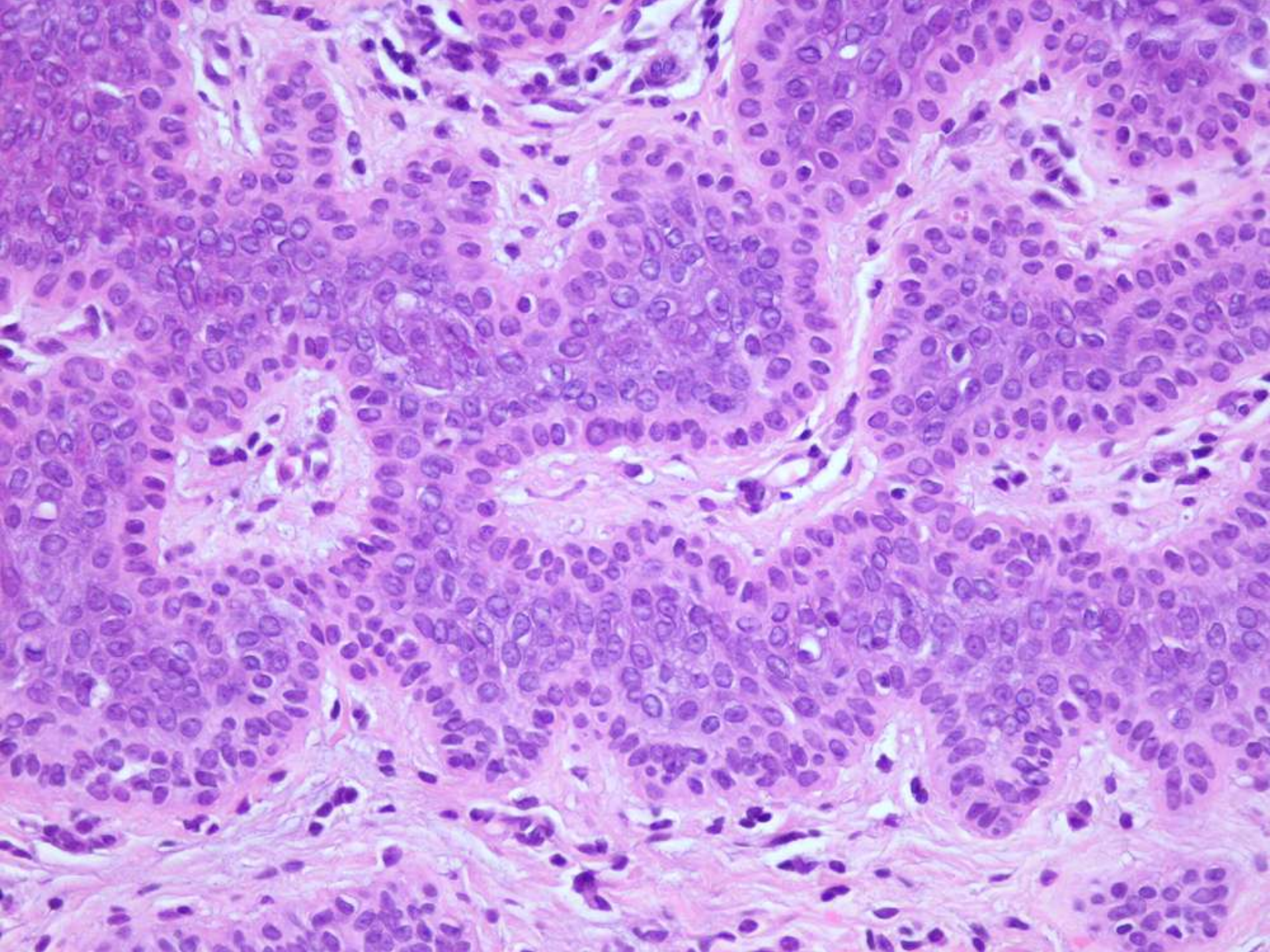












Folliculocystic and collagen hamartoma of tuberous sclerosis complex

Antonio Torrelo, MD,[a] Smail Hadj-Rabia, MD,[b] Isabel Colmenero, MD,[c] Robert Piston, MD,[d] Virginia P. Sybert, MD,[d] Helena Hilari-Carbonell, MD,[e] Angela Hernández-Martín, MD,[a] Joan C. Ferreres, MD,[f] Sergio Vañó-Galván, MD,[a] Daniel Azorín, MD,[c] Javier Enríquez de Salamanca, MD,[g] Luis Requena, MD,[h] Christine Bodemer, MD,[b] Rudolf Happle, MD,[i] Vicente García-Patos, MD,[e] and Sylvie Fraitag, MD[j]

Madrid and Barcelona, Spain; Paris, France; Seattle Washington; and Marburg, Germany

Background: Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by tumors and hamartomas in several organs including the skin.

Objective: We sought to describe a new type of complex hamartoma in patients with TSC.

Methods: This was a retrospective clinical and histopathologic evaluation of 6 cases.

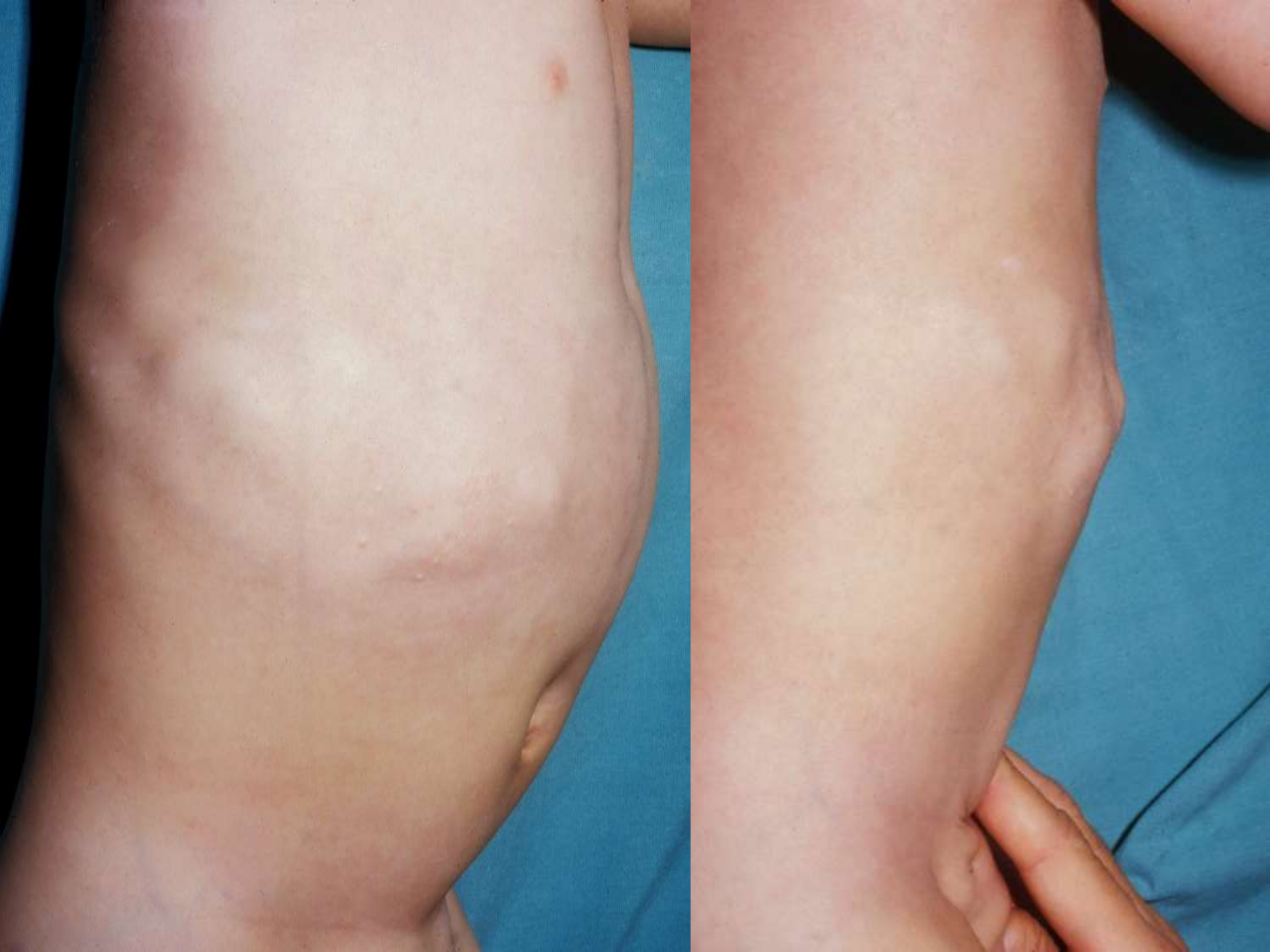
Results: The skin lesions consisted of large, painless, infiltrated plaques that were first noticed at birth or during early infancy on the abdomen, thigh, back, or scalp. In time, the plaques became studded with numerous follicular comedo-like openings and cysts containing and draining a keratinous or purulent material. The main histopathologic features were: abundant collagen deposition in the dermis and extending into the underlying fat; concentric, perifollicular fibrosis surrounding hair follicles; and comedones and keratin-containing cysts lined by infundibular epithelium, some of which were ruptured with secondary granulomatous reaction. Five of the 6 patients had a clinical diagnosis of TSC.

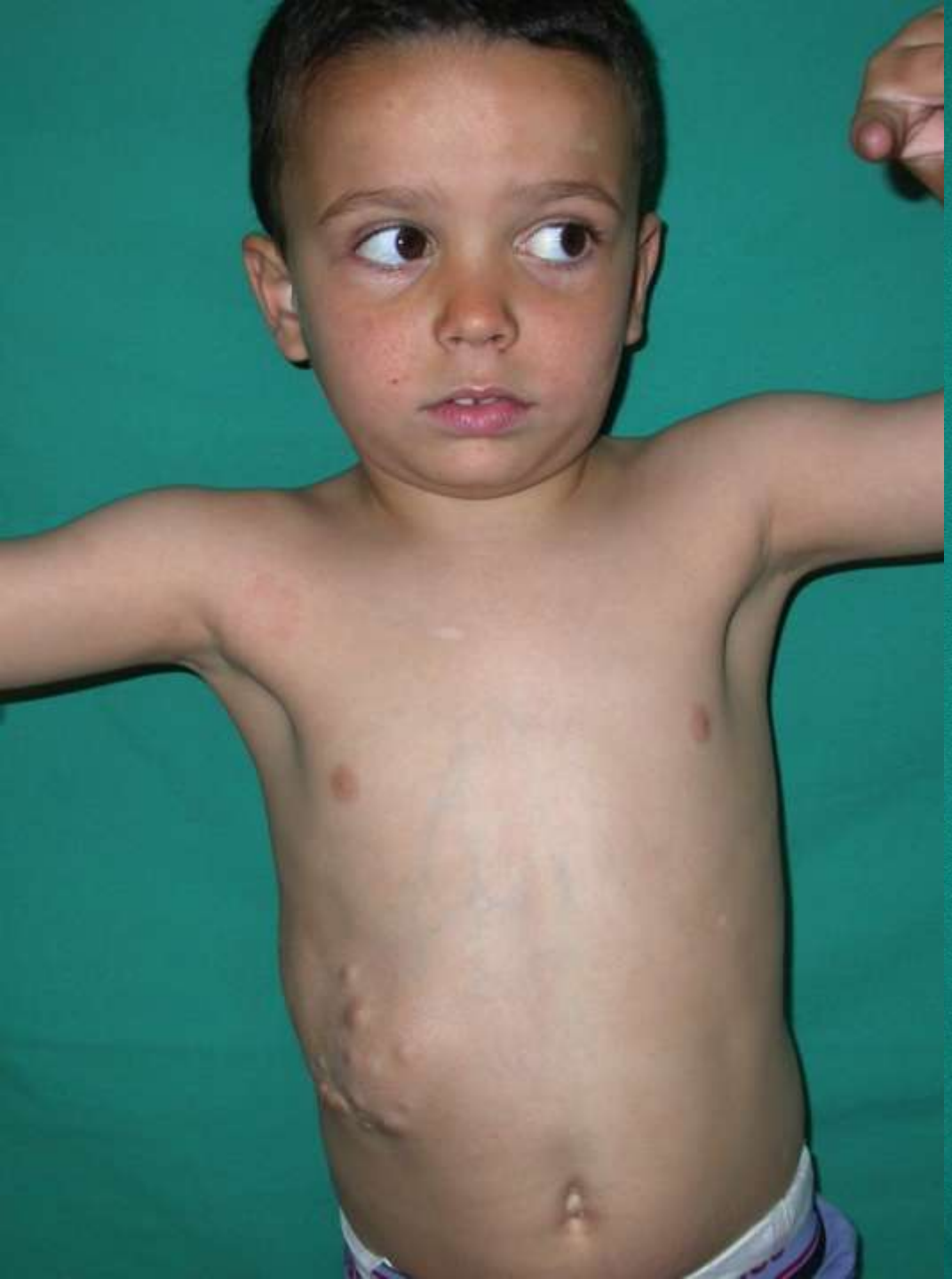
Limitations: Genetic testing was performed in only one patient.

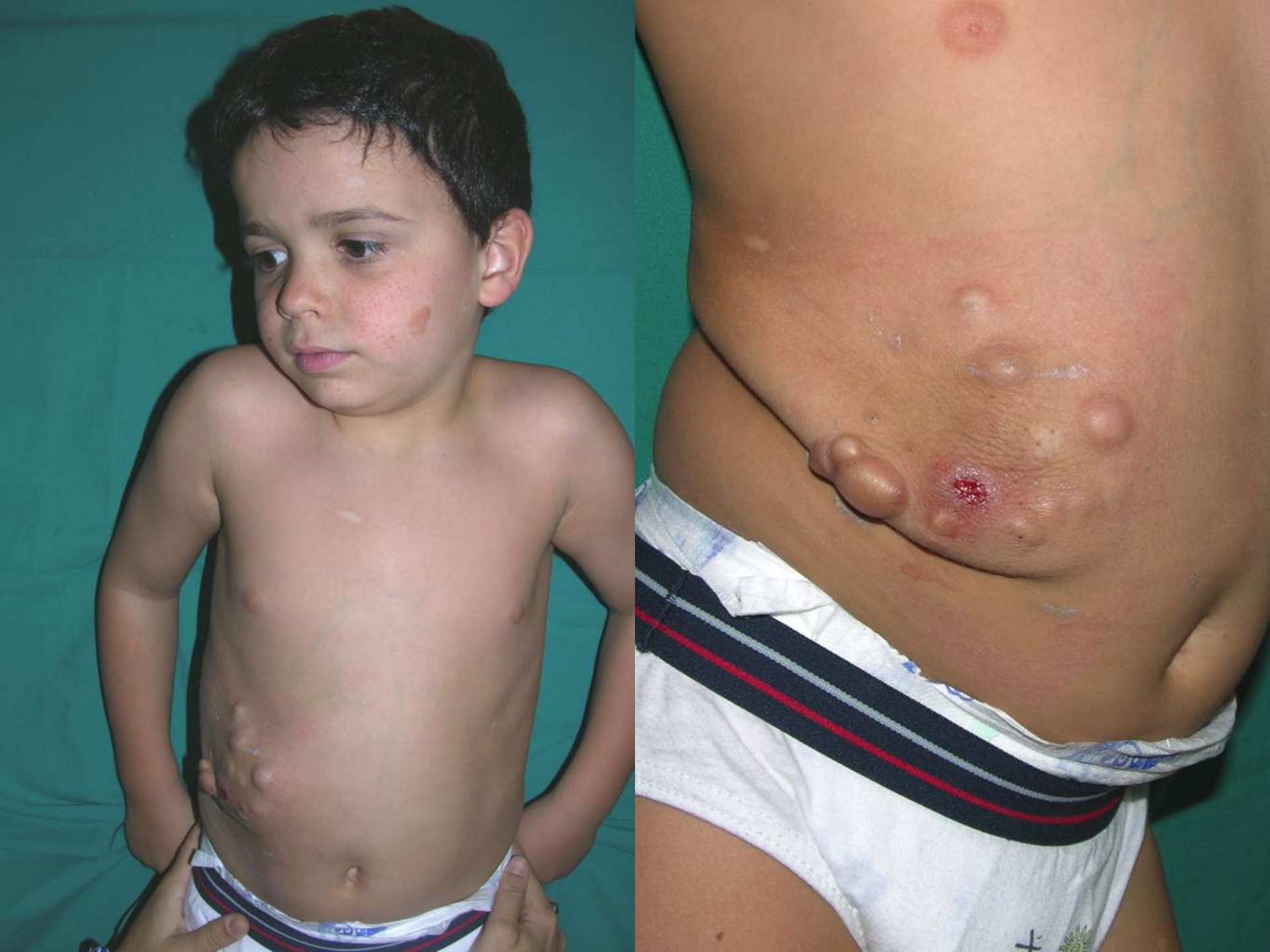
Conclusion: This distinctive folliculocystic and collagen hamartoma has not been recognized previously in association with TSC. (J Am Acad Dermatol 10.1016/j.jaad.2011.04.002.)

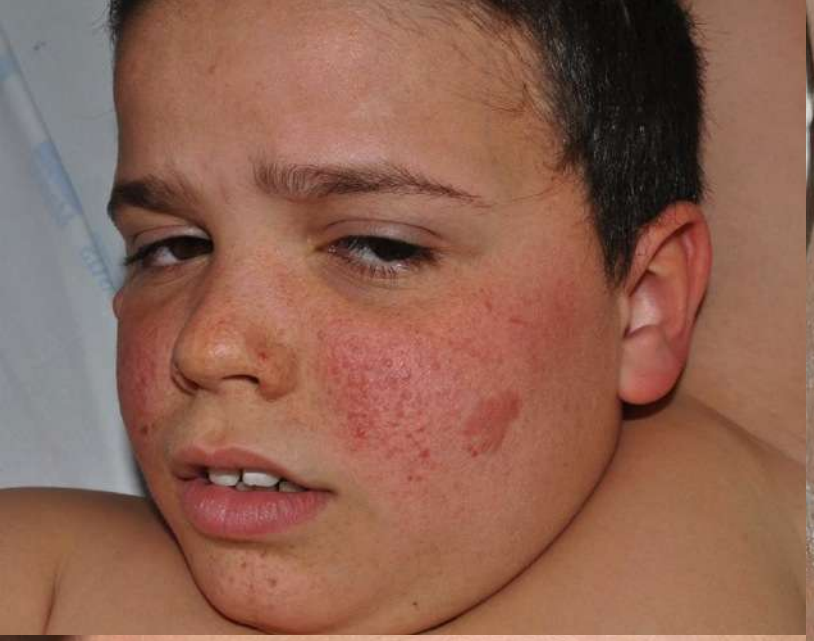
Primer caso

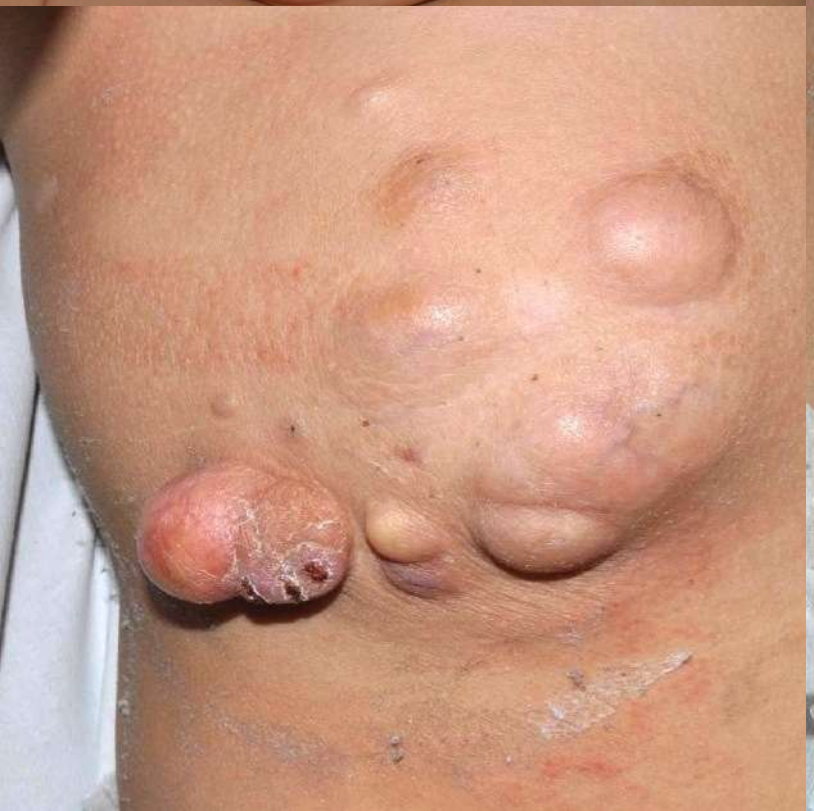
- Niño con esclerosis tuberosa
- Gran lesión en el abdomen desde muy pequeño
- Formación de comedones
- Grandes quistes infundibulares, que drenan y supuran

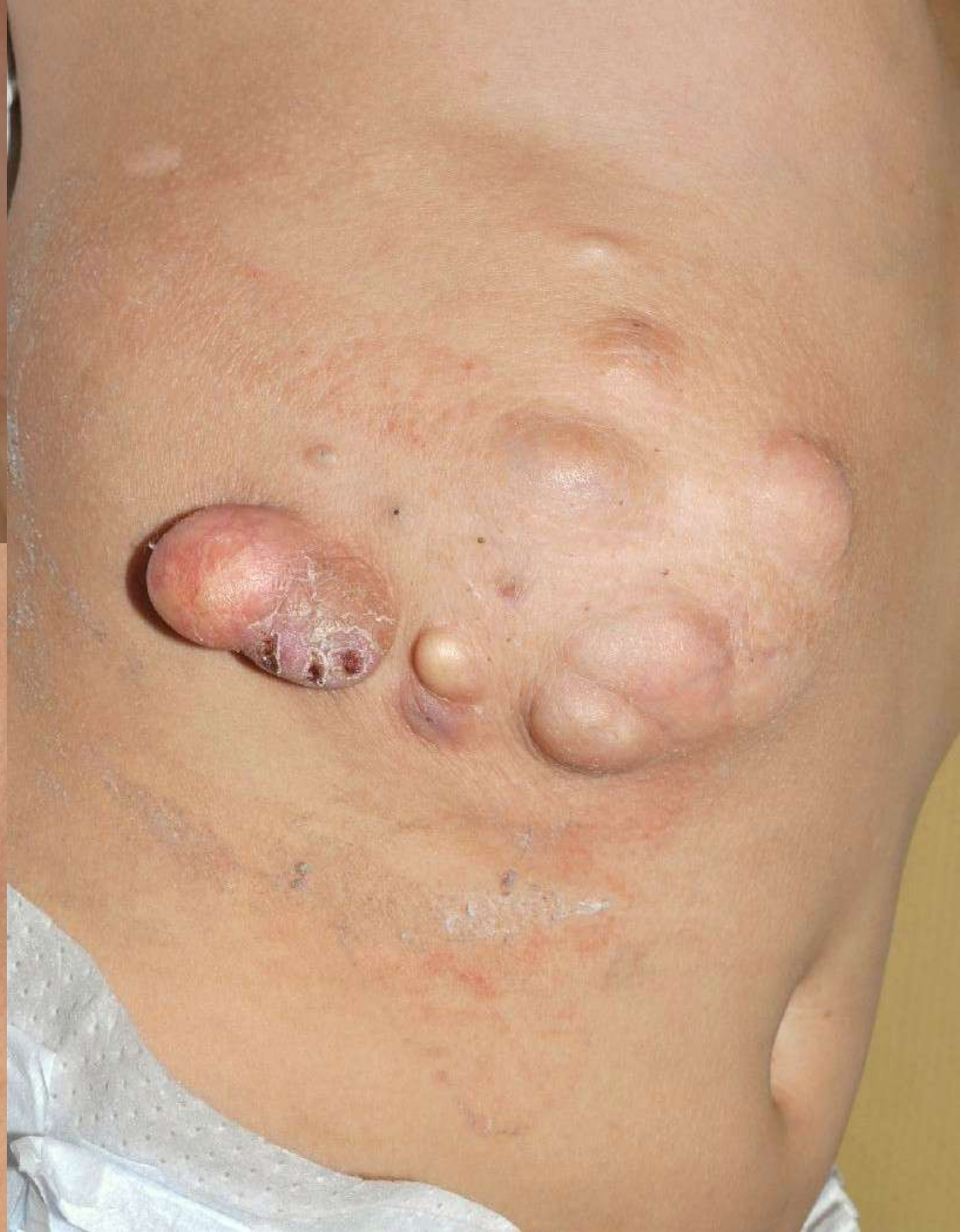






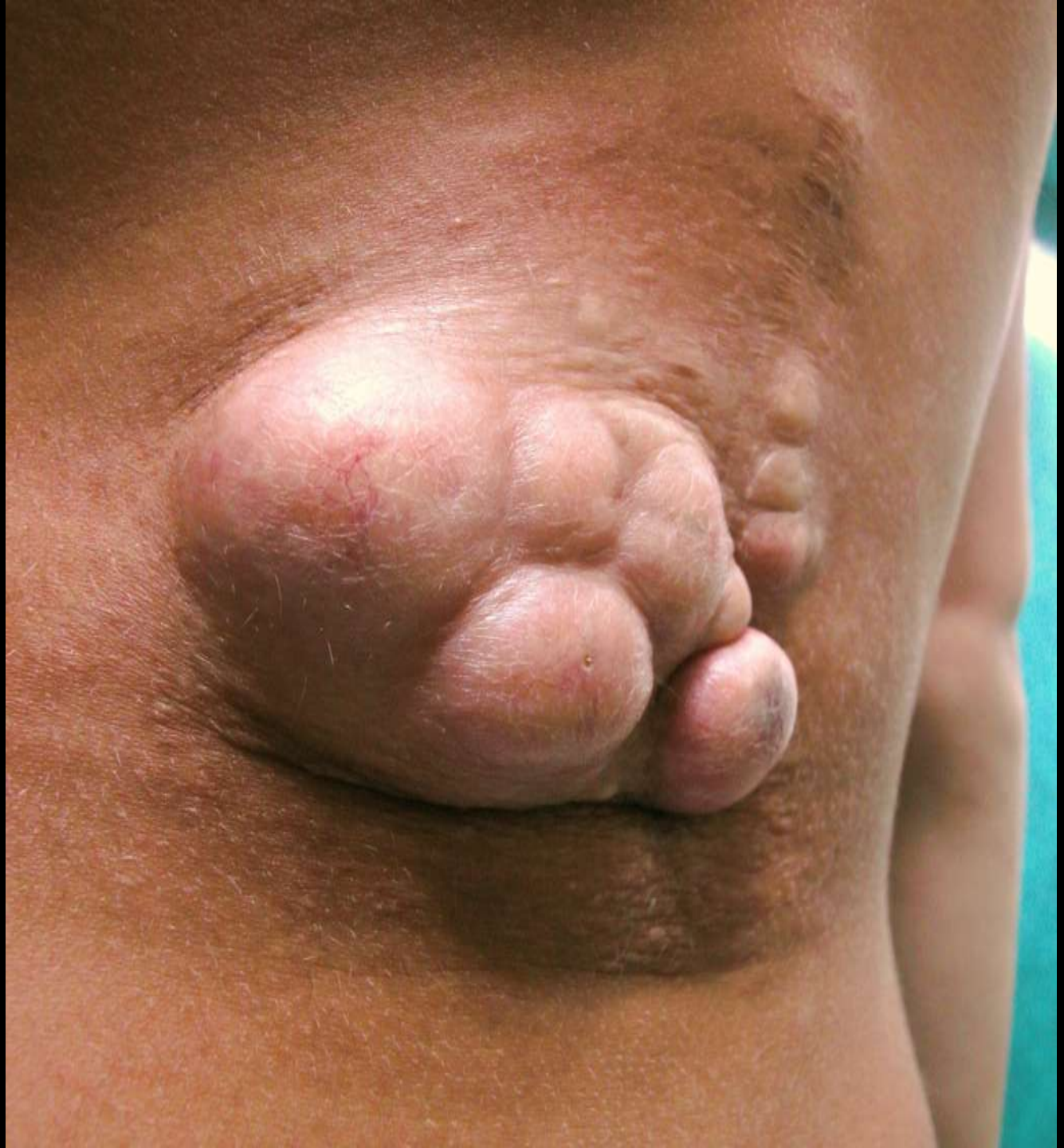


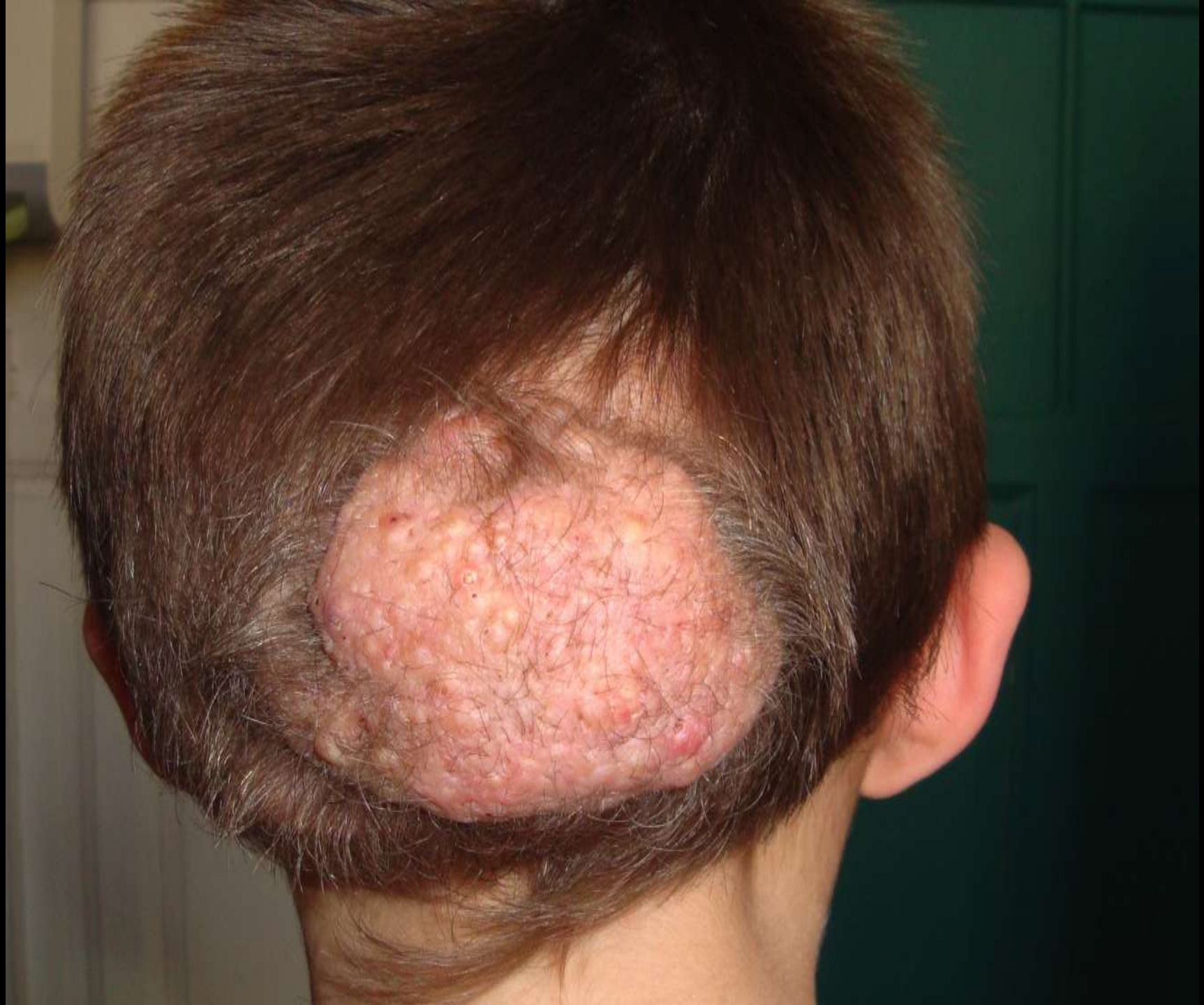


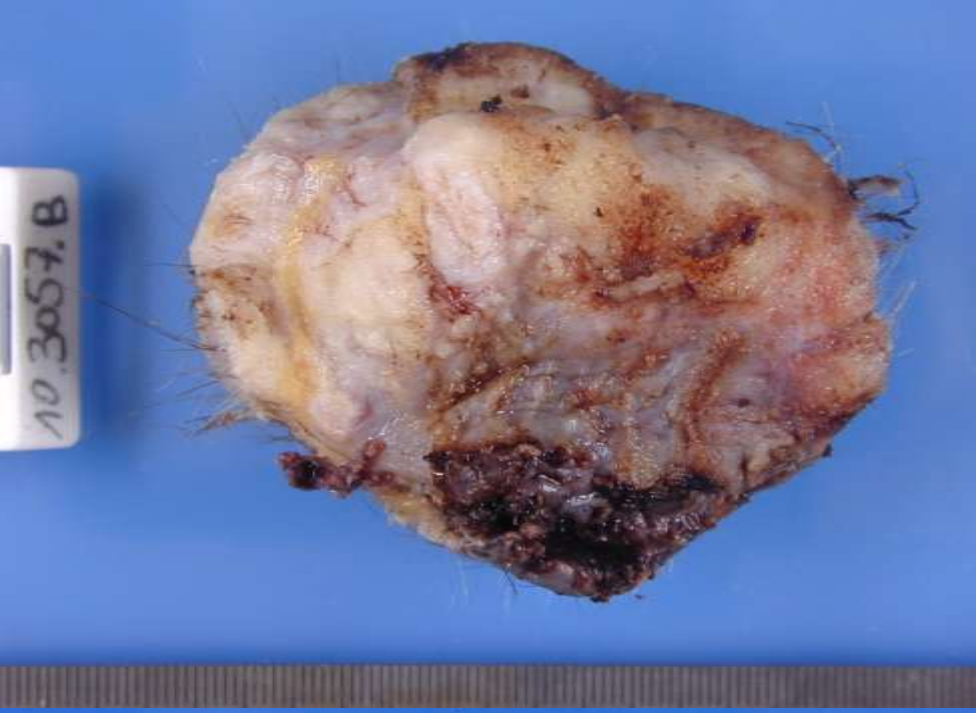


Resumen de los casos clínicos

Patient	Sex	Age of onset	Location	Illness
1	M	Early infancy	Abdomen	Definite TS
2	M	Birth	Posterior right thigh	None
3	M	Birth	Back	Definite TS
4	M	Birth	Jaw, back	Definite TS
5	M	Birth	Scalp	Definite TS
6	M	Birth	Scalp	Definite TS



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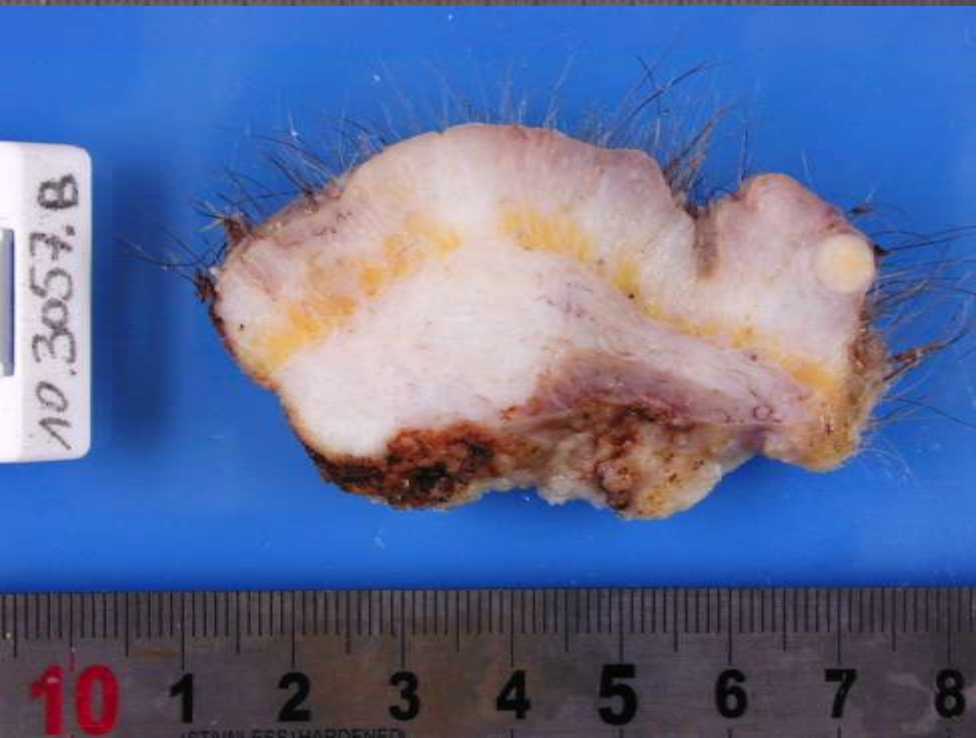
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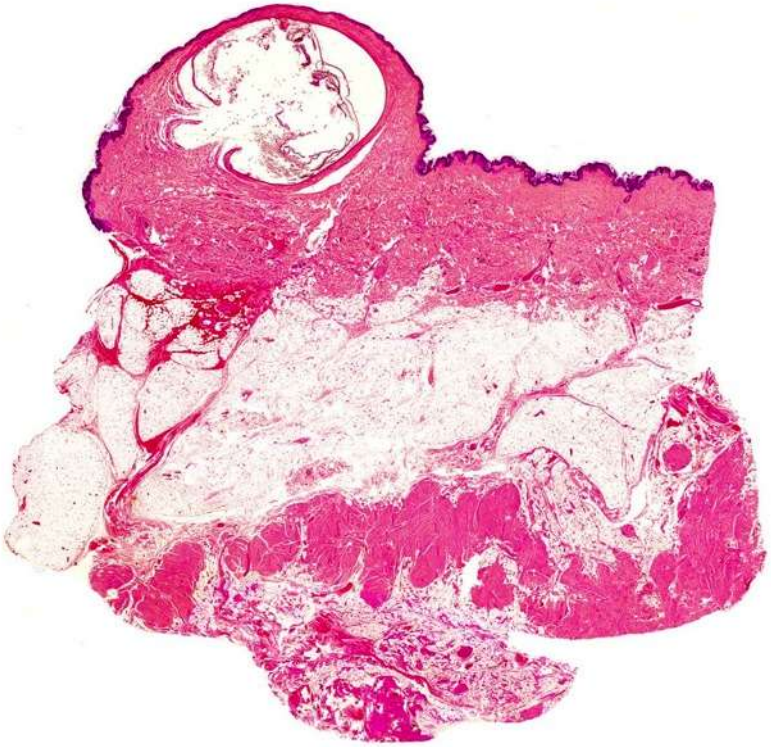
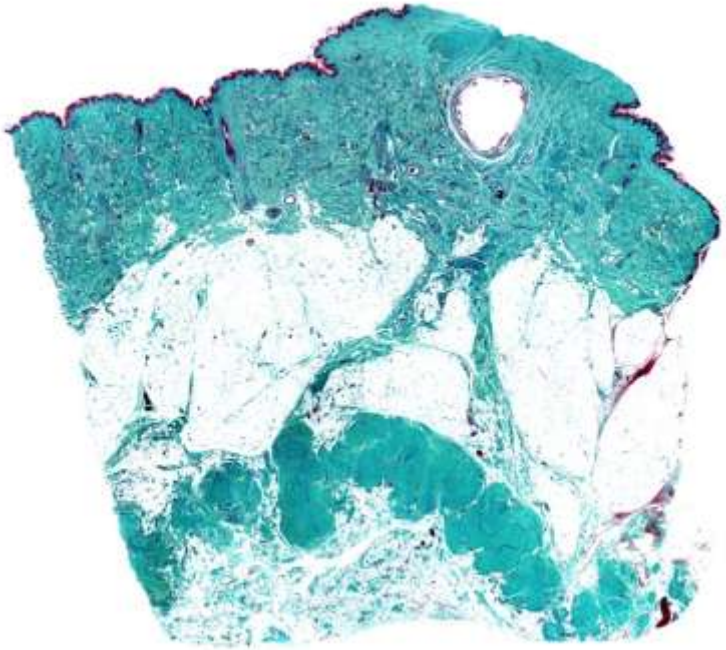
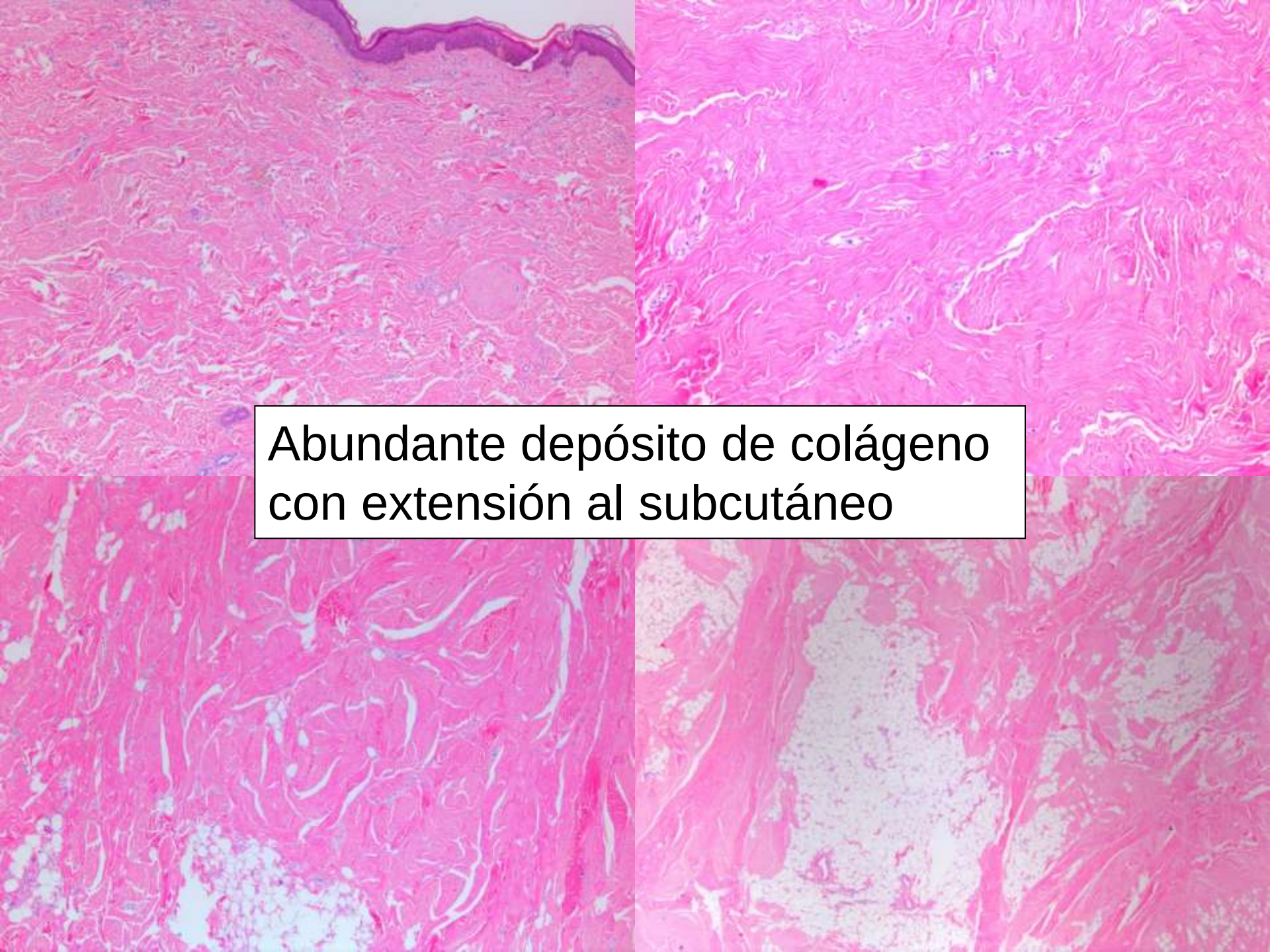
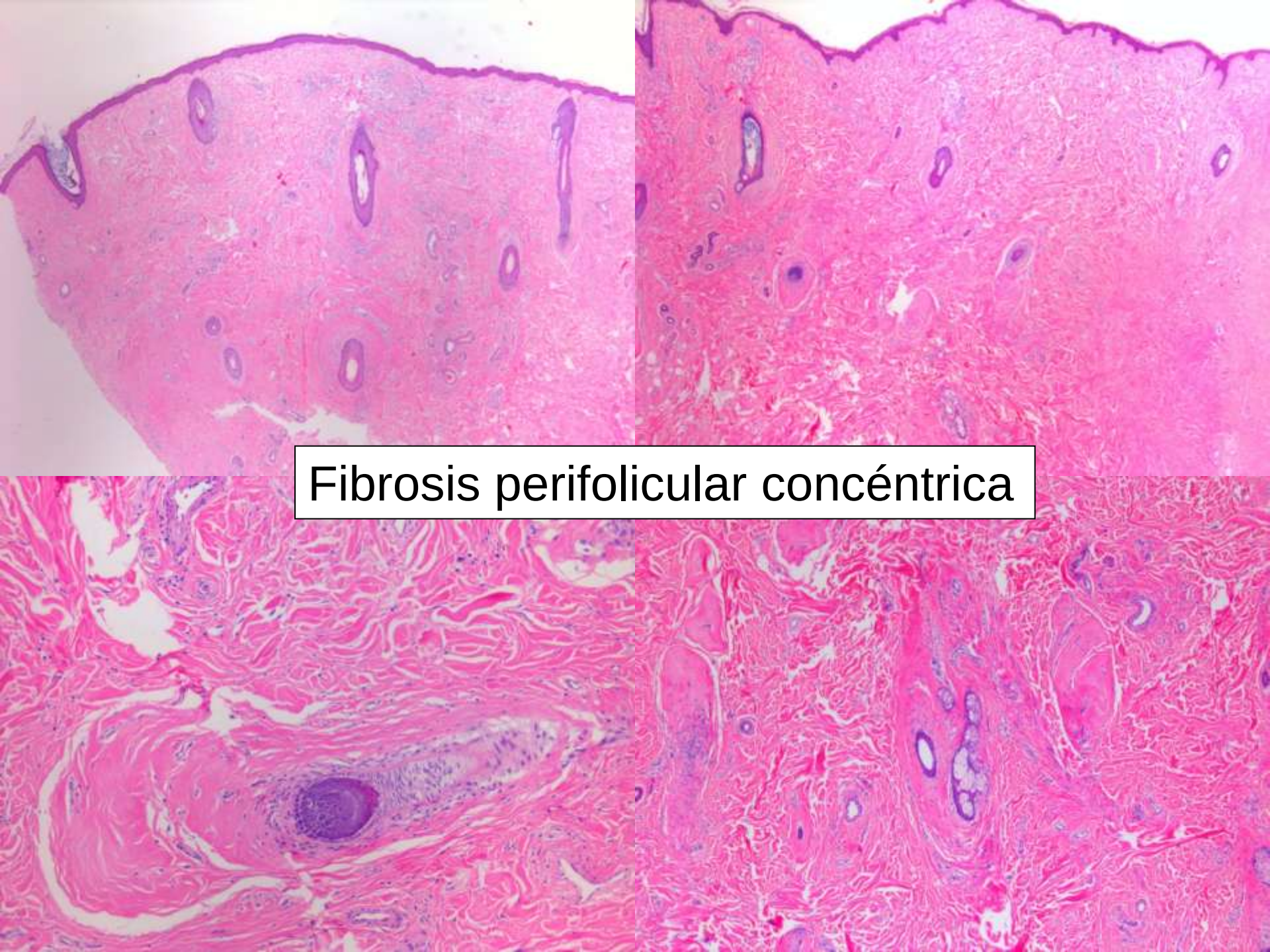
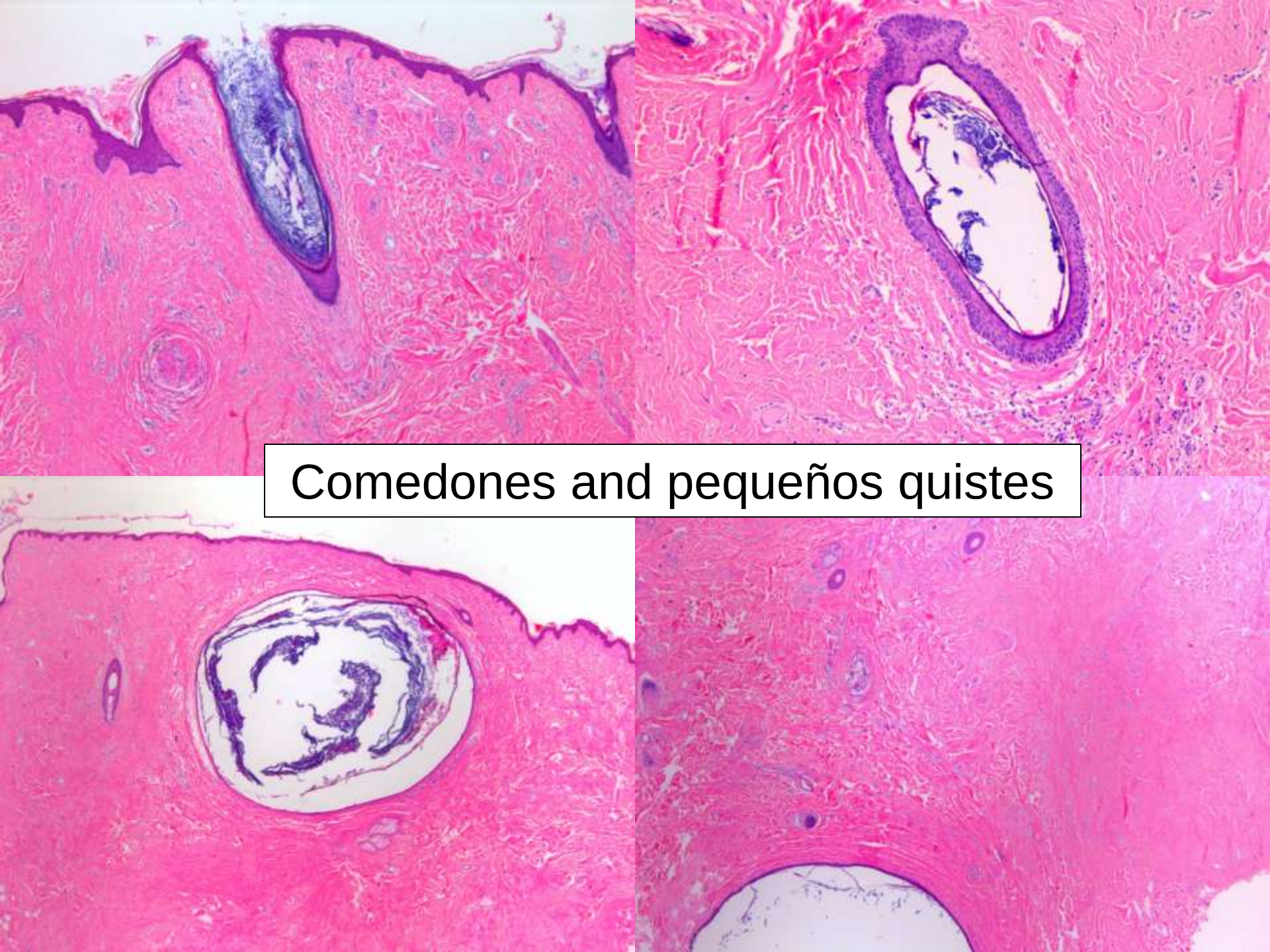




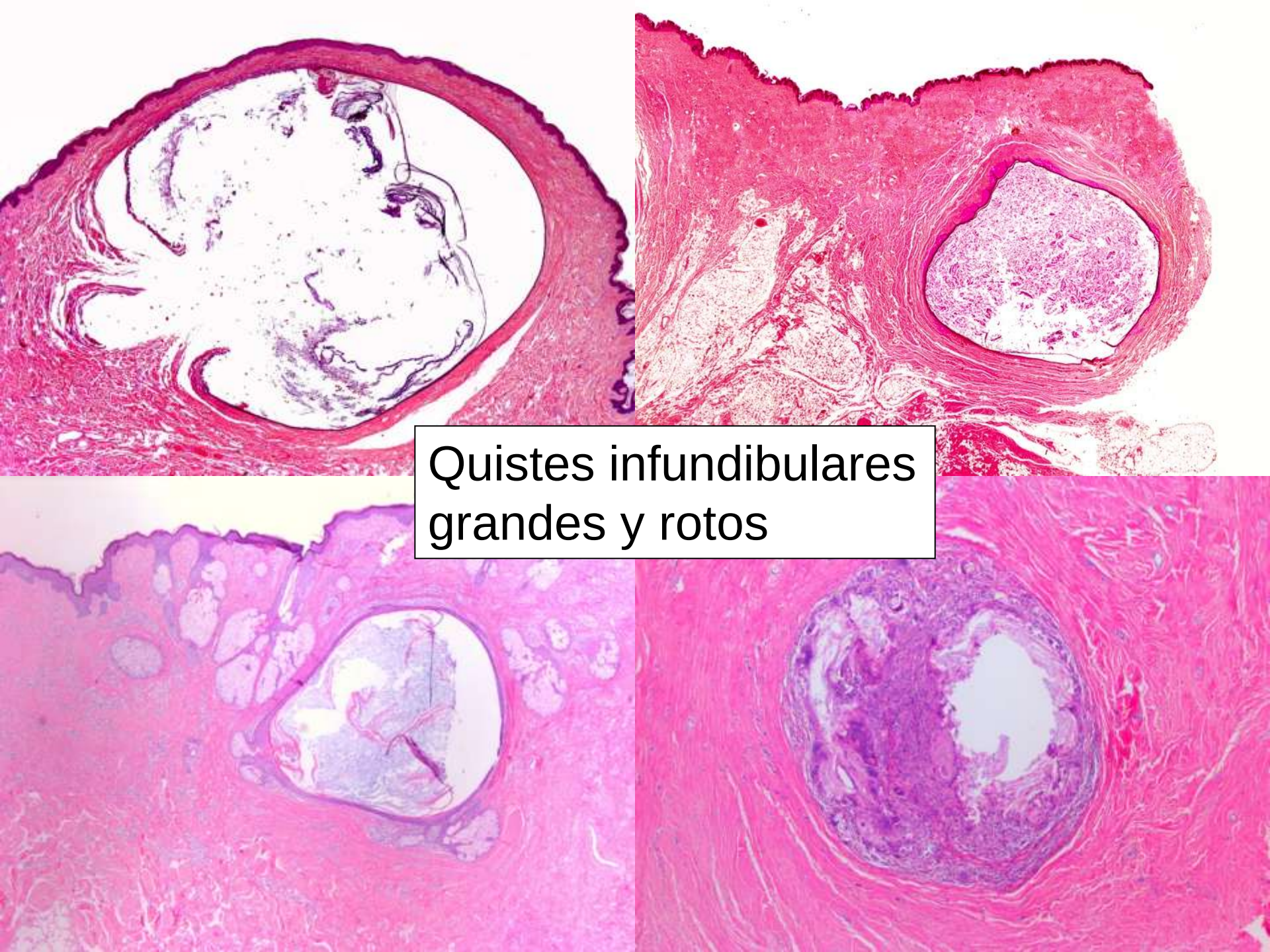


Abundante depósito de colágeno con extensión al subcutáneo


Fibrosis perifolicular concéntrica



Comedones and pequeños quistes



Quistes infundibulares grandes y rotos

Diagnóstico diferencial: otros nevus de colágeno

- Colagenoma familiar
- Nevus colágeno aislado
- Nevus colágeno gigante
- Placa chagrín / frontal

Un ‘nuevo’ tipo de hamartoma colágeno y foliculoquístico

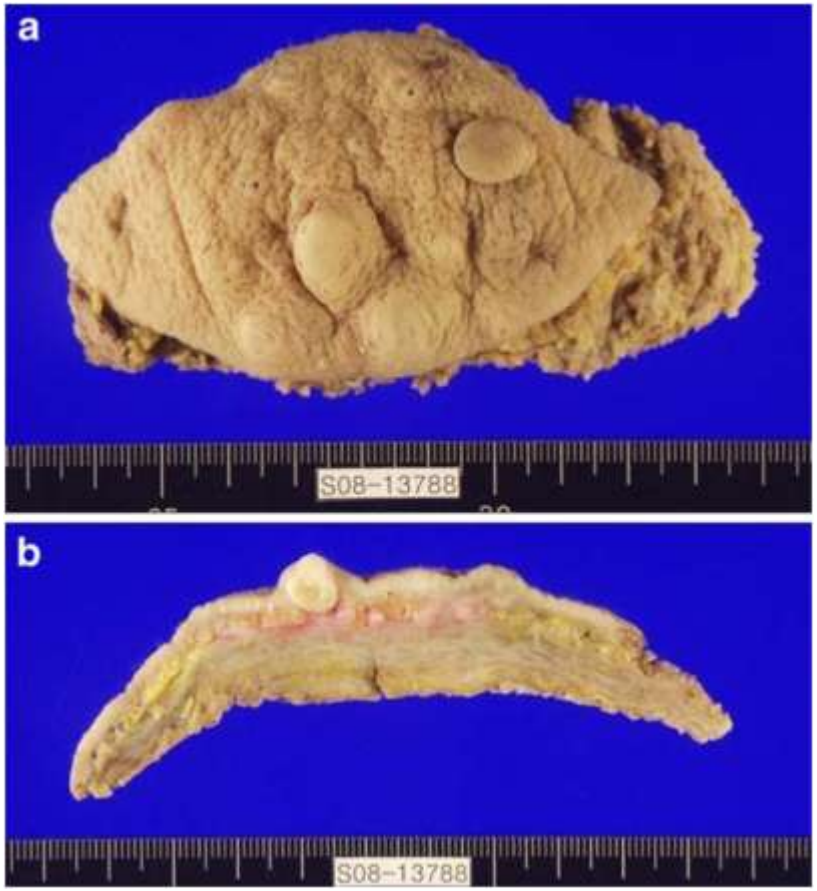
Casos de la literatura

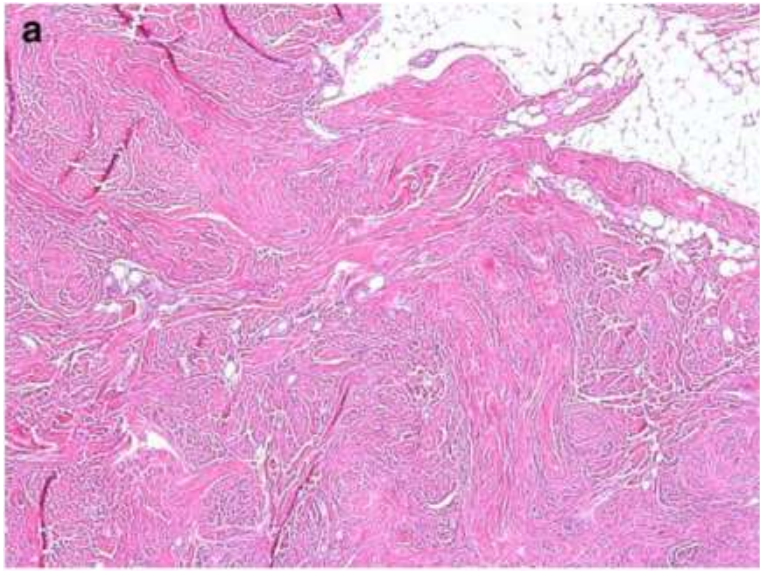
Pediatr Radiol (2009) 39:743–746
DOI 10.1007/s00247-009-1218-5

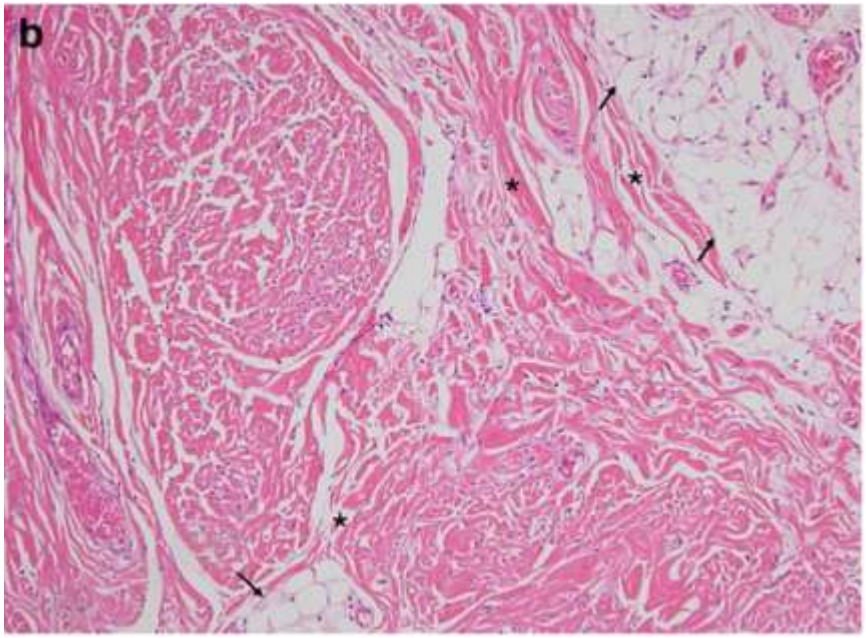
CASE REPORT

A large infiltrating fibrous hamartoma of infancy in the abdominal wall with rare associated tuberous sclerosis

Hye-Jeong Han · Gye-Yeon Lim · Chang-Young You







IPPA Advanced Courses in Paediatric Pathology

Prof.Dr. Elisabeth Bruder

Institute of Pathology
University Hospital Basel
Schoenbeinstrasse 40
CH-4031 Basel
Switzerland

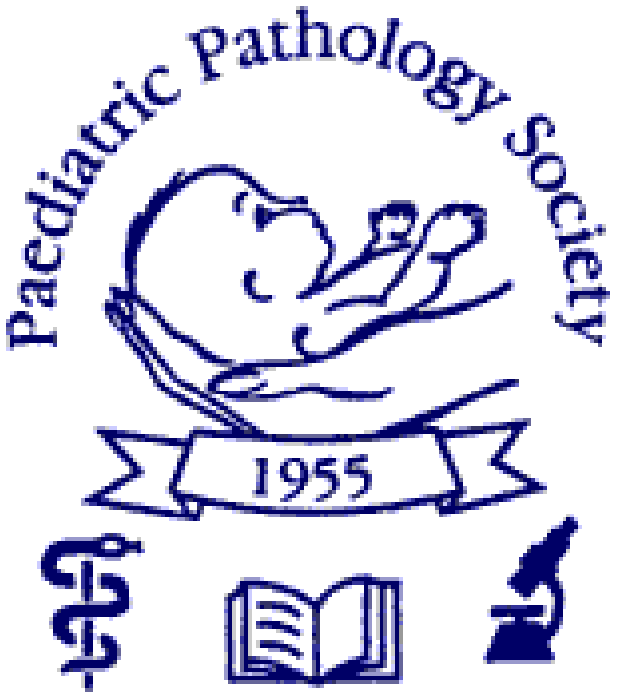
Telephone:+41 61 265 2022
Fax: +41 61 265 3194

e-mail: elisabeth.bruder@unibas.ch
(Include your short CV).

FutureCourses:

XXXIVth IPPA Advanced Course in Paediatric Pathology

La Granja, Spain
15-21 September 2012



PPS 2012: 58th Annual Meeting

Madrid, Spain

12th WORLD CONGRESS OF PEDIATRIC DERMATOLOGY

PALACIO DE CONGRESOS
MADRID
25th to 27th
september
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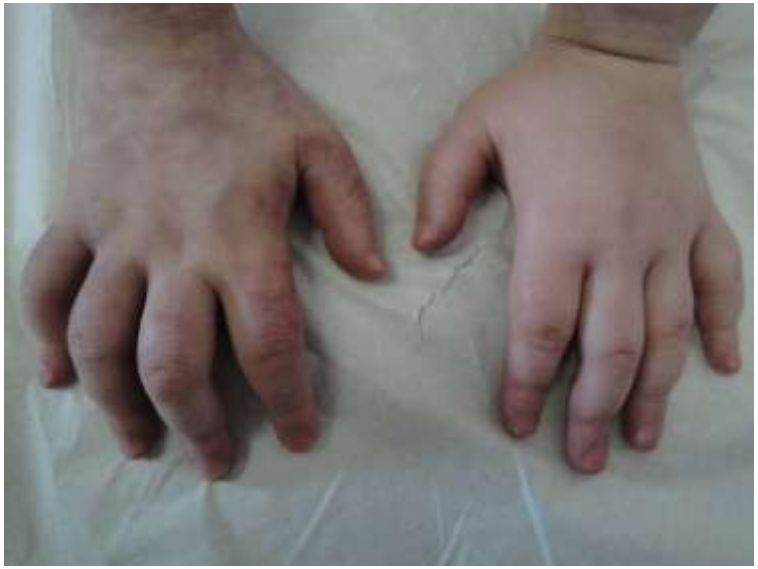
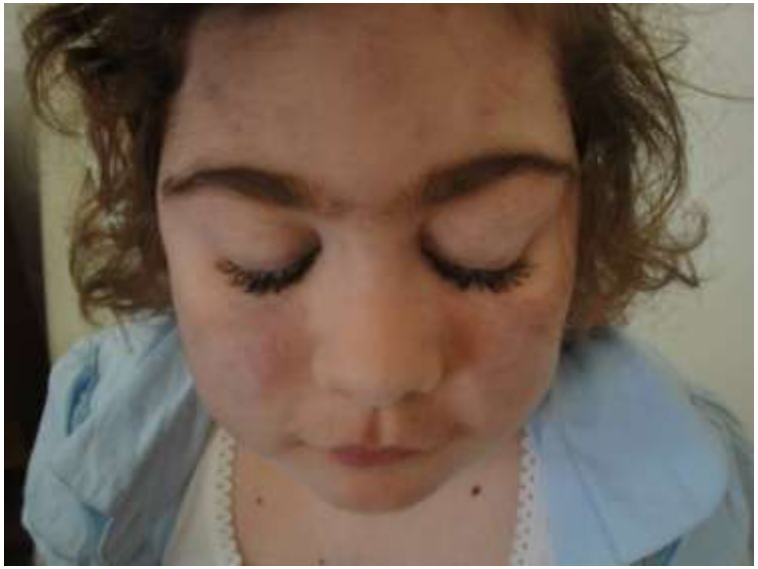
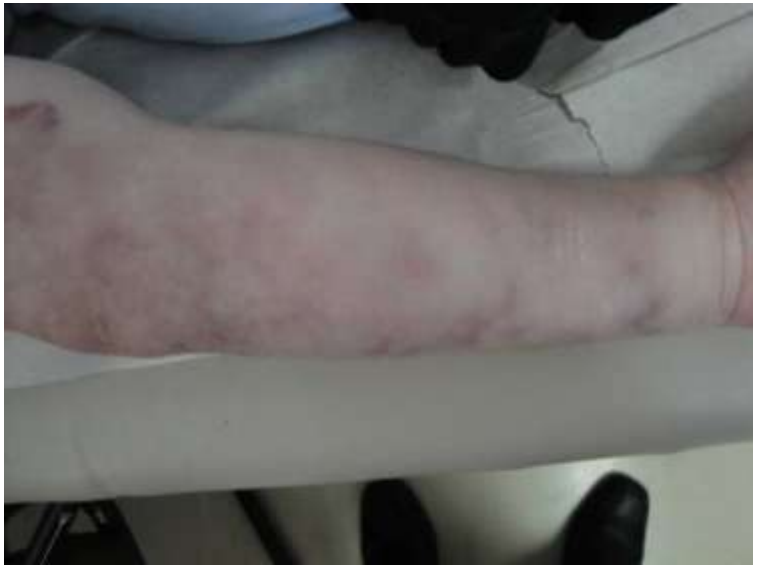
Tel.: +34 91 204 26 00 • Fax: +34 91 547 88 87
E-mail: wcpd2013@viajeseci.es

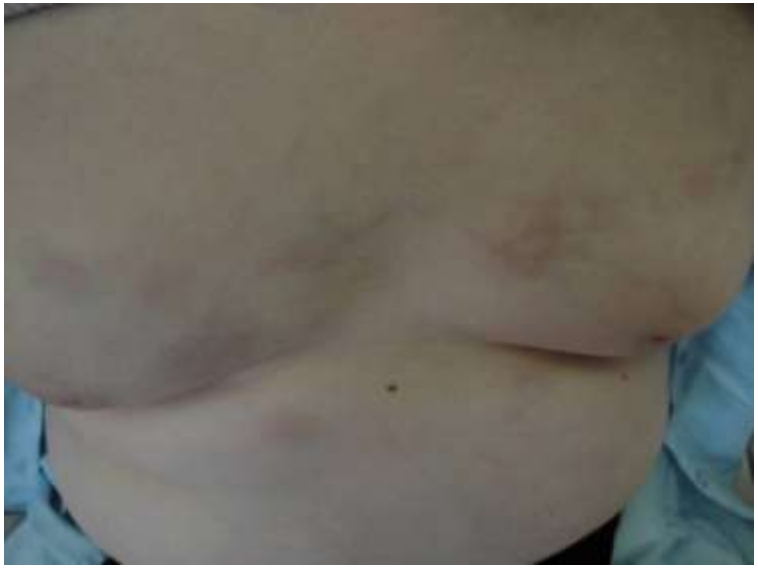
ISPD
International Society of Pediatric Dermatology

Additional patient from Israel ??









A Syndrome With Nodular Erythema, Elongated and Thickened Fingers, and Emaciation

Yukio Kitano, MD; Etsuji Matsunaga, MD; Toshie Morimoto, MD; Natsuko Okada, MD; Shigeharu Sano, MD

• A 5-year-old boy had a nodular erythema, elongated and thickened fingers, and emaciation. His condition was a rare congenital disease inherited as an autosomal recessive trait. Eleven cases have been previously reported in the Japanese literature. The onset is early in childhood, and nodular erythema is an essential and initial finding. Growth retardation and emaciation progress slowly with age. The characteristic clinical features include large eyes, nose, lips, and ears, disproportionately long and thick fingers, and the loss of adipose tissue from the upper half of the body. Cardiomegaly and hypertrophy of the periosteum of the phalanges have been described in some cases.

(*Arch Dermatol* 1985;121:1053-1056)

of previously reported cases, and to draw the attention of dermatologists elsewhere in the world to this unusual syndrome.

REPORT OF A CASE

A 5-year-old boy was first seen in July 1981 for recurrent erythema and atrophy of the upper extremities. The family history was noncontributory, except for the consanguineous marriage of paternal grandparents. The patient had a normal, healthy 7-year-old sister.

Our patient was born at full term and weighed 3,380 g at birth. An erythema of the right cheek developed at 2 months of age in August 1976. Thereafter, erythematous patches appeared on the face, hands, abdomen, legs, and soles in symmetrical distribution. Each lesion disappeared within two to three weeks, leaving slight pigmentation, but resolution of previous inflammatory lesions. Manual muscle examination revealed slight weakness, especially in the upper extremities.

Laboratory studies disclosed the following results: RBCs, 438 × 10⁴/cu mm; WBCs, 6,000/cu mm; hemoglobin level, 9.3 g/dL; hematocrit reading, 31.4%; mean corpuscular volume, 72 cu μm; mean corpuscular hemoglobin, 21.2 pg; mean corpuscular hemoglobin count, 29.6%. The findings were consistent with a hypochromic, microcytic anemia. Other laboratory tests revealed the following values: ESR, 40 mm/hr; serum total cholesterol, 122 mg/dL; lactic dehydrogenase, 462 units/L (normal, 100 to 400 units/L); creatine kinase, 51 IU/L (normal, 0 to 50 IU/L); aldolase, 3 IU/L (normal, 0 to 10 IU/L); total protein, 8.0 g/dL; albumin, 4.8 g/dL; globulin, 3.2 g/dL; IgG, 1,011 mg/dL; (normal, 1,100 ± 234 mg/dL); IgA, 156 mg/dL (normal, 230 ± 76 mg/dL); IgM, 66 mg/dL (normal, 110 ± 48 mg/dL); cryoglobulin, negative; cryofibrinogen, positive. The electromyogram was normal. An ECG showed ST-wave depression in leads II, III, and aV$_F$, changes suggestive of the presence of ventricular hypertrophy. Roentgenographic examination revealed a retardation of bone age, but neither the changes associated with cardiorespiratory dysfunction nor hypertrophy of the periosteum could be

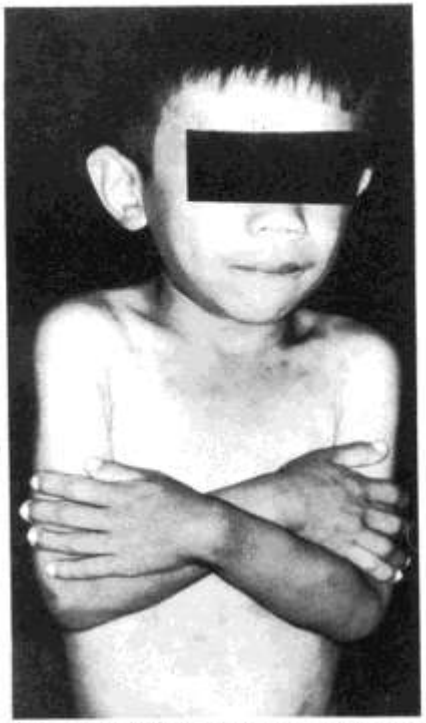


Fig. 1.—Five-year-old boy with atrophic mandible and large protruding ears. Hands are disproportionally large. Erythematous nodules are disseminated over face, chest, and abdomen.

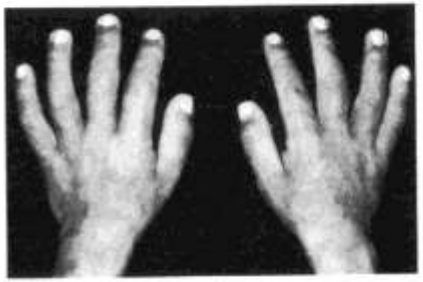


Fig. 2.—Patient's hands showing long, thickened fingers that are clubbed slightly at tips (palms were atrophic). There are numerous small, erythematous nodules.

Acta Neuropathol (Berl) (1987) 73:313–319

Acta Neuropathologica

Regular papers

An autopsy case of a syndrome with muscular atrophy, decreased subcutaneous fat, skin eruption and hyper γ-globulinemia: peculiar vascular changes and muscle fiber degeneration*

K. Oyanagi[1], K. Sasaki[2], E. Ohama[2], F. Ikuta[2], A. Kawakami[3], N. Miyatani[3], T. Miyatake[3], and S. Yamada[4]

Departments of [1] Neuropathology, [2] Pathology, and [3] Neurology, Brain Research Institute, Niigata University, 1 Asahimachi, Niigata 951, Japan

* Department of Neurology, Akita Red Cross Hospital, Akita 010, Japan

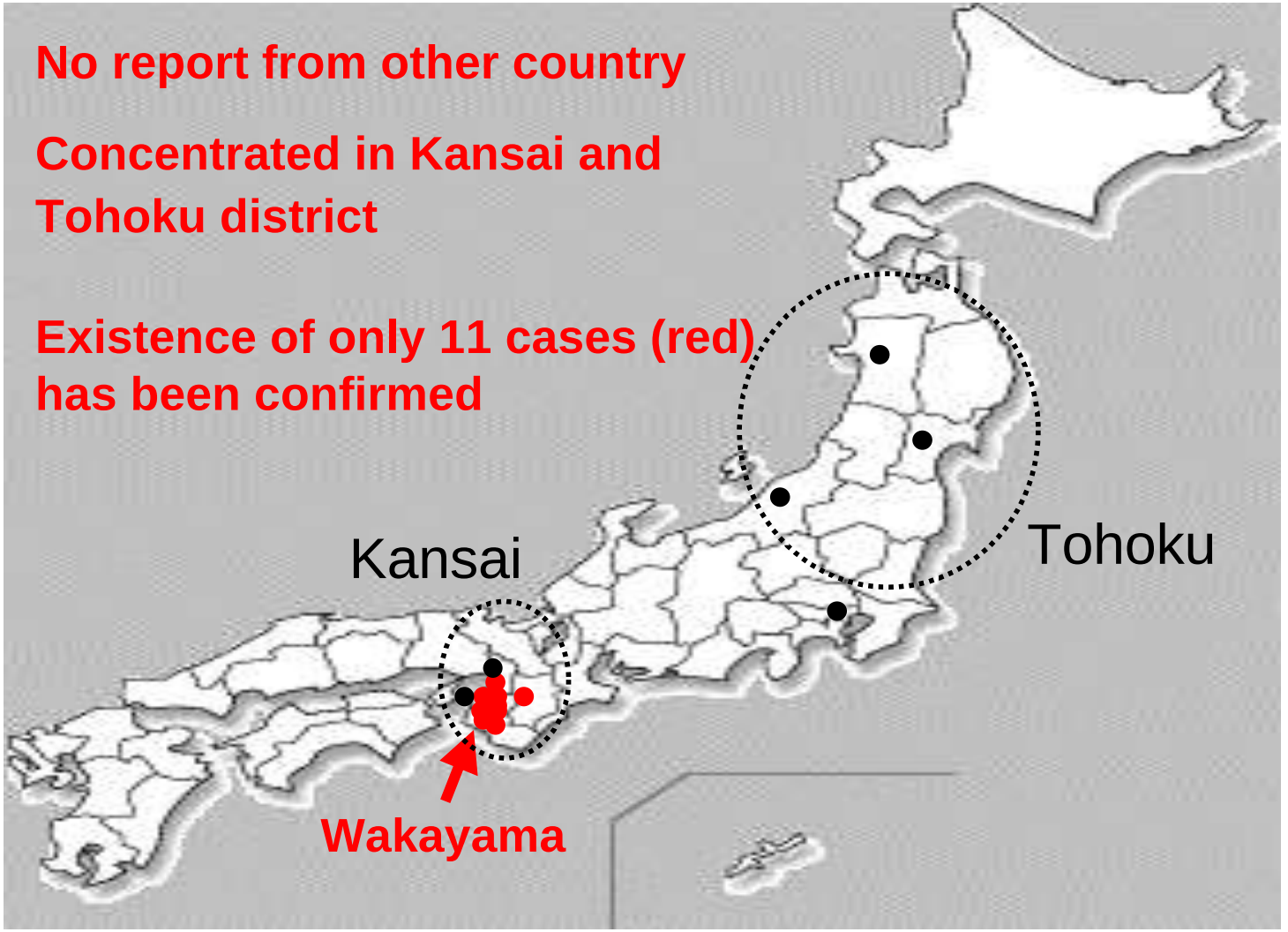
Hereditary Lipo-Muscular Atrophy with Joint Contracture, Skin Eruptions and Hyper-γ-Globulinemia: a New Syndrome

Masami Tanaka, Nobuyuki Miyatani, Shigeru Yamada, Kotaro Miyashita, Itaru Toyoshima, Kaori Sakuma, Keiko Tanaka, Tatsuhiko Yuasa, Tadashi Miyatake and Tadao Tsubaki*

We previously reported two siblings with decreased subcutaneous adipose tissue, muscular atrophy, joint contractures, recurrent skin eruptions, hyper-γ-globulinemia, and reduced natural killer cell activity. Some of their clinical features are similar to those of partial lipodystrophy, but they are distinct in that muscular atrophy, joint contractures and recurrent skin eruptions are not found in patients with partial lipodystrophy. Thirteen other Japanese patients with similar clinical manifestations have been reported. We propose that such cases should be considered a distinct clinical entity.

(Internal Medicine 32: 42–45, 1993)

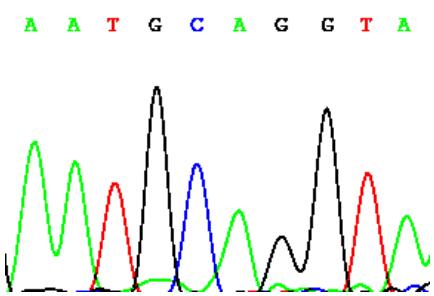
A novel autoinflammatory syndrome



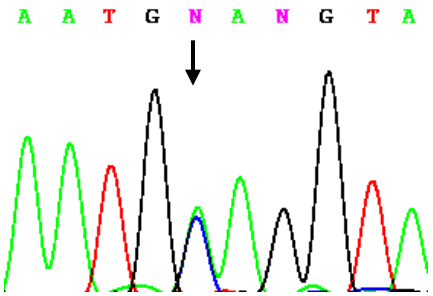
“Familial Japanese fever (FJF)”

Sequencing of *PSMB8*

Israeli patient #1

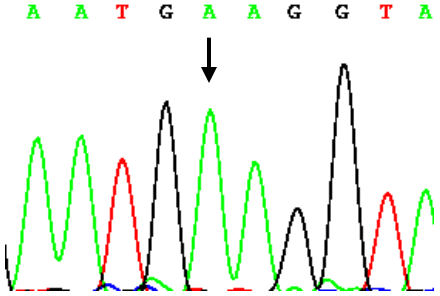


Wildtype



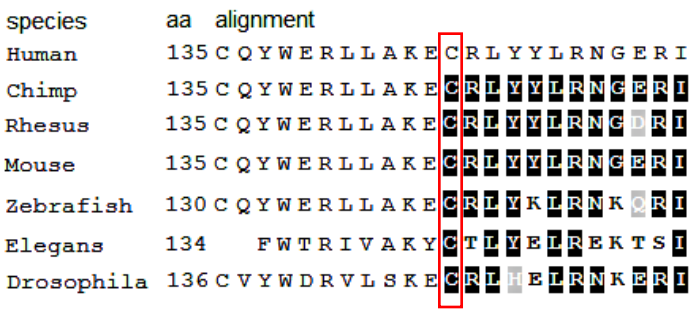
Heterozygote

Family D
(c.405C>A)



Homozygote

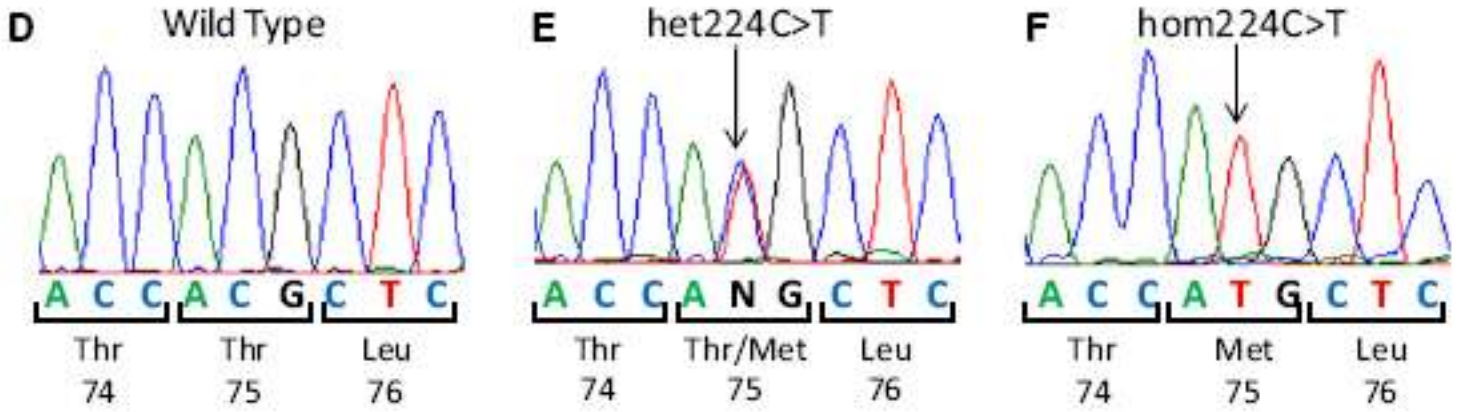
Family D
(c.405C>A)



p.C135Z

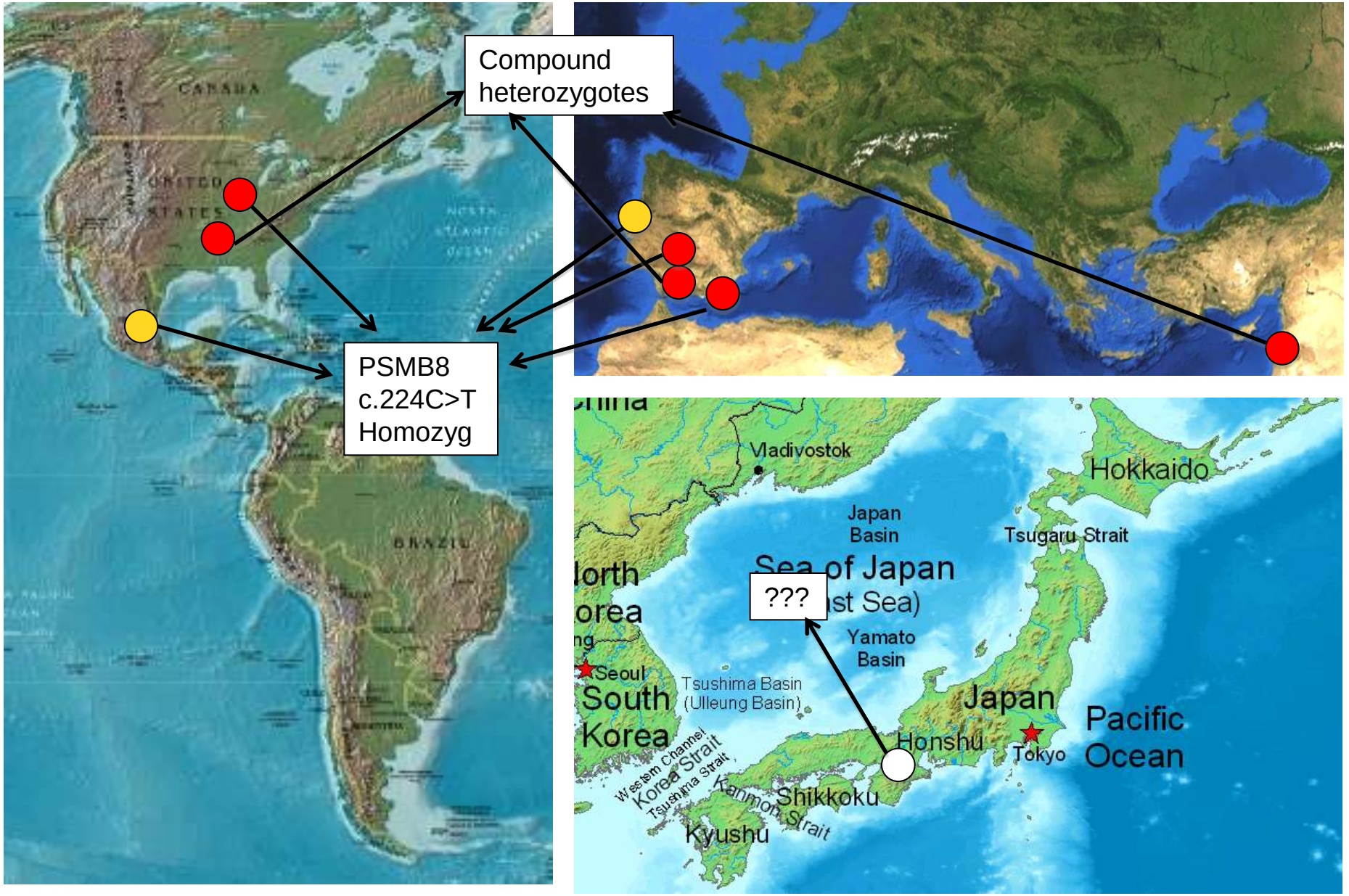
The mutation found in 3 patients: c.224C>T

Same mutation as our Spanish patients

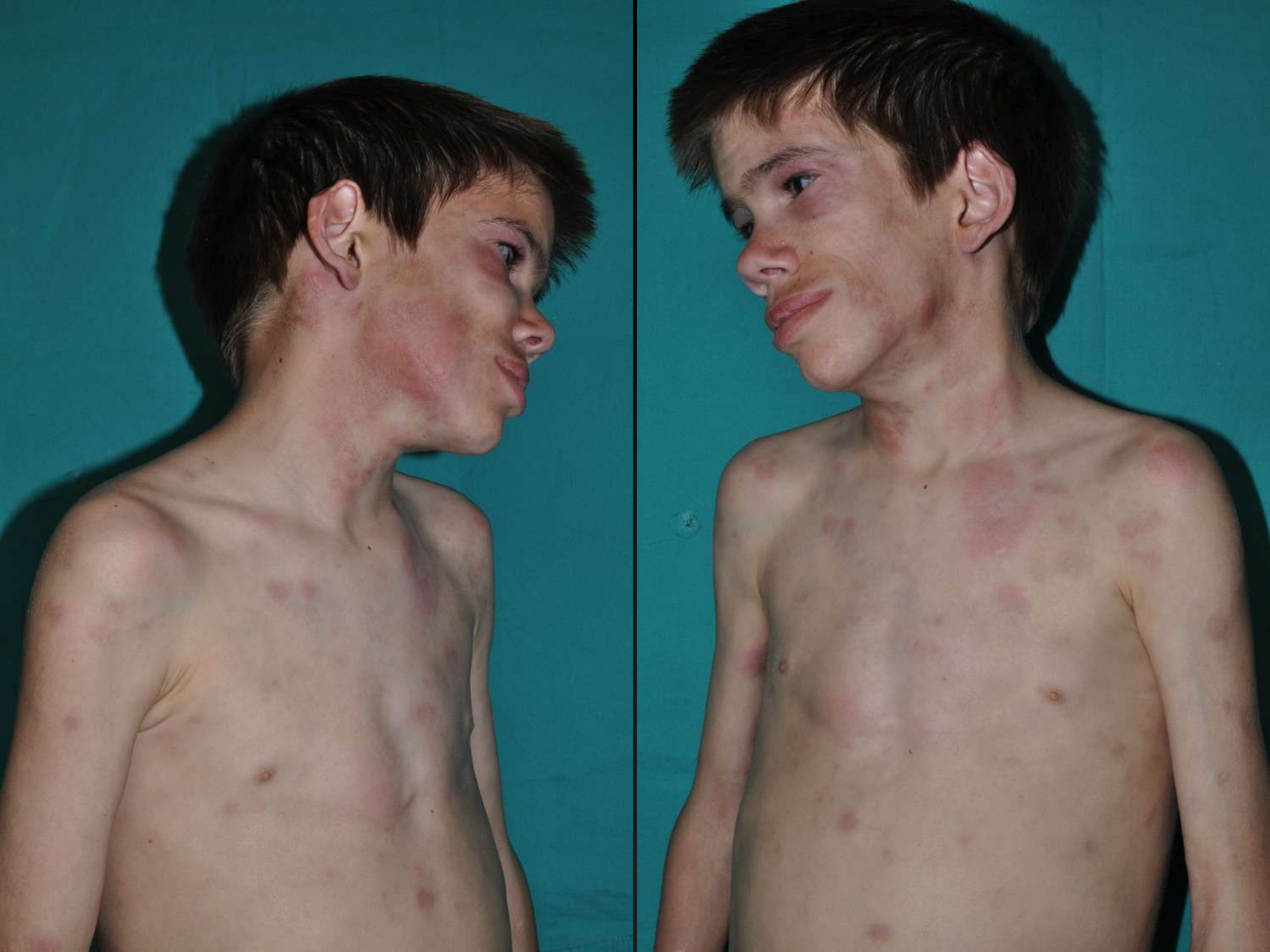


Summary

Family	Mutation
Original Spanish families (3 families)	T75M (c.224C>T, c.224C>T)
Israeli patient #1	C135Z
Patient from Malaga	c.224C>T; ?
USA patient #1	c.224C>T; ?
USA patient #2	?



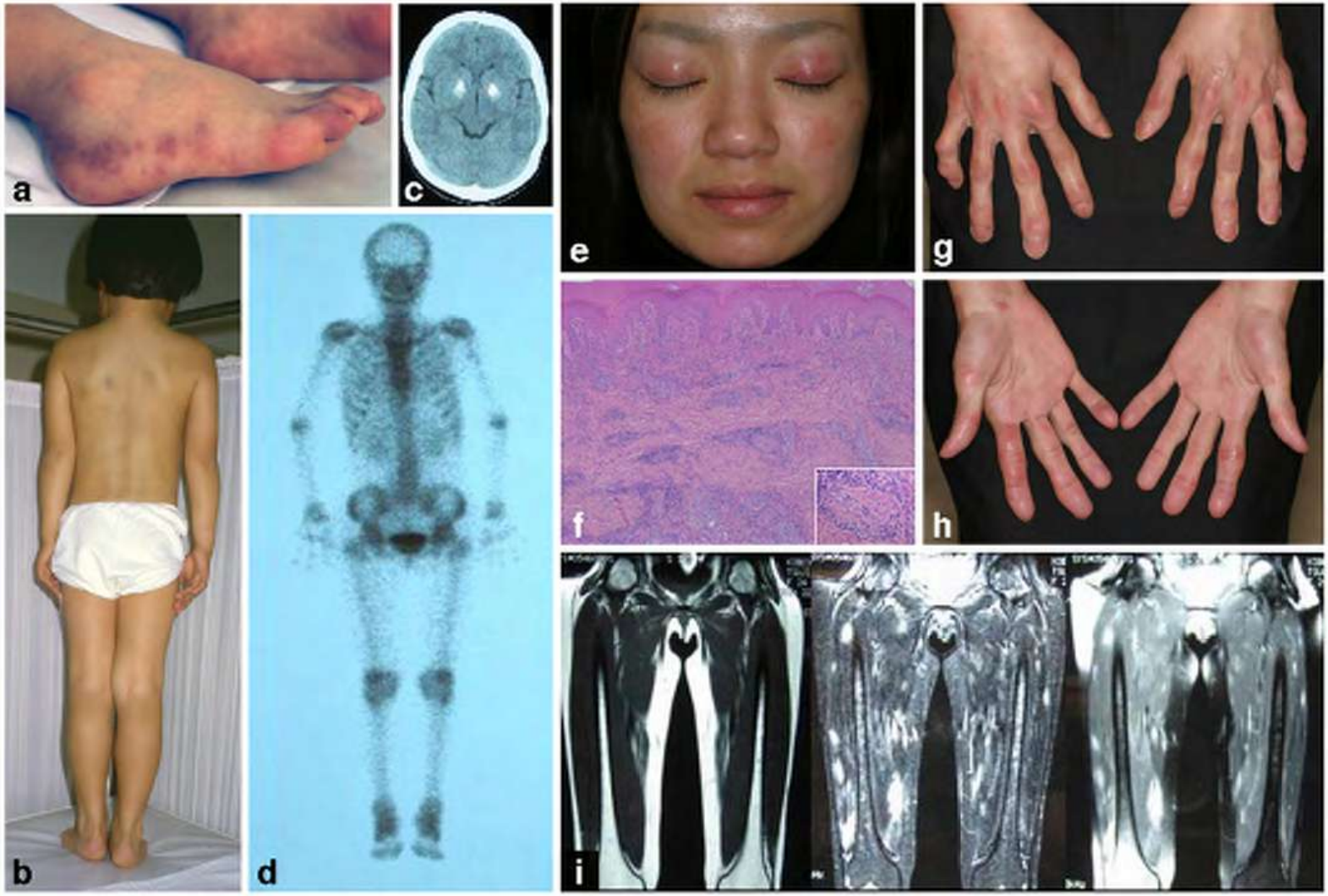
CANDLE JMP NAKAJO-NISHIMURA



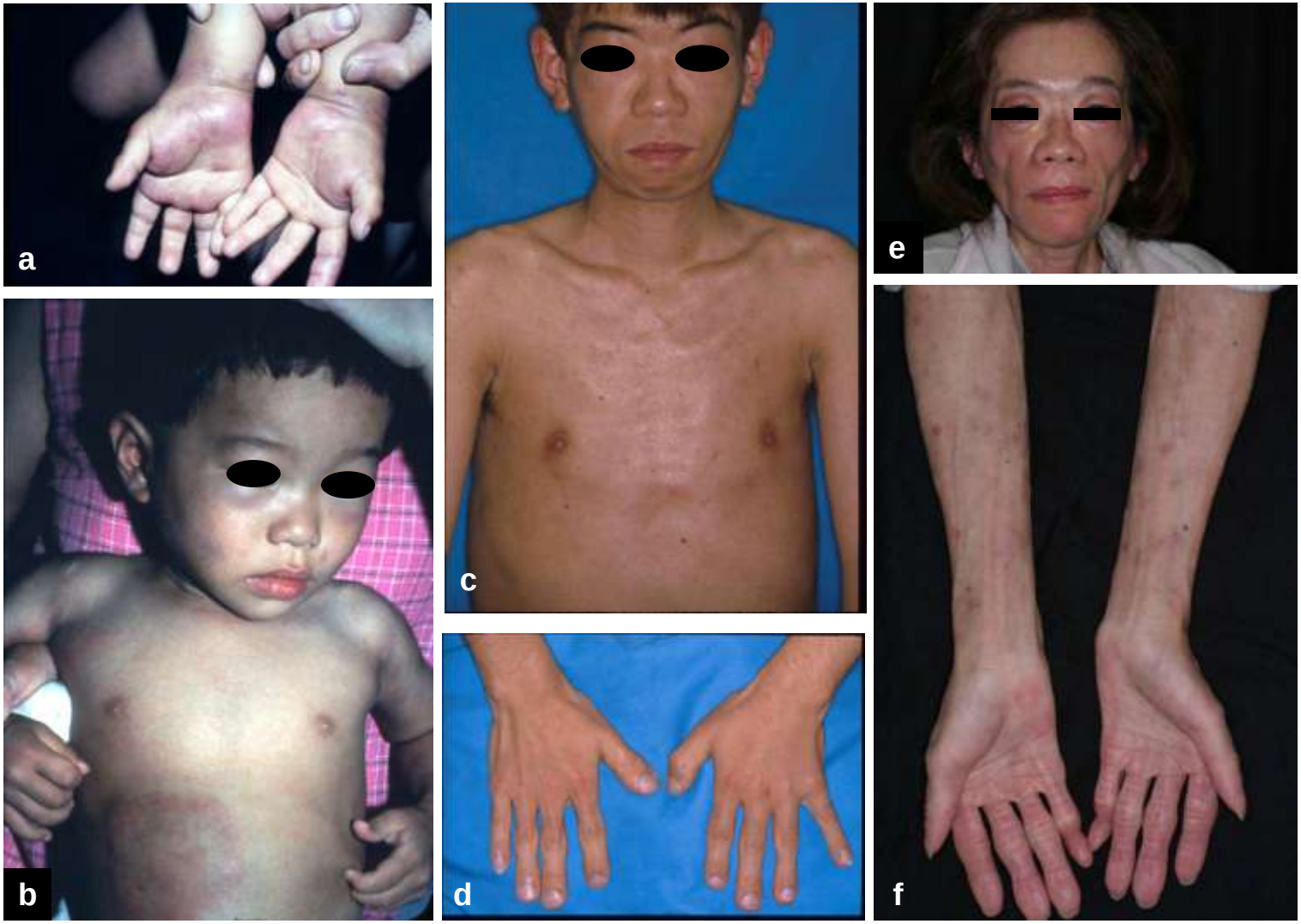

CANADA
UNITED STATES
BRAZIL
SAHARA
ALGERIA
LIBYA
EGYPT
CHAD
NIGERIA
SIBERIA
RUSSIA
CHINA
INDIA
AUSTRALIA
NORTH ATLANTIC OCEAN
SOUTH ATLANTIC OCEAN
INDIAN OCEAN
NORTH PACIFIC OCEAN
SOUTH PACIFIC OCEAN
Antarctica

Summary of 12 cases in Wakayama

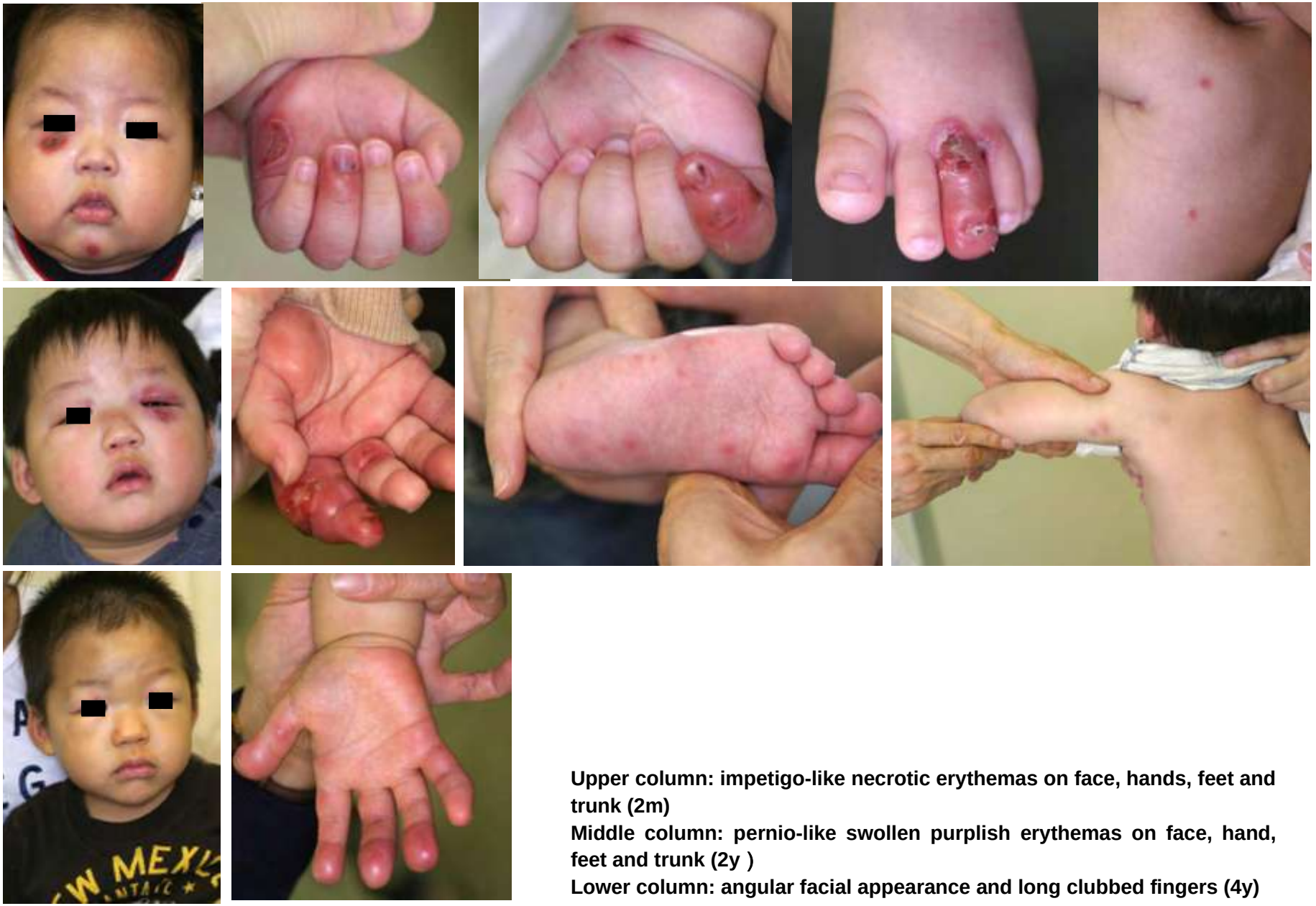
Case	0	1	2	3	4	5	6	7	8	9	10	11
Present ageat death)	5y	31y	43y	(32y)	38y	41y	32y	33y	(46y)	60y	(47y)	(44y)
Sex	M	F	F	M	M	M	M	M	M	M	F	M
Parental consanguinity	-	+	+	+	-	-	-	-	-	+	+	-
Family history	-	-	+	+	-	-	-	-	-	-	+	-
Age at onset of pernio	2m	6m	6m	1y10m	3m	infancy	infancy	1y	3y	Child-hood	5y	Child-hood
Eruptions in trunk	+	±	+	-	++	++	++	+	++	++	++	++
Age at onset of fever	3m	11m	2y	3y	7y	-	-	2y4m	8y	6y	Un-known	Un-known
Long clubbed fingers	+	+	+	+	+	+	+	+	+	+	+	+
Hyperhidrosis	-	+	+	+	+	+	+	-	+	+		
Partial lipoatrophy	±	±	+	±	±	++	++	++	++	++	+++	++
Hepatosplenomegaly	+	+	+	+	+	+	-	+	+	+		+
Joint contractures	-	+	-	-	+	+	+	++	+++	+++	+++	+
Loss of muscle power	-	-	-	-	-	+	+	+	+	+	+	
Dyspnea	-			+		-	-	-		+		+
Basal ganglia calcification	+	+	+	+	+	+	+	+	+	+		
Electrocardiogram	np	np	LVH	LVH	np	nd	nd	CRBBB	CRBBB	CRBBB	CRBBB	LAD
Homozygous X mutation	+	nd	nd	+	+	+	+	+	nd	nd	nd	nd



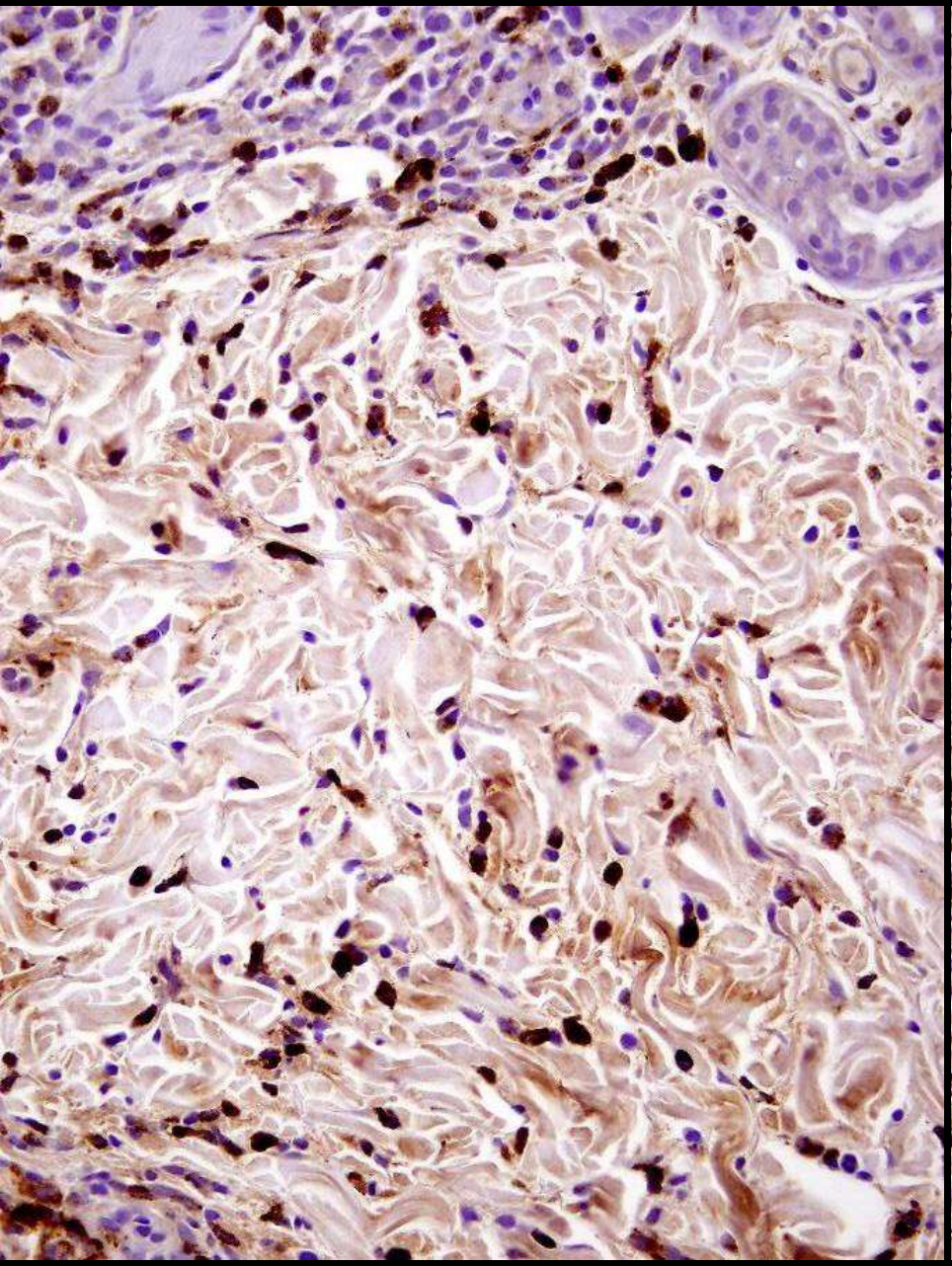
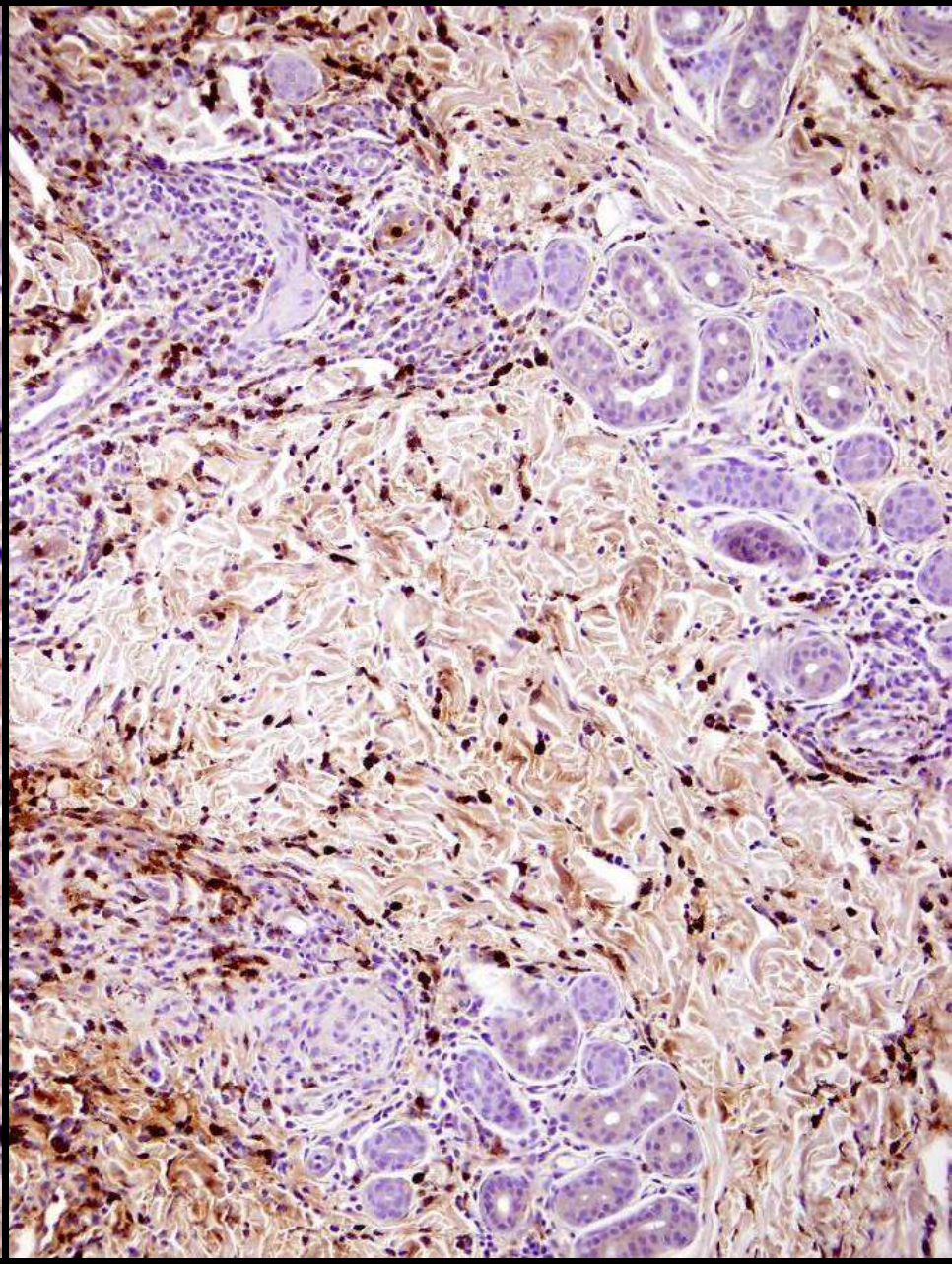
a: pernio-like purplish rash on feet (5y), b: dispasia due to gastrocnemius muscle pain, c: basal ganglia calcification on head CT (24y), d: accumulation of Tc in multiple joints on bone scintigram, e: facial appearance with emaciation and heliotrope-like periorbital rash (27y), f: histopathology of an erythematous nodule on a hand (HE, x40/400), g: long clubbed fingers, h: erythematous nodules on hands, i: MRI images of both thighs (from left to right: T1, T2, Gd-enhansed T1; 24y)

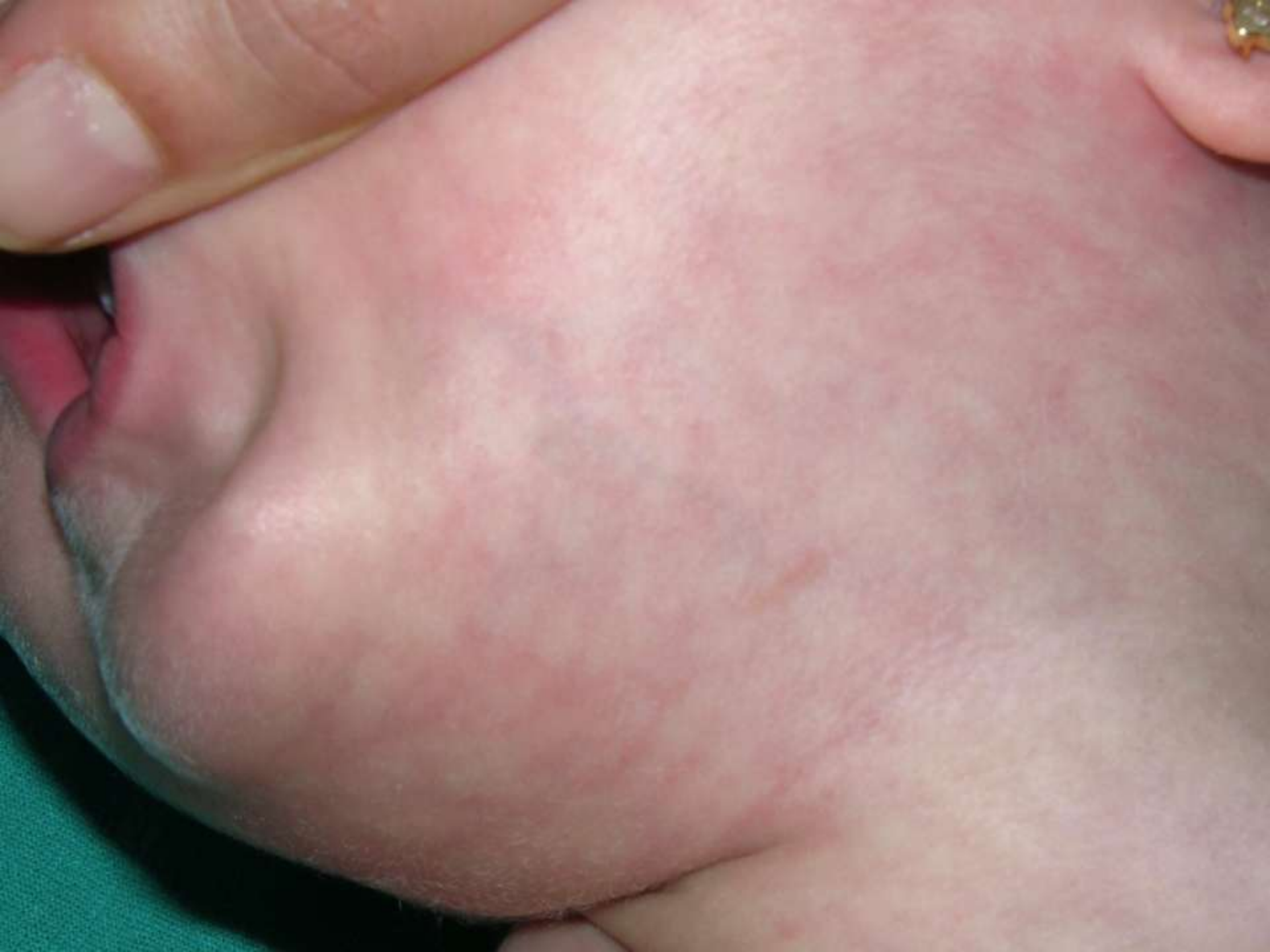


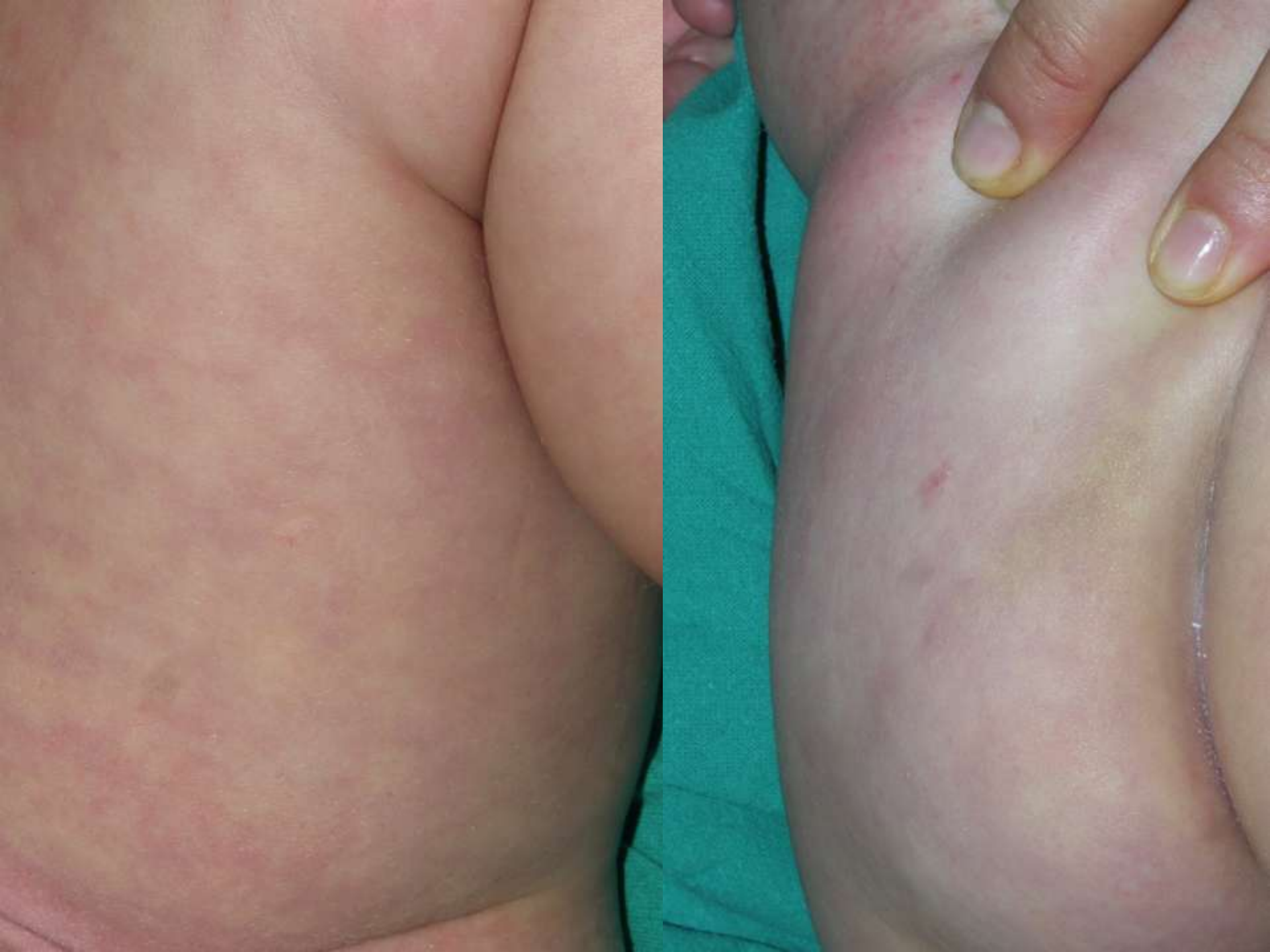
a: pernio-like swollen erythema on hands of Case 3 (3y), b: erythematous nodules on face and large circumscribed erythema on chest of case 2 (2y), c: emaciation of face and chest of Case 3 (23y), d: clubbed fingers of Case 3, e: wasting facial appearance of Case 2 (39y), f: long clubbed fingers and erythematous nodules in hands and forearms of Case 2

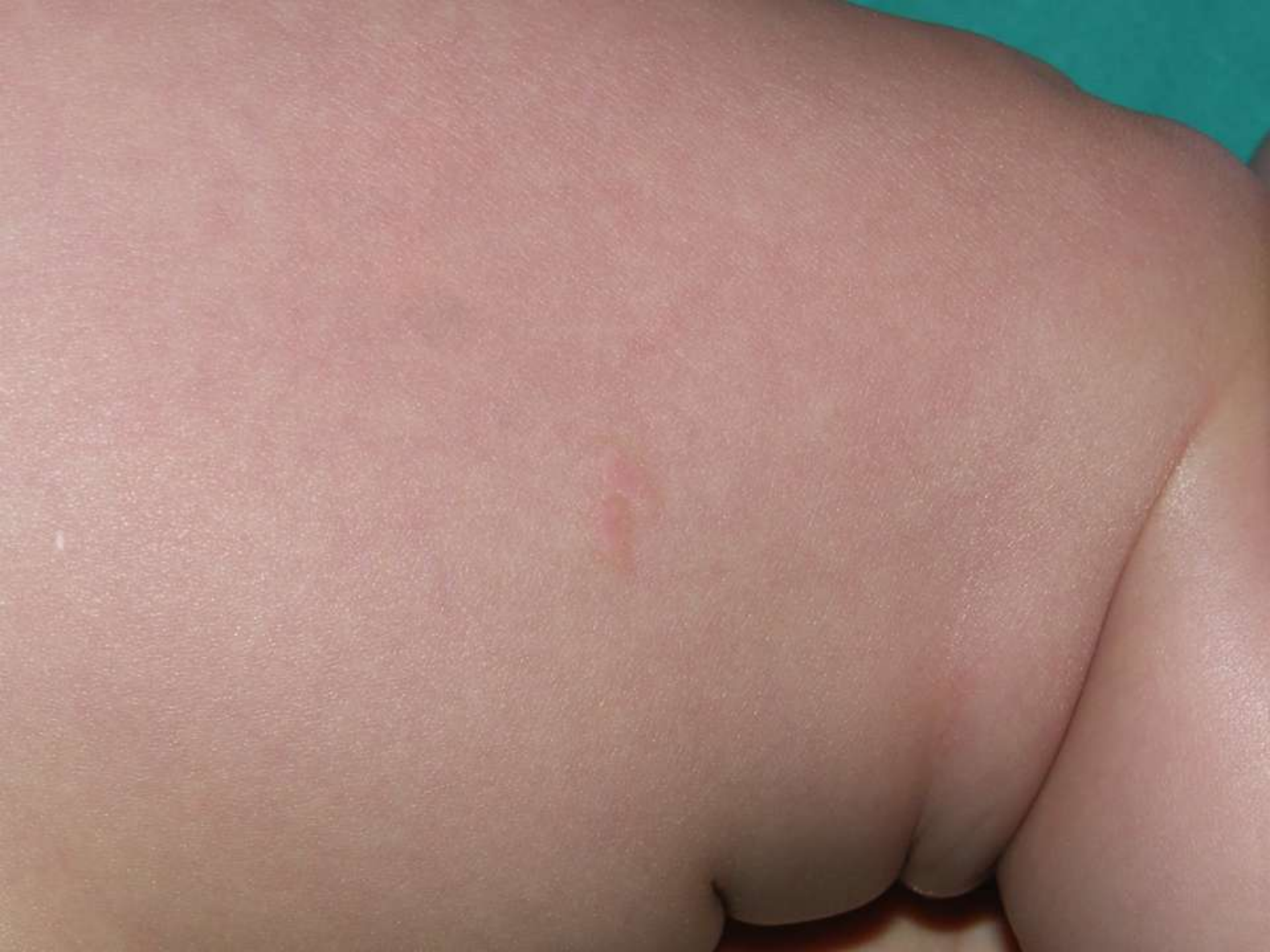


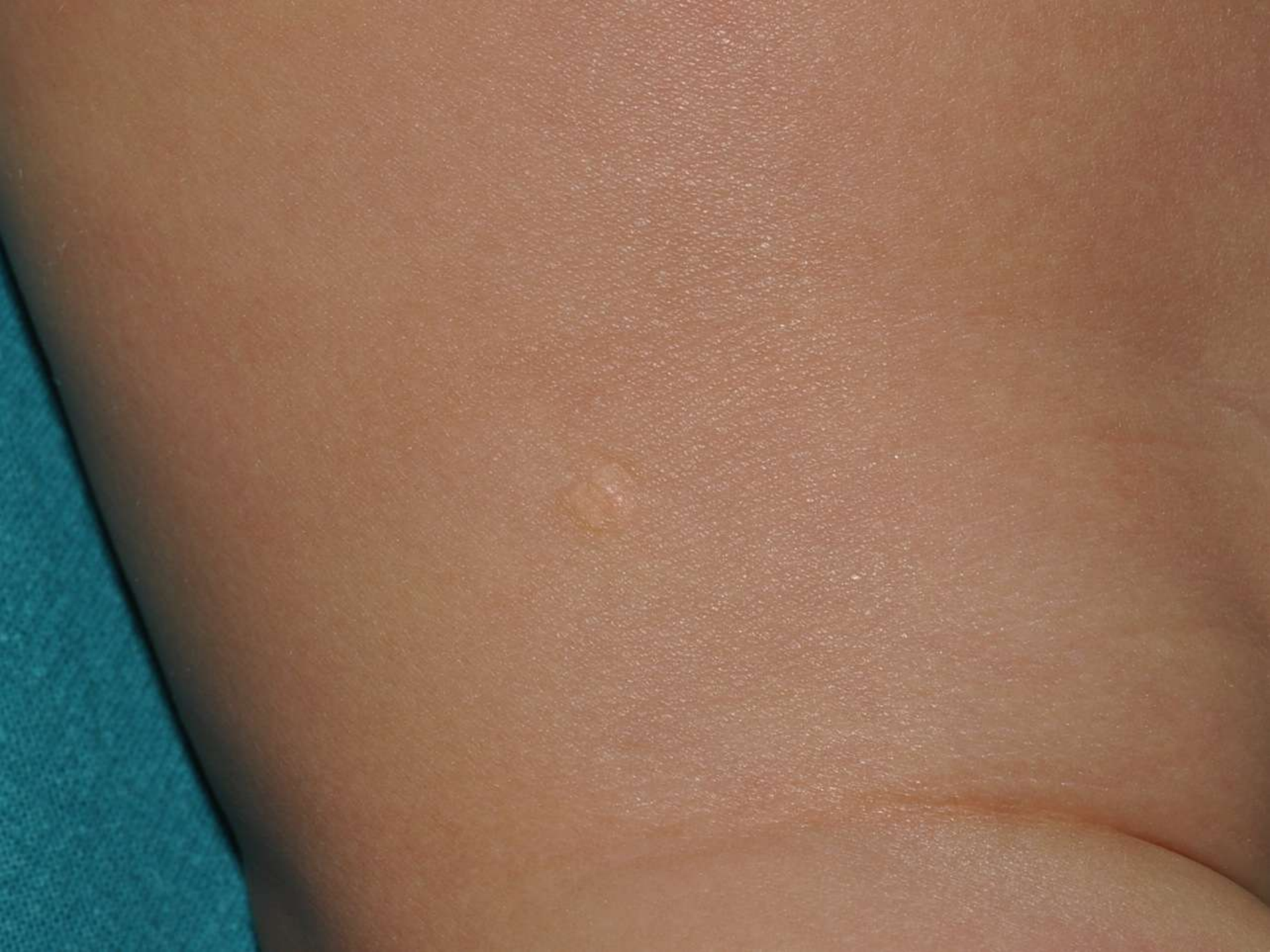
Upper column: impetigo-like necrotic erythemas on face, hands, feet and trunk (2m)
Middle column: pernio-like swollen purplish erythemas on face, hand, feet and trunk (2y)
Lower column: angular facial appearance and long clubbed fingers (4y)

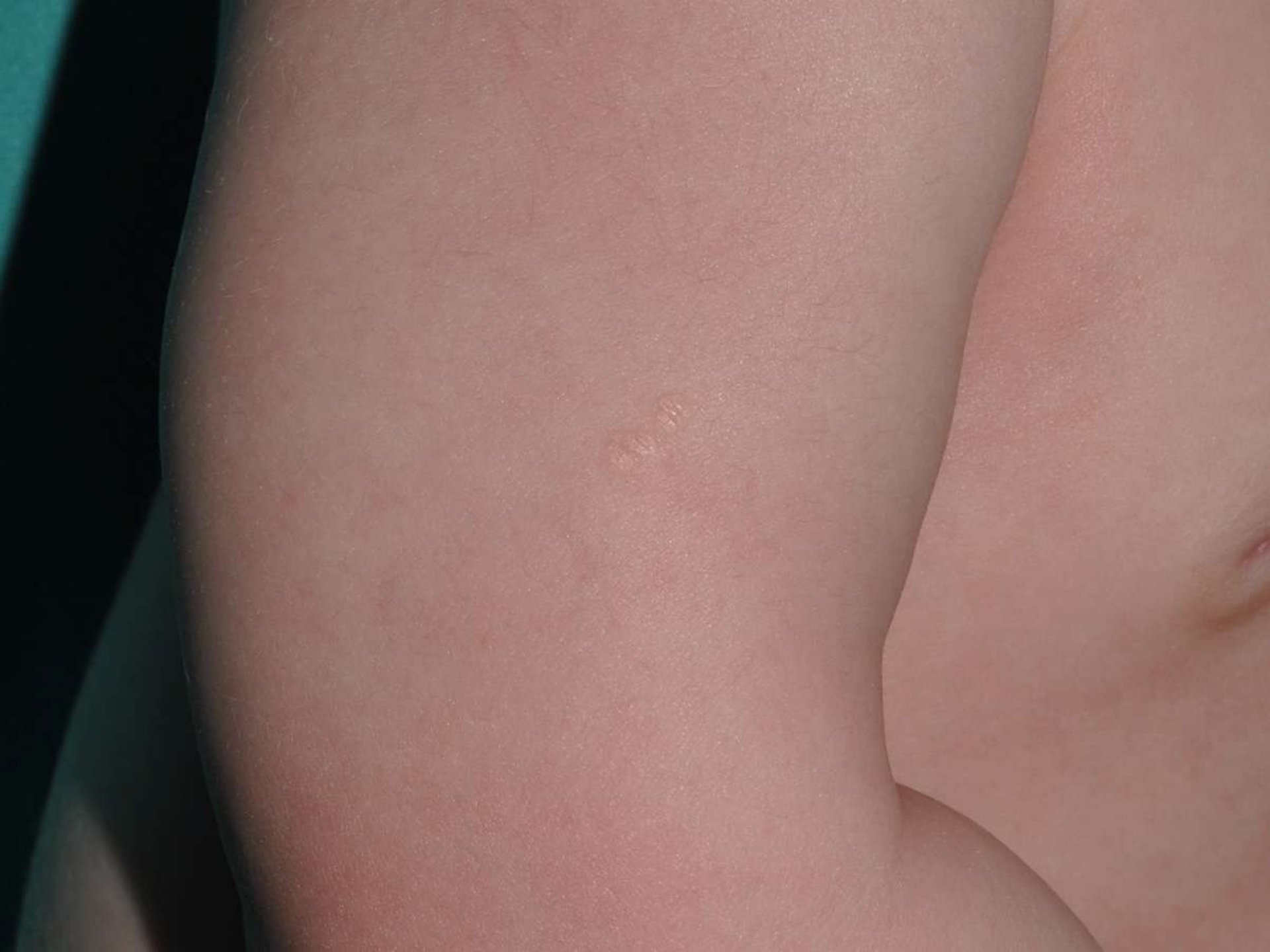



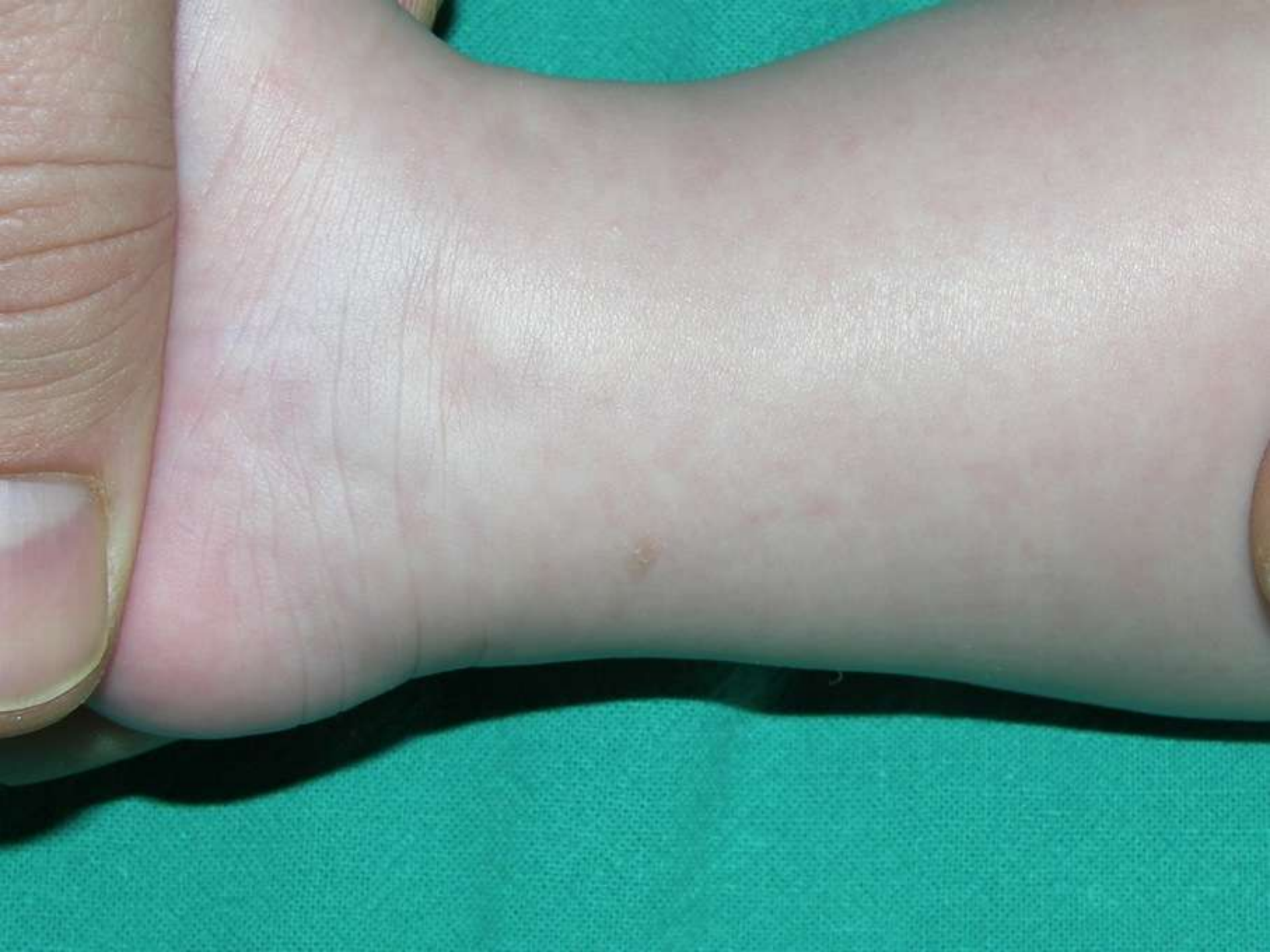


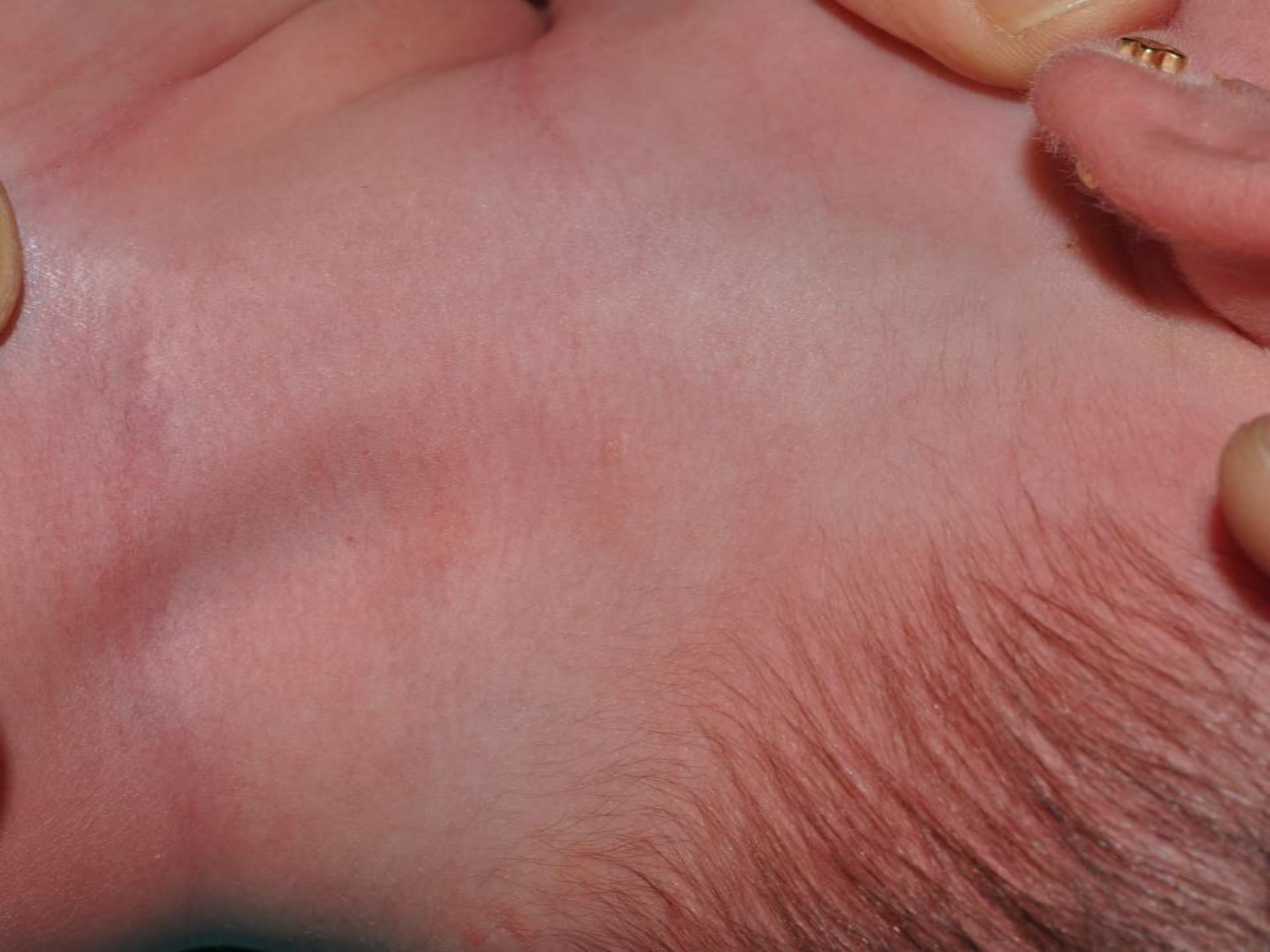








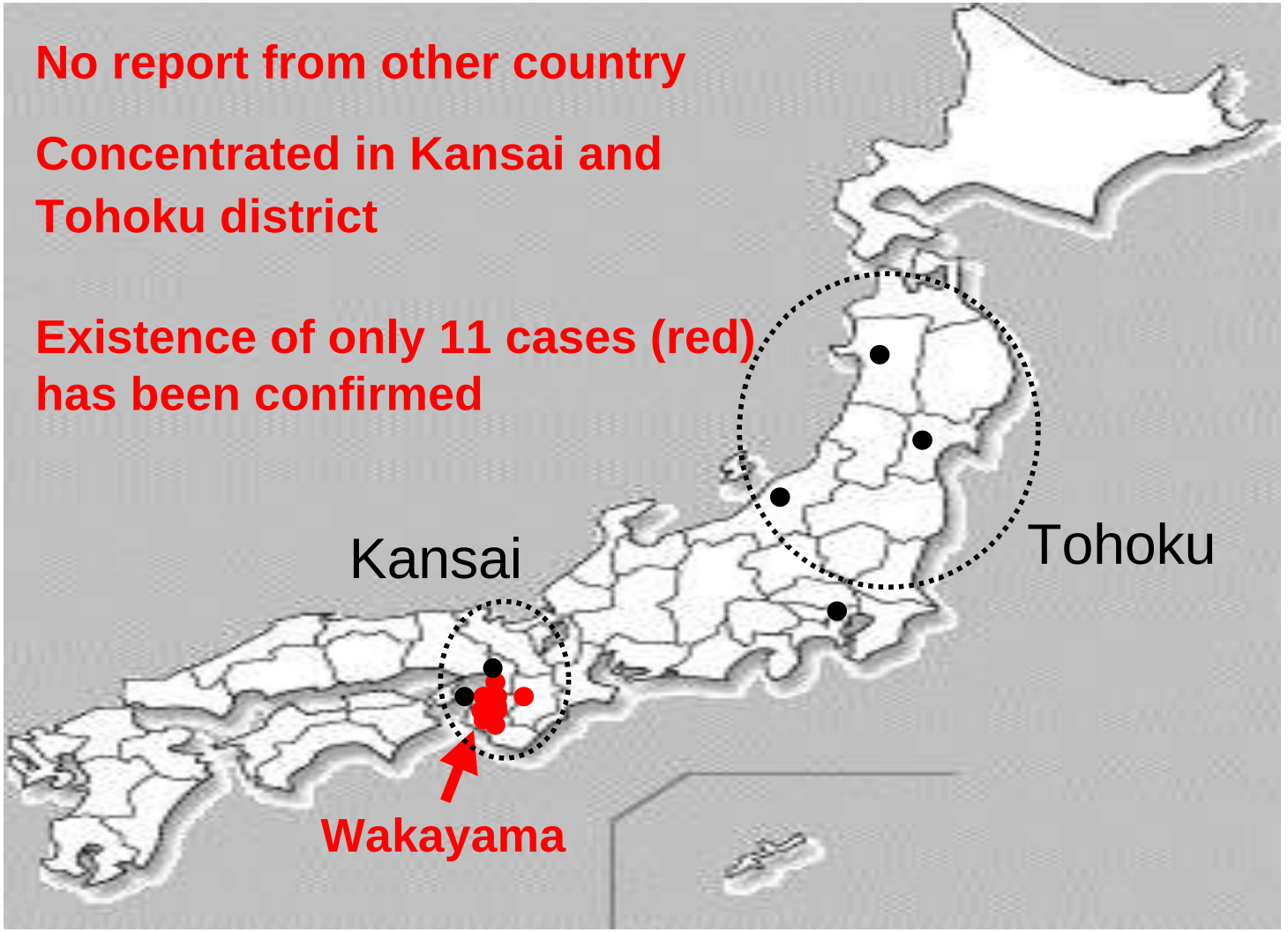




Hipótesis?

- ET tiene que estar relacionada (5/6 casos)
- Mutaciones en hamartina o tuberina – tendencia a desarrollar tumores y hamartomas
- Mosaicismo: LOH del gen de la ET durante embriogénesis precoz
  - Manifestación segmentaria tipo 2 de una enfermedad autosómica dominante
  - Puede explicar casos no asociados a ET
  - Todos los casos en varones – impronta?

A novel autoinflammatory syndrome



“Familial Japanese fever (FJF)”