Nail and Periungual Changes Related to COVID-19 Infection: Histopathologic Features

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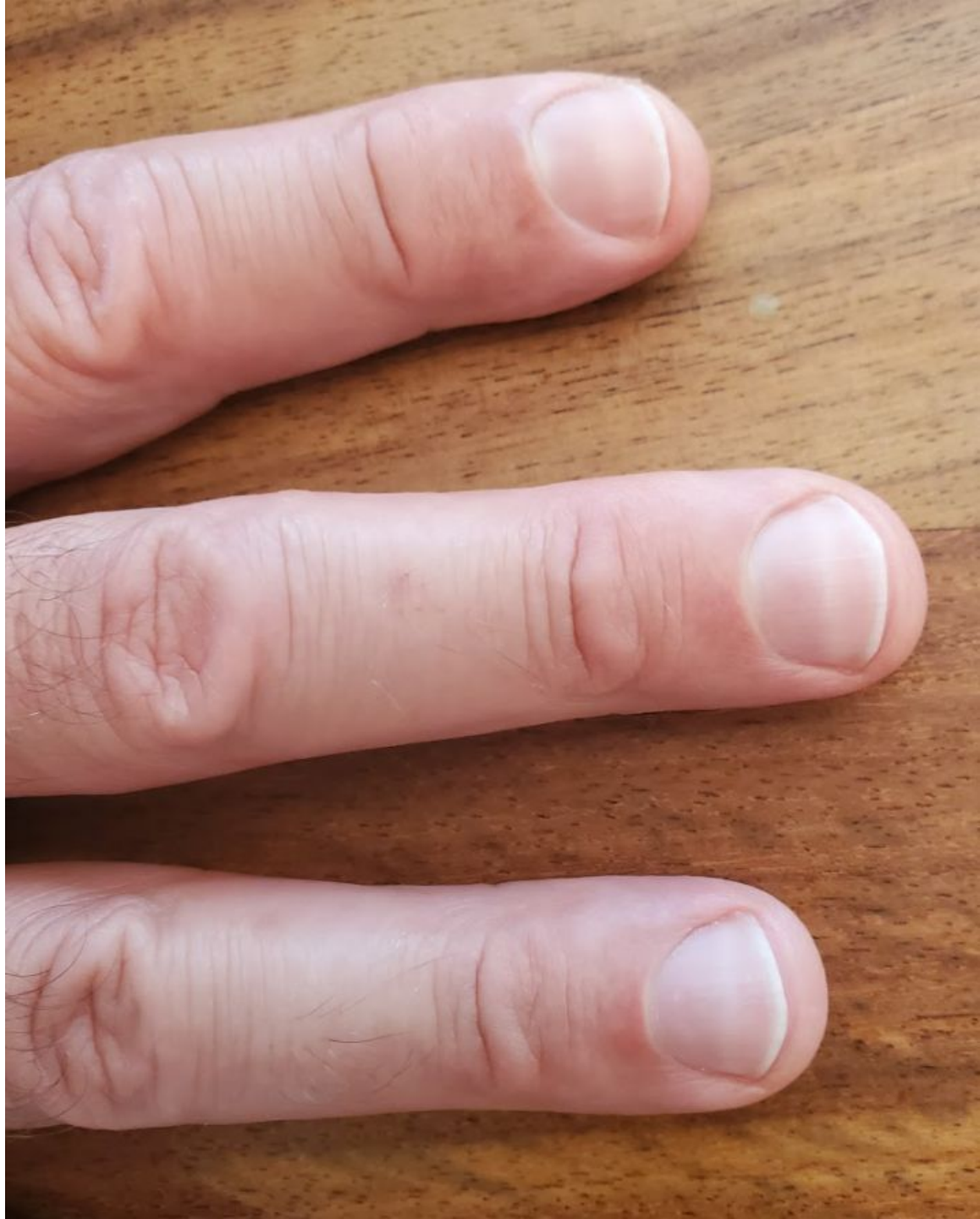
COVID-19 Nail Reported

- Mees and Beau’s Lines and Red Half-Moon Sign
- Chilblains
- Thrombotic



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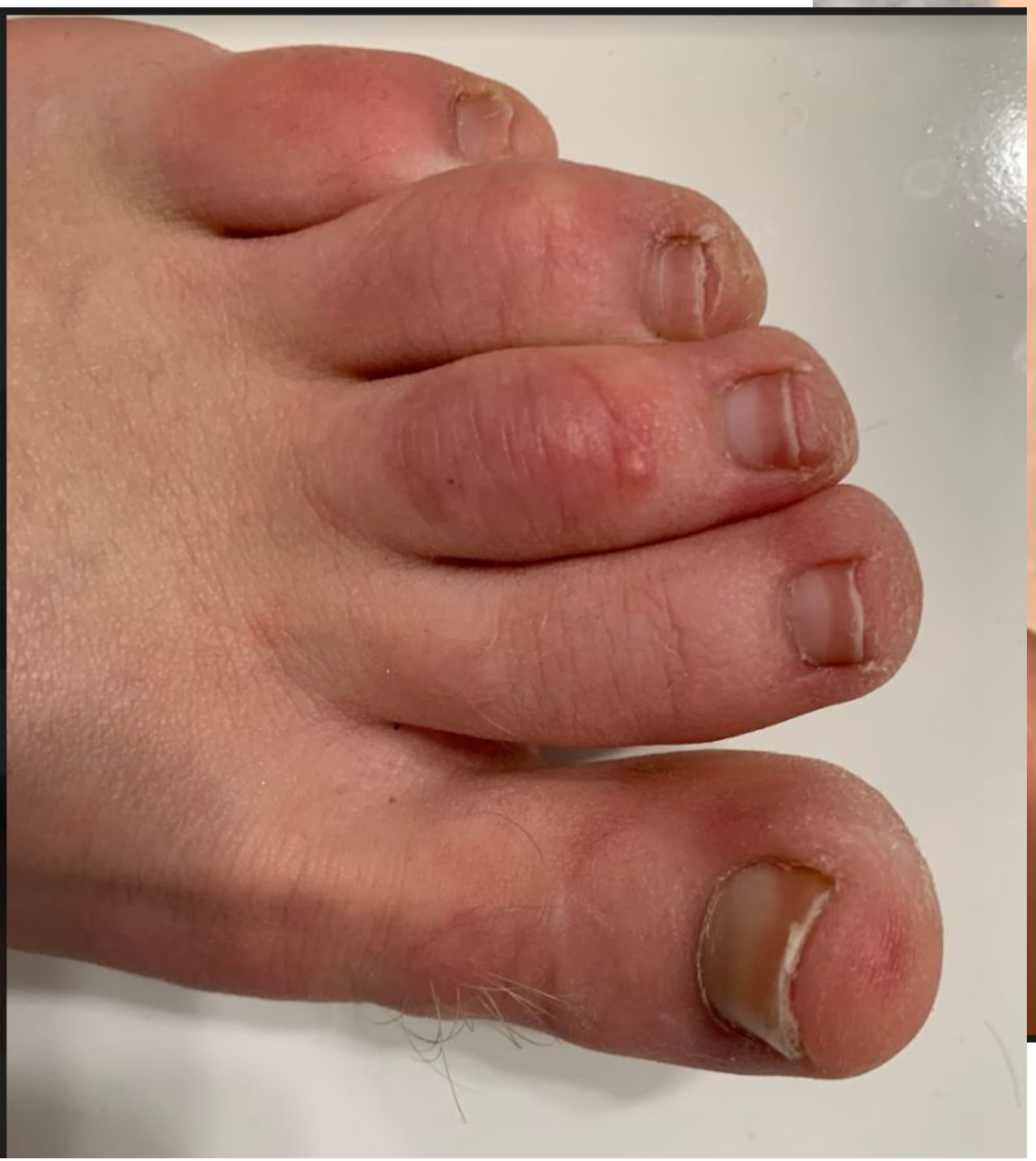
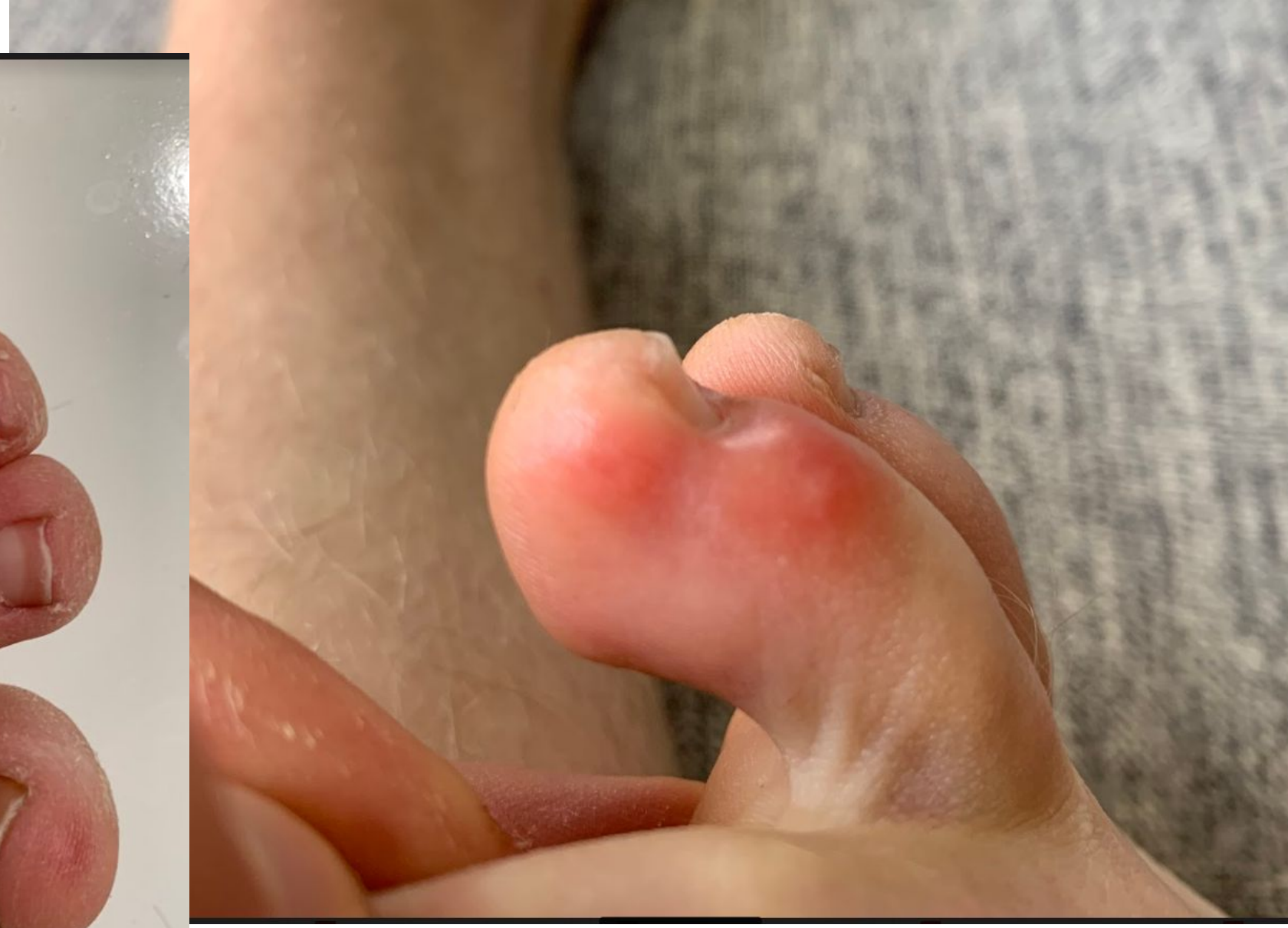
J Eur Acad Dermatol Venereol. 2020 Jun 29 : 10.1111/jdv.16747.
doi: 10.1111/jdv.16747 [Epub ahead of print]
PMCID: PMC7323324
PMID: 32535979

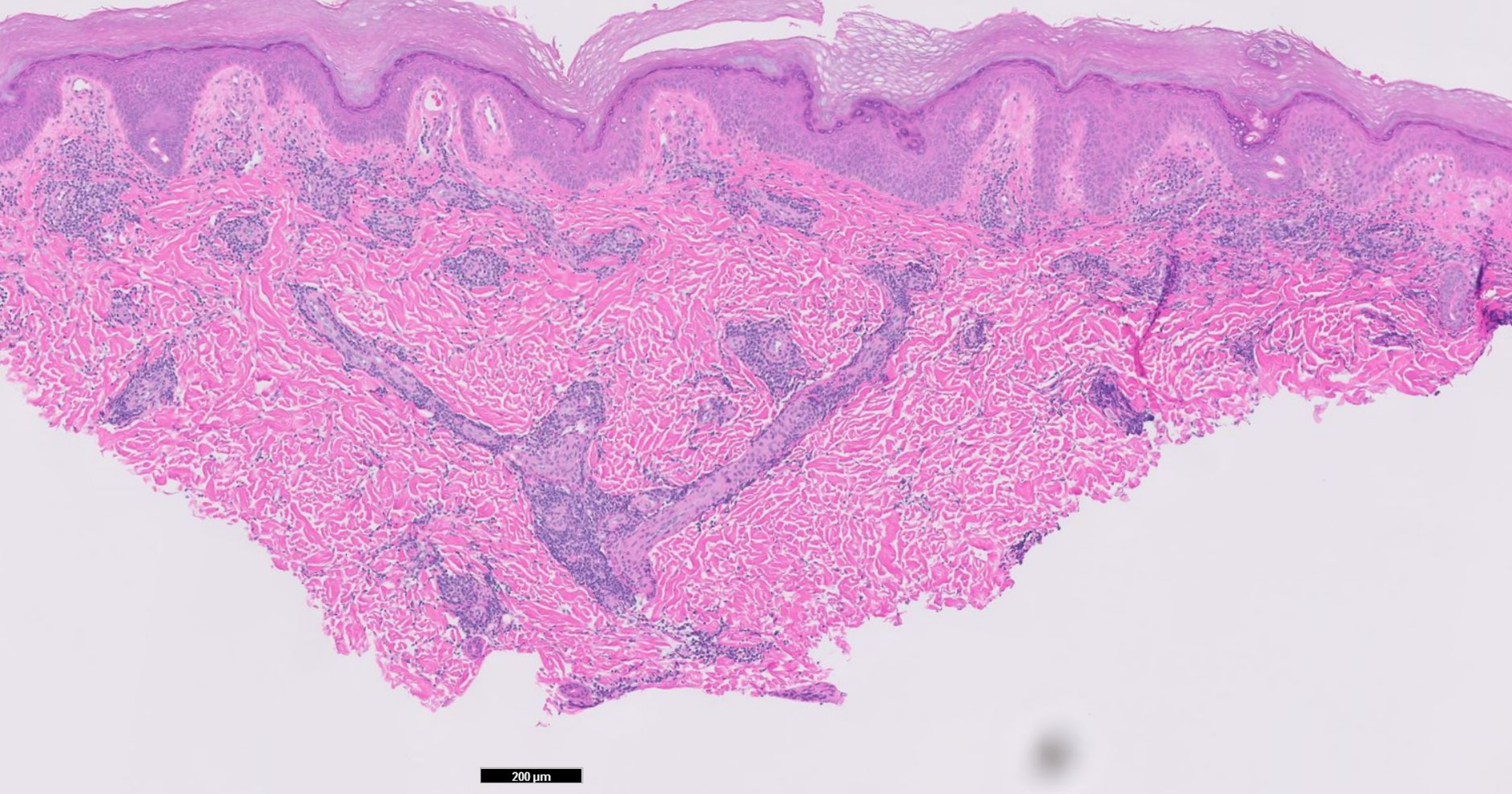
The red half-moon nail sign: a novel manifestation of coronavirus infection

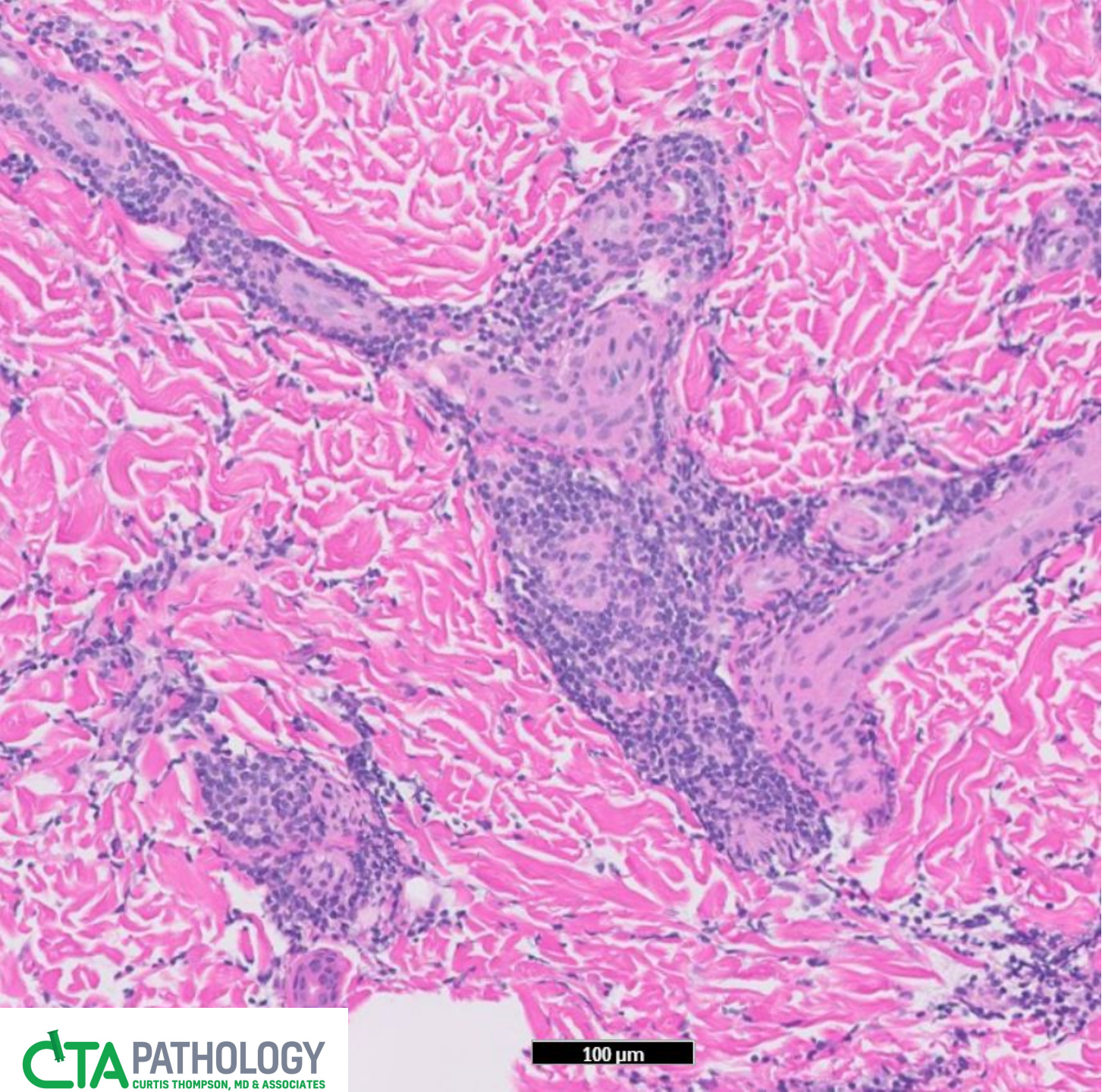
I. Neri, [1] A. Guglielmo,[✉] [1] A. Virdi, [1] V. Gaspari, [1] M. Starace, [1] and B.M. Piraccini [1]

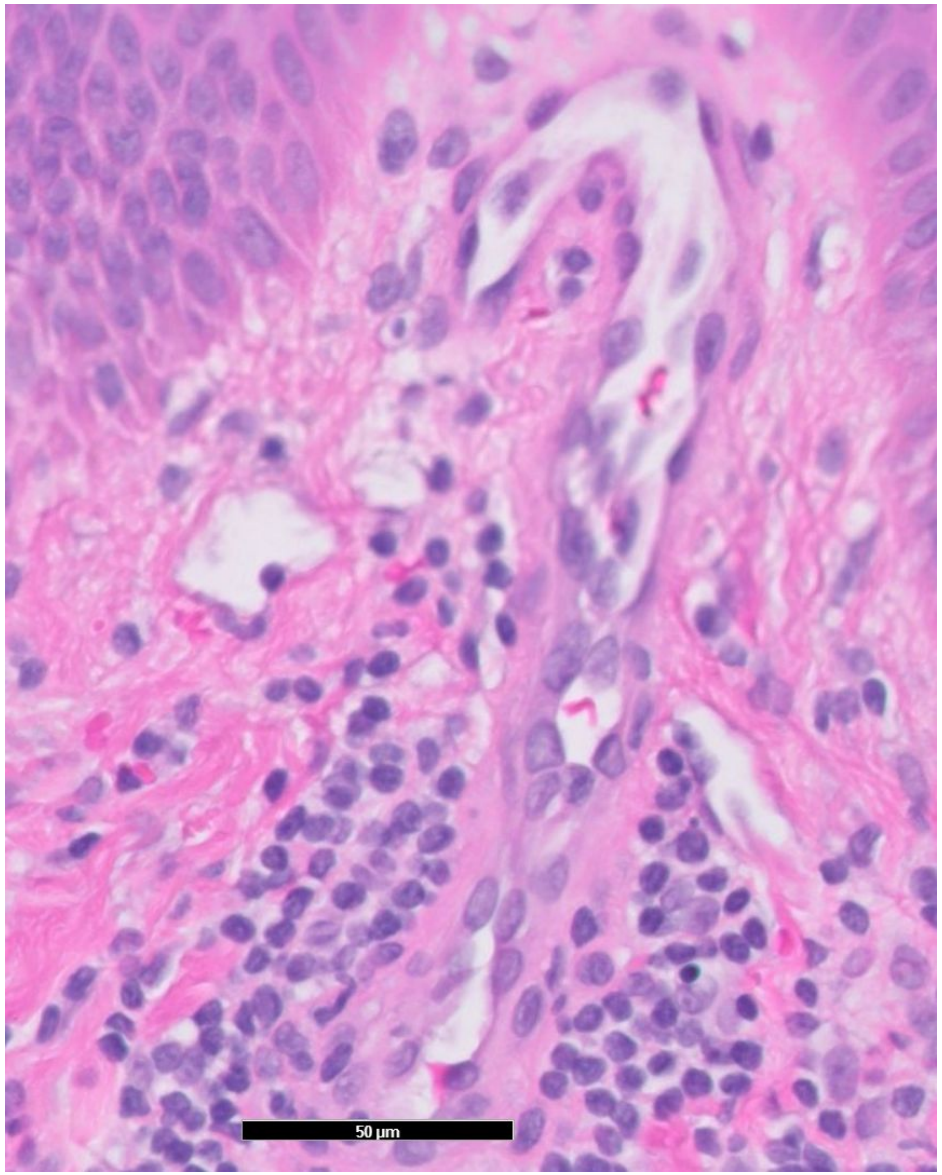




31 y/o male with acute onset of toe papules


200 µm





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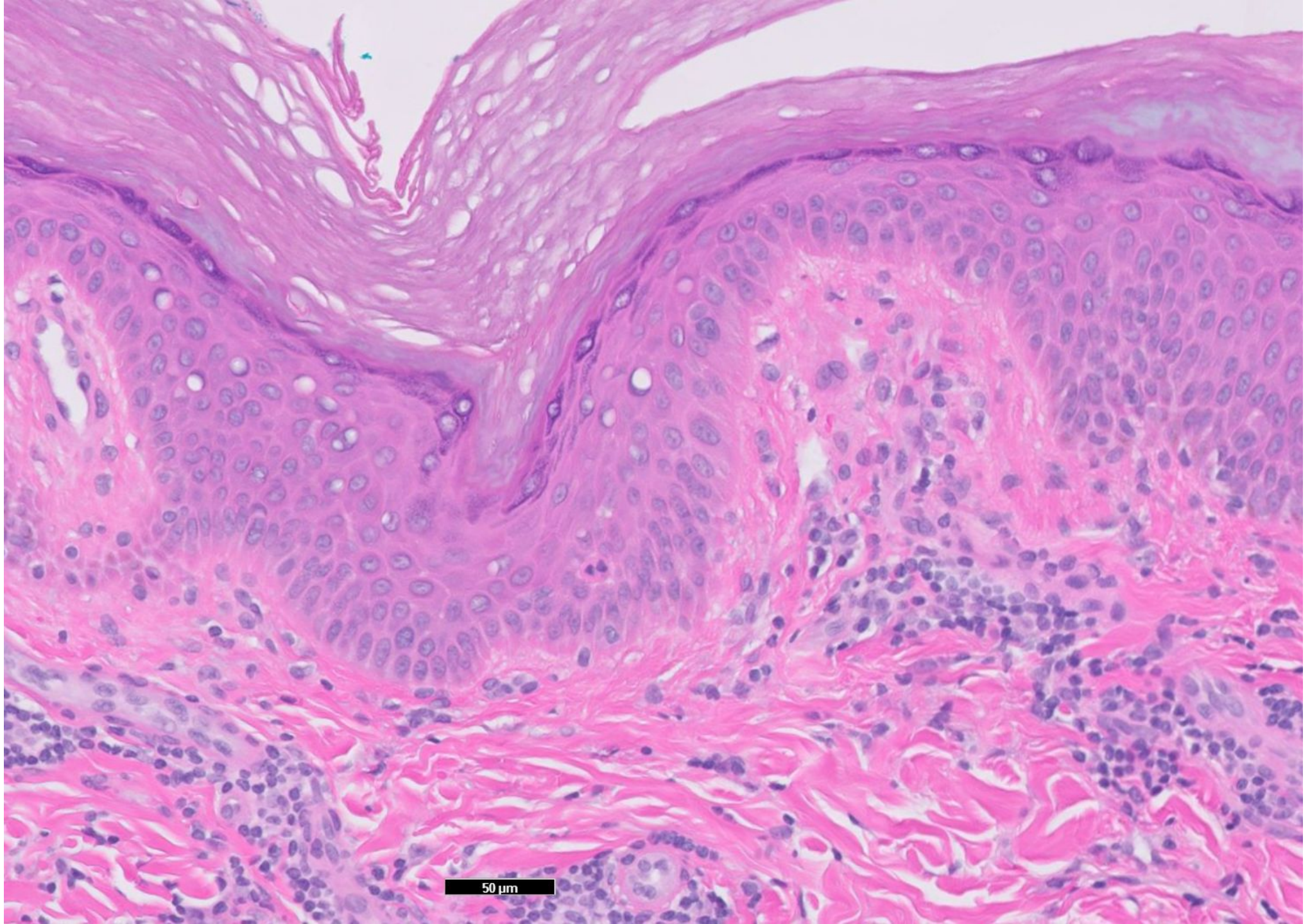

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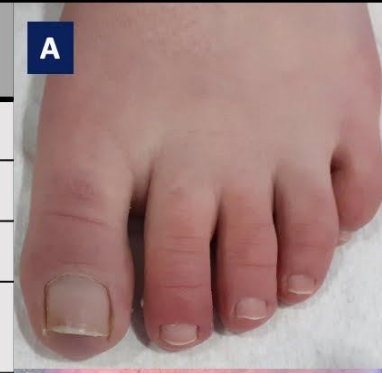
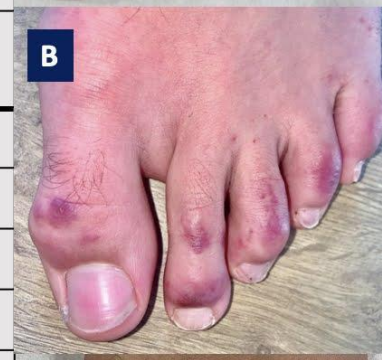
Prospective Brussels Study—32 patients

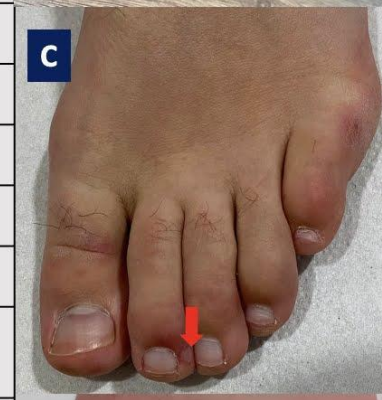
- PCR nasopharyngeal—32 patients
- Thoracic CT—28 patients
- Blood and urine labs—31 patients
- Skin biopsy—24 patients
- Direct immunofluorescence studies—24 patients
- Electron microscopy—4 patients

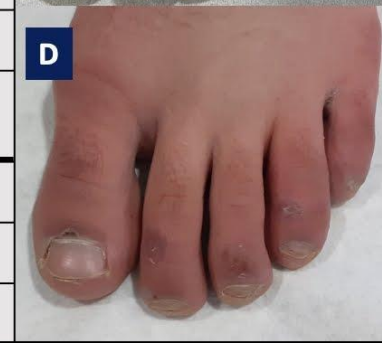
Clinical lesions

Clinical description of COVID-19 induced chilblains			Included patients	Patients after exclusion criteria
Diffuse erythema and edema	Location	Digits	30/32 (93.75%)	27/29 (93.10%)
		Lateral border of feet	2/32 (6.25%)	2/29 (6.89%)
		Soles	1/32 (3.12%)	1/29 (3.44%)
	Individual lesions with diffuse erythema and edema		22/32 (28.75%)	19/29 (65.61%)
	Diffuse erythema and edema only		10/32 (31.25%)	10/29 (34.48%)
Individual lesions	Location	Dorsal side of digits	30/32 (93.75%)	27/29 (93.10%)
		Ventral side of digits	2/32 (6.25%)	2/29 (6.89%)
		Lateral border of feet	2/32 (6.25%)	2/29 (6.89%)
		Soles	1/32 (3.12%)	1/29 (3.44%)
	Primary elementary lesions	Macules	2/32 (6.25%)	2/29 (6.89%)
		Papules and plaques	18/32 (56.25%)	15/29 (51.72%)
		Nodules	0/32	0/29
		Vesicles	0/32	0/29
		Bullae	1/32 (3.12%)	1/29 (3.44%)
	Secondary elementary lesions	Erosions/ulcerations and/or crusting	17/32 (53.12%)	15/29 (51.72%)
		Excoriations	0/32	0/29
		Violaceous color/purpuric	14/32 (43.75%)	13/29 (44.82%)
Associated findings		Distal digital necrosis	0/32	0/29
		Livedo racemosa	0/32	0/29
		Retiform purpura	0/32	0/29









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Clinical Details

- No patient with autoimmune disease
- No evidence of thrombosis
- Cold exposure only 1/29
- Decreased physical activity 2/29
- Contact with COVID-19 in 3/29 (11%)
- PCR positive 1/29 (3.45%)

Clinical characteristics and complementary studies		Included patients		Patients after exclusion criteria	
Clinical history	Age (years)	See text			
	Gender	Female 19/32 (59.37%)	Male 13/32 (40.63%)	Female 16/29 (55.17%)	Male 13/29 (44.83%)
	Race/ethnicity	White 28/32 (87.5%), North African 4/32 (12.5%)		White 26/29 (89.65%), North African 3/29 (10.35%)	
	Raynaud	5/32 (15.62%)		3/29 (10.71%)	
	Smoking	3/32 (9.37%)		2/29 (7.14%)	
	Photosensitivity	0/32		0/29	
	Arthralgia/arthritis	0/32		0/29	
	Lupus, systemic sclerosis or other auto-immune disease	0/32		0/29	
	Thrombosis	0/32		0/29	
	Exposure to cold	1/32 (3.12%)		1/29 (3.57%)	
	Decrease of physical activities during lockdown	3/32 (9.37%)		2/29 (7.14%)	
	Contact with hospital, nursing home, assisted living facility	1/32 (3.12%)		1/29 (3.57%)	
	Contact with patient suspected of COVID-19 infection	13/32 (40.62%)		10/29 (35.71%)	
	Contact with confirmed COVID19 infected patient	4/32 (12.5%)		3/29 (10.71%)	
	Delay between general symptoms and chilblains	See text			
	Delay between chilblains and baseline visit	19.69 days in 32 patients		16.92 days in 29 patients	
	Symptomatic chilblains (pain and/or pruritus)	24/32 (75%)		21/29 (72.41%)	
Clinical examination	Temperature	37.47°C in 31 patients (35.6°C – 37.3°C)		36.51°C in 28 patients (35.6°C – 37.3°C)	
	Oxygen saturation	97.83% in 30 patients (95%-100%)		97.77 in 27 patients (95%-100%)	
	Heart rate	84.64/min in 31 patients (60-118/min)		85.07/min in 28 patients (60-118/min)	
	Respiration rate	17.72/min in 11 patients (15-19/min)		17.72 in 11 patients (15-19/min)	
Clinical evolution	Complete resolution without recurrence and total duration	After 2 weeks: 14/31 (45.16%) Total duration: 32.42 days	After 6 weeks: 15/24 (62.5%)	After 2 weeks: 11/28 (39.28%) Total duration: 32.75 days	After 6 weeks: 12/21 (57.14%)
	Partial resolution without recurrence	After 2 weeks: 12/31 (38.70%)	After 6 weeks: 5/24 (20.84%)	After 2 weeks: 12/28 (42.85%)	After 6 weeks: 5/21 (23.8%)
	No improvement	After 2 weeks: 2/31 (6.46%)	After 6 weeks: 2/24 (8.33%)	After 2 weeks: 2/28 (7.15%)	After 6 weeks: 2/21 (9.53%)
	Recurrence	After 2 weeks: 3/31 (9.68%)	After 6 weeks: 2/24 (8.33%)	After 2 weeks: 3/28 (10.72%)	After 6 weeks: 2/21 (9.53%)
Other studies	Positive COVID-19 PCR of nasopharyngeal swab	2/32 (6.25%)		1/29 (3.45%)	
	Abnormal findings on CT-Scan	0/28		0/25	
	Abnormal laboratory tests: Positive COVID-19 serology	6/31 (19.35%)		6/31 (19.35%)	
	Abnormal laboratory tests: Other abnormal findings	See text			

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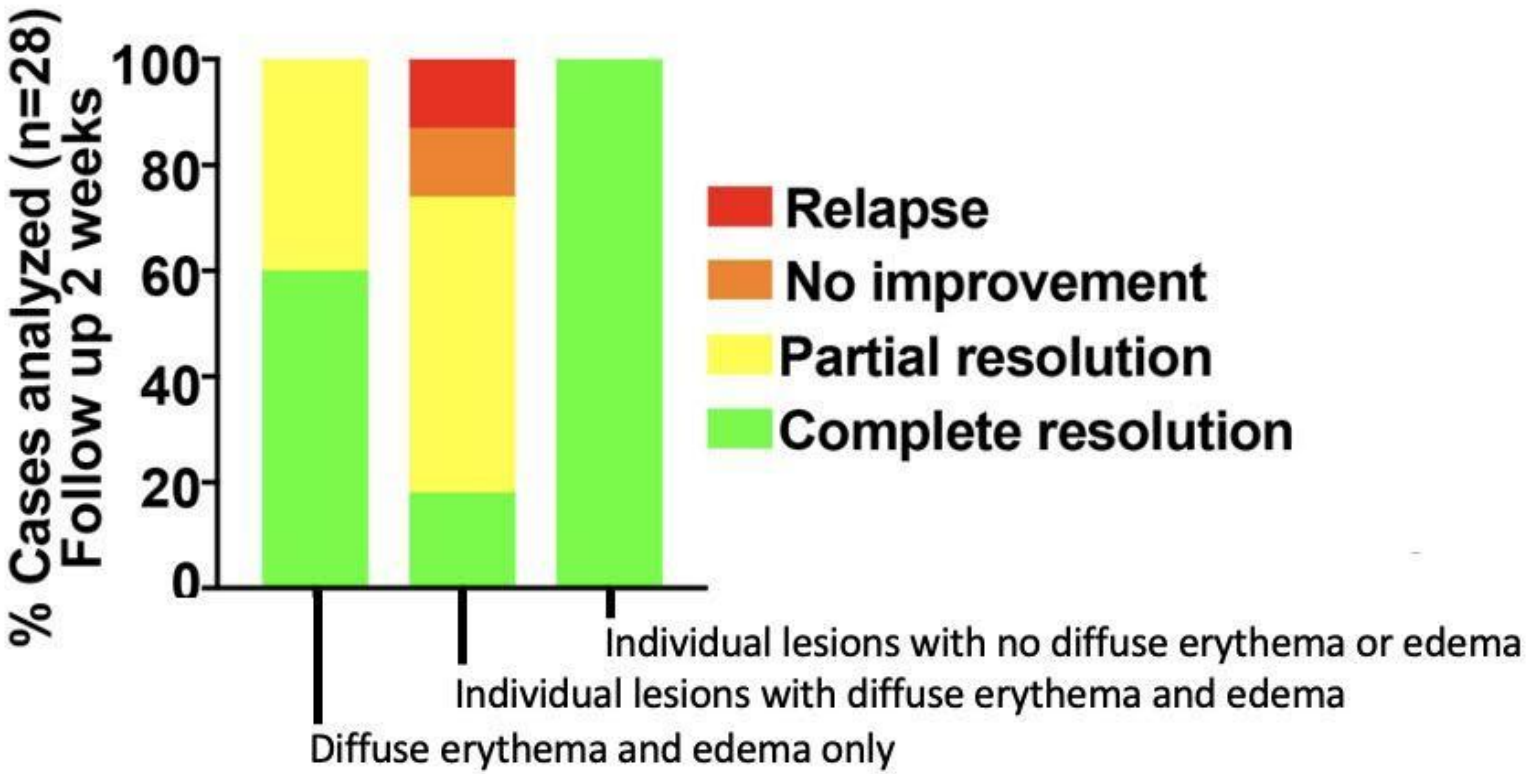
Clinical Course



Histopathologic findings:

- Interface with apoptotic keratinocytes in 100%
- Red cell extravasation in 76%.
- Lymphocytes in venule walls in 86%.
- Vessel wall thickening in 86%.
- Deep dermal lymphocytes 95%
- Peri-eccrine lymphocytes in 94%
- Peri-eccrine mucin in 95%

Histopathological findings		% of patients (n=21) with this finding present or absent	
		Present	Absent
Epidermal changes	Acanthosis	86	14
	Hyperkeratosis	100	0
	Parakeratosis	14 (upper) 43 (lower)	43
	Humid parakeratosis	38 (humid) 19 (dry)	43
	Spongiosis	33	67
	Exocytosis	48	52
Interface dermatitis	Vacuolar interface	62 (focal) 19 (Diffuse) 19 (Continuous)	0
	Number of apoptotic keratinocytes (x20)	48 (1 keratinocyte) 38 (2-3 keratinocytes) 14 (≥4 keratinocytes)	0
	Basal membrane thickening	48 (focal) 10 (diffuse)	42
	Lichenoid infiltrate	0	100
	Pigmentary incontinence	5 (focal)	95
Papillary dermal changes	Papillary dermal edema	28	72
	Red cell extravasation	76	24
	Fibrin deposition	14	86
Lymphocytic vasculitis	Peri-vascular lymphocytic infiltrate	14 (discrete) 43 (moderate) 43 (intense)	0
	Post-capillary venule wall infiltration	86	14
	Swollen endothelial cells	57	43
	Vessel wall thickening	86	14
	Fibrin deposition	5 (focal)	95
	Red cell extravasation	43	57
	Intraluminal thrombi formation	5 (focal)	95
Lymphocytic infiltrate	Superficial infiltrate	95	5
	Deep infiltrate	95	5
	Distribution	21 (top heavy) 5 (bottom heavy)	74 (no difference)
	Perivascular	14 (discrete) 43 (moderate) 43 (intense)	0
	Interstitial	48 (discrete) 24 (moderate) 10 (intense)	18
	Peri-eccrine	42 (discrete) 26 (moderate) 26 (intense)	6
Other	Interstitial mucin deposition	71 (focal) 29 (diffuse)	0
	Peri-eccrine mucin deposition	25 (focal) 71 (diffuse) 25 (intense)	5
	Collagen necrobiosis	0	100
	Subcutaneous infiltration	31 (discrete) 31 (moderate) 7 (intense)	31

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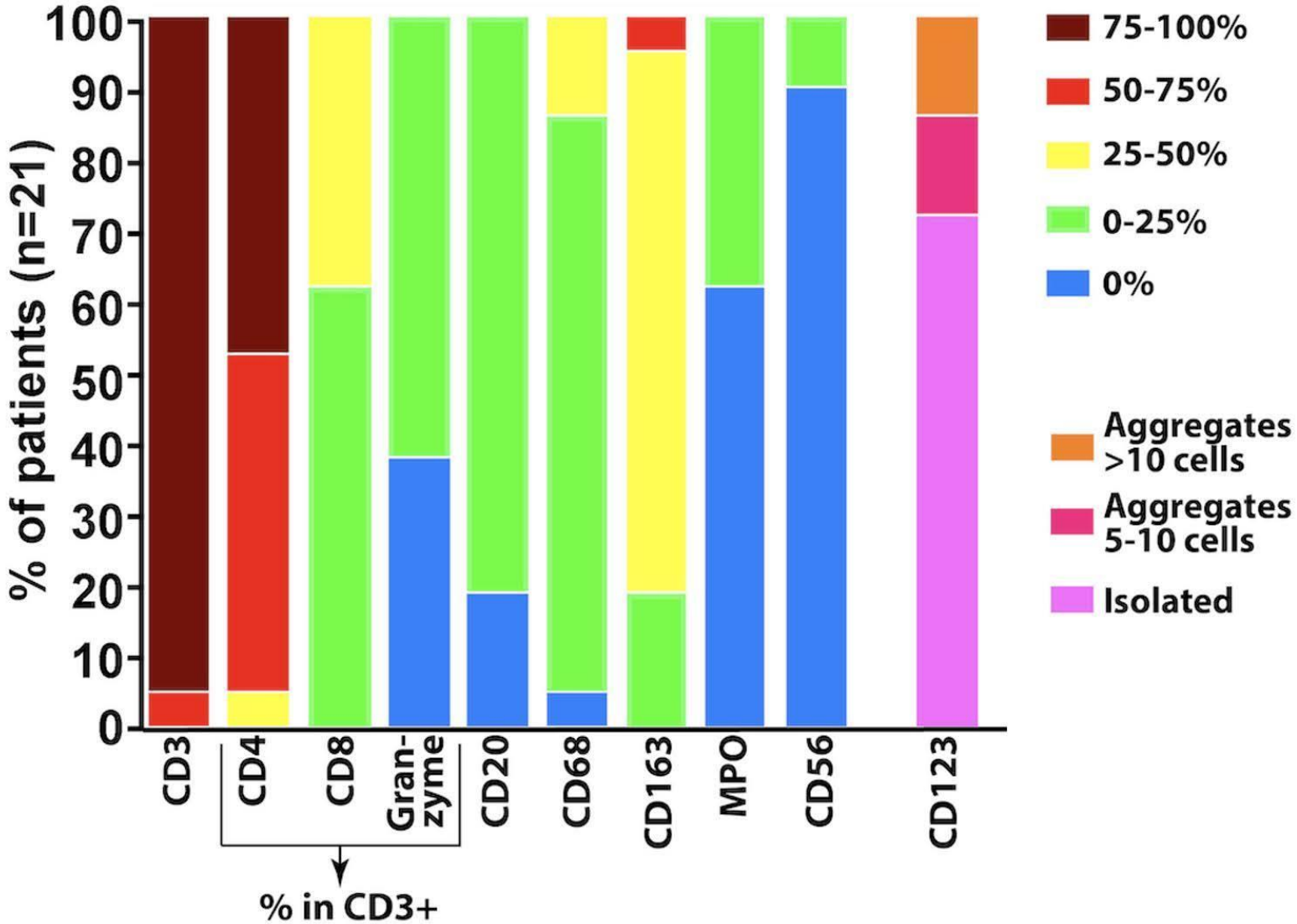
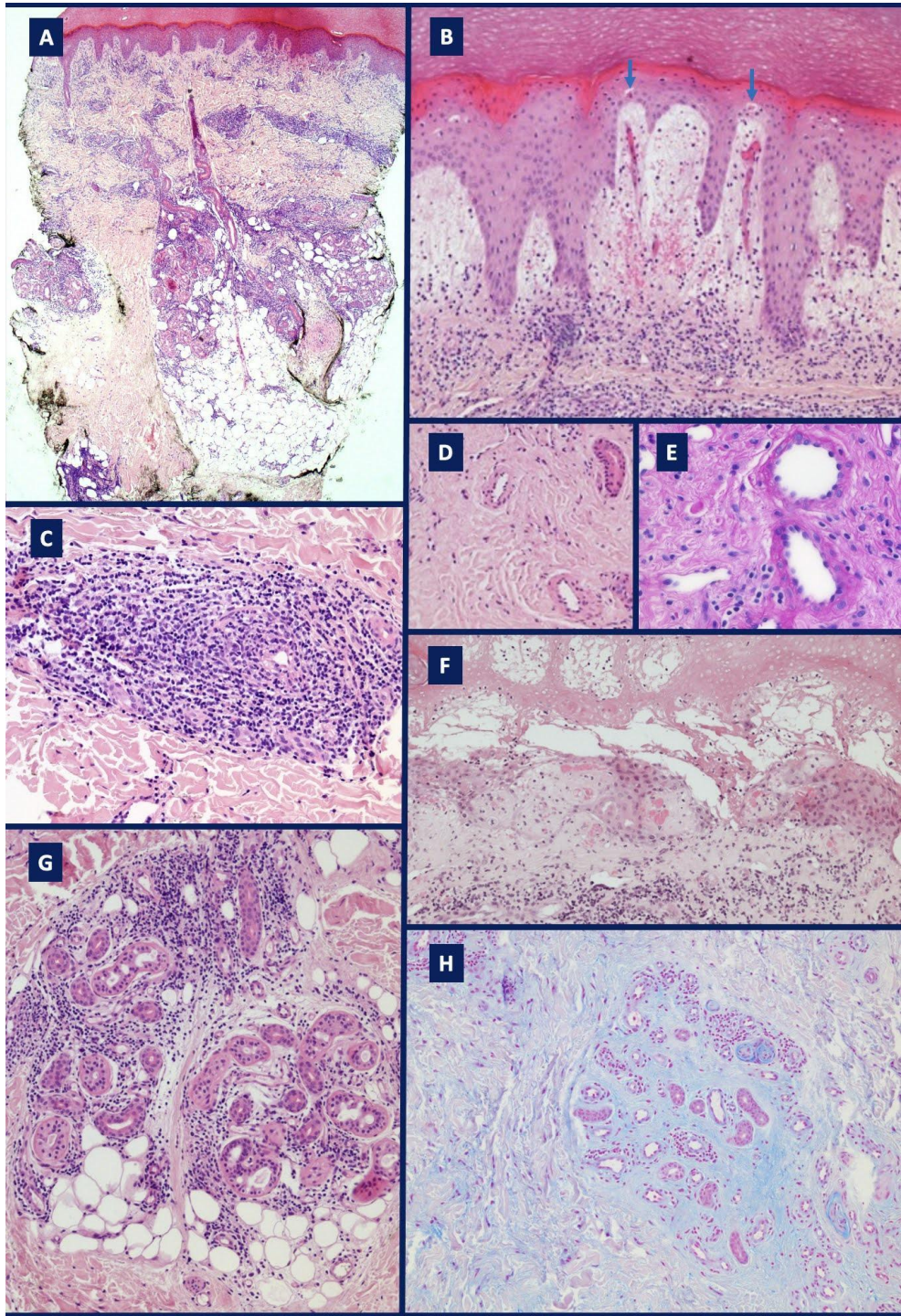
Immunohistochemistry



Direct immunofluorescence (DIF)		% of patients (n=21) with positive DIF				
		IgG	IgA	IgM	C3	Fibrinogen
Blood vessel walls	Superficial dermis	0	0	23 (focal)	23 (focal)	35 (focal) 35 (moderate)
	Deep dermis	0	0	23 (focal)	0	35 (focal) 8 (moderate)
Dermo-epidermal junction		0	0	0	8 (granular)	4 (linear continuous) 4 (linear discontinuous)

Histopathology identical to chilblains from other causes



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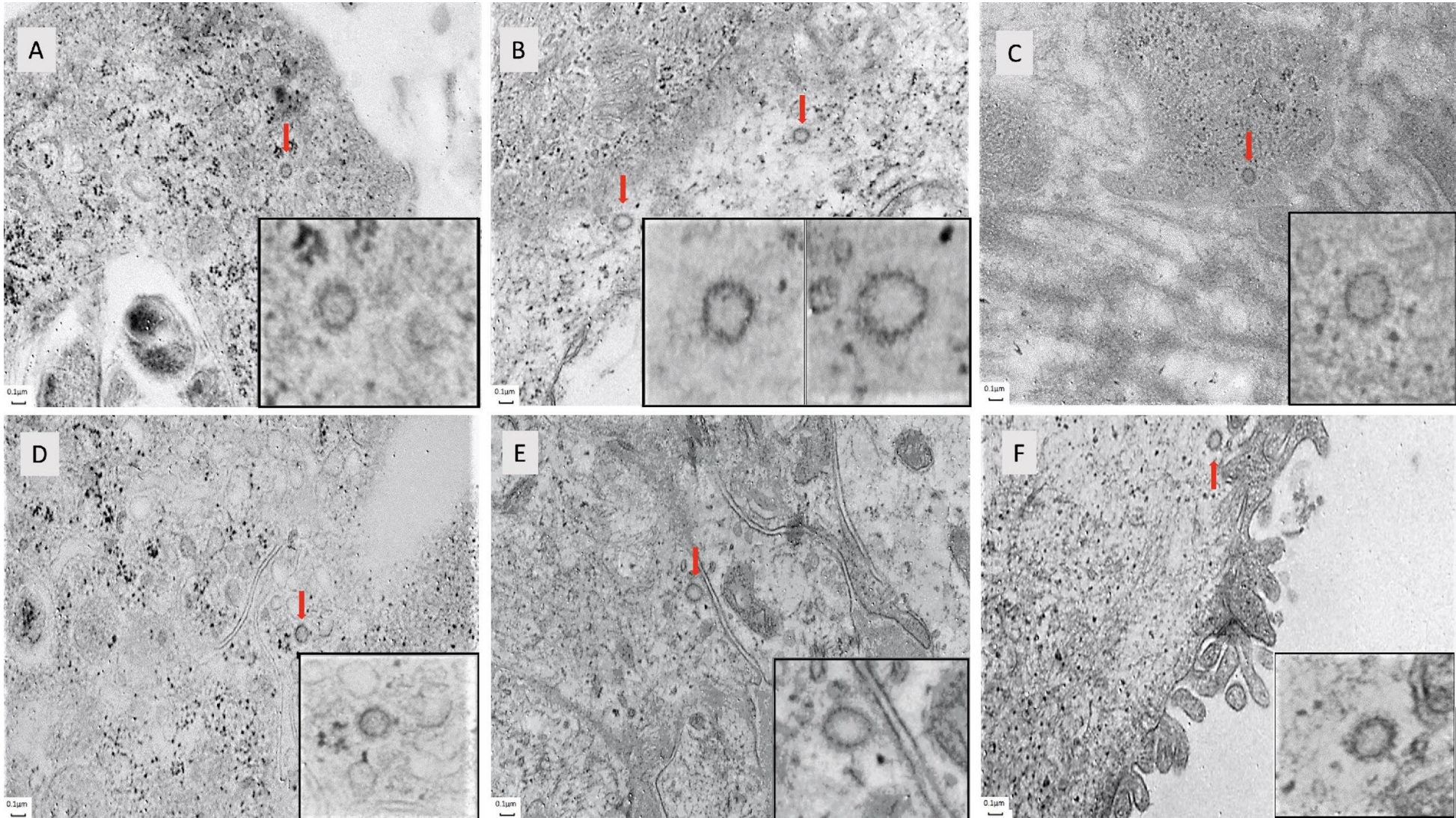
Probable viral particles 120-133µm



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Chilblains vs Chilblain lupus erythematosus

- Chilblain LE is a manifestation of chronic cutaneous LE (CCLE)
  - Discoid lesions on hands/fingers and feet/toes
  - Subungual (nail bed) hyperkeratosis
  - Atropic digital ulcers similar to those seen in systemic sclerosis
  - Proximal nail fold capillary alterations (dermoscopic)
  - Histopathology—Interface dermatitis

- Chilblains—digits are normal
  - Swelling = Papillary dermal edema
  - No interface dermatitis

Parvovirus B19 simulating SLE

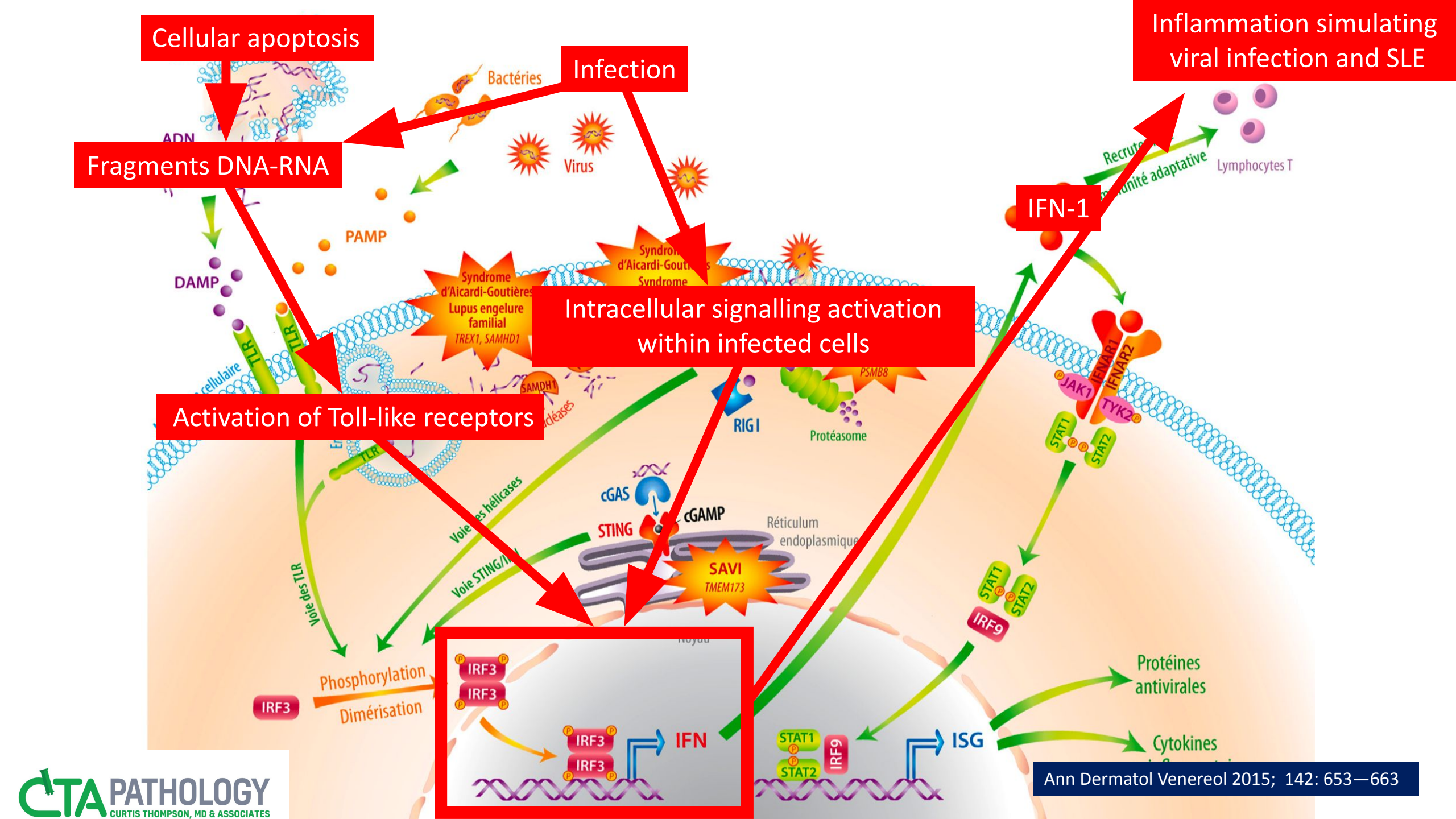
- Accumulation of nucleic acids after apoptosis

- Transient ANA titer and other serologies
  - RF, anti-DS-DNA, anti-phospholipids,
  - Ribonucleoprotein, Sjögren syndrome A/B
  - Topoisomerase scl-70

- When the ANA is positive, the patient is no longer considered to be infectious.

Parvovirus B19 simulating SLE

Clinical feature	Parvovirus B19 infection	Lupus
Course	Self-limiting	Persistent
Severity	Mild	Mild to severe
Persistent fevers	Rare	May be present
Anemia	Secondary to bone marrow suppression	Secondary to autoimmune hemolysis
Reticulocyte count	Low in presence of bone marrow suppression	Normal to high in presence of evidence of hemolysis
Splenomegaly	Rare	May be present
Discoid lesions, alopecia	Absent	May be present
Oral ulcers	Rare	May be present
Raynaud phenomenon	Absent	May be present
Neurologic (seizures, psychosis, chorea) and ocular symptoms	Rare	May be present
Gastrointestinal involvement (peritonitis, pancreatitis, obstruction/pseudo-obstruction)	Rare	May be present
Cardiac involvement	Rare	May be present
Renal involvement	Rare	May be present



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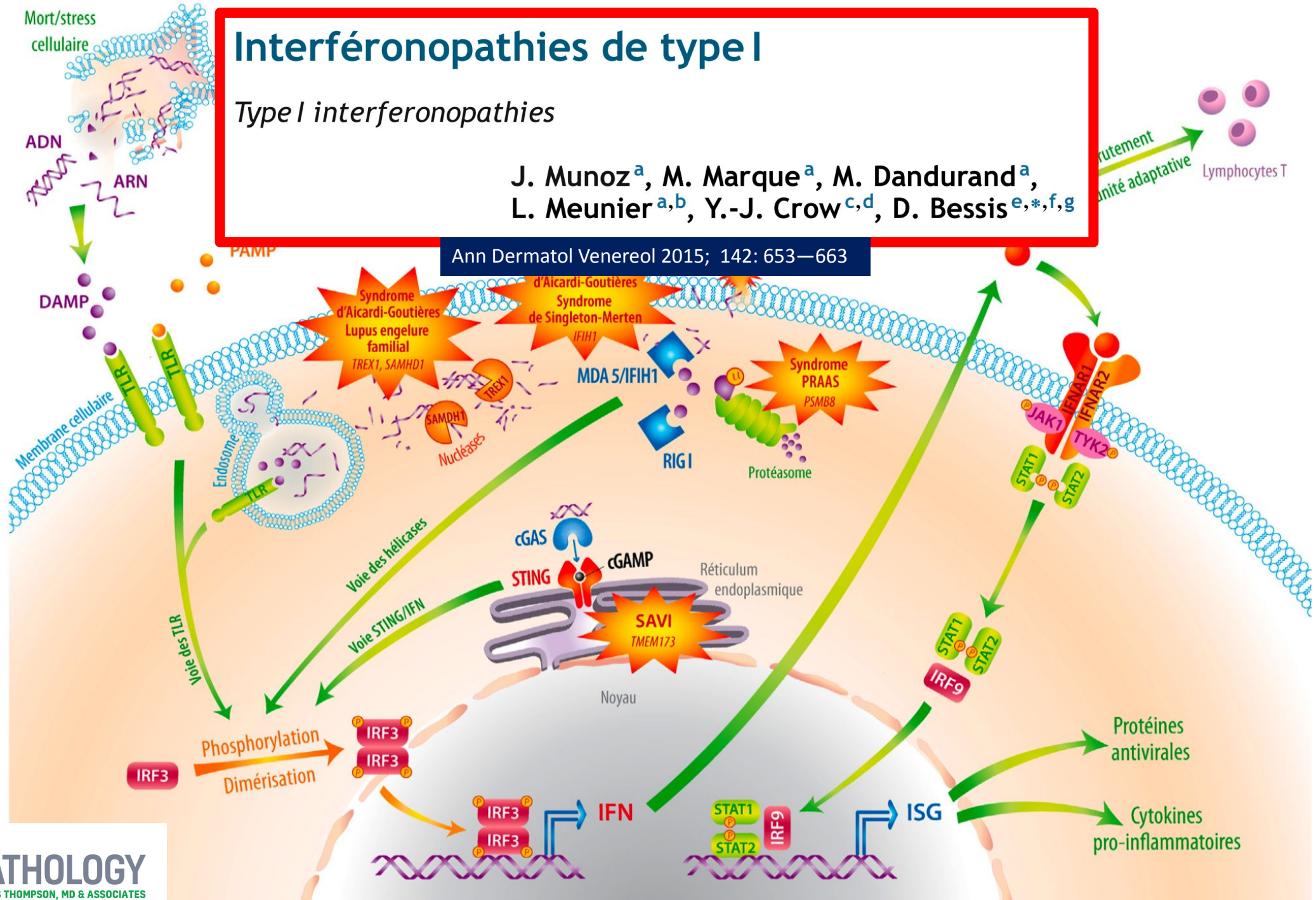
Ann Dermatol Venereol 2015; 142: 653—663

Interféronopathies de type I

Type I interferonopathies

J. Munoz[a], M. Marque[a], M. Dandurand[a], L. Meunier[a,b], Y.-J. Crow[c,d], D. Bessis[e,*,f,g]

Ann Dermatol Venereol 2015; 142: 653—663



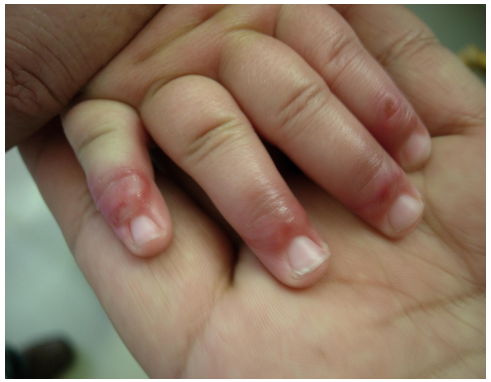
Type I Interferonopathy	Major cutaneous findings	Major extra-cutaneous findings	SLE-like
Aicardi-Goutières syndrome (AGS)	Chillblains, digital amputations, ear tissue loss, panniculitis	Severe neurological disease with developmental delay and intracranial calcification	+++
Familial chillblain lupus (FCL)	Chillblains, digital amputations, ear tissue loss	-	+
Spondylenchodrodysplasia (SPENCD)	Chillblains, digital amputations	Skeletal dysplasia, neurological developmental delay with intracranial calcification	+++
Stimulator of interferon genes (STING) - associated vasculopathy with onset in the infancy (SAVI)	Chillblains, digital amputations, ear tissue loss	Interstitial lung disease	+++

Ann Dermatol Venereol 2015; 142: 653—663

Cutaneous histopathological findings of Aicardi–Goutières syndrome, overlap with chilblain lupus

Athanassios Kolivras[1], Alec Aeby[2], Yanick J. Crow[3], Gillian I. Rice[3], Ursula Sass[1] and Josette André[1]

J Cutan Pathol 2008; 35: 774–778



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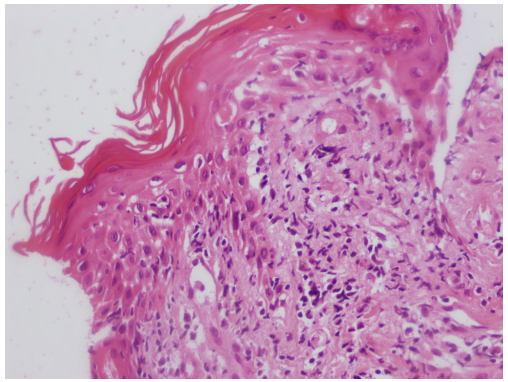

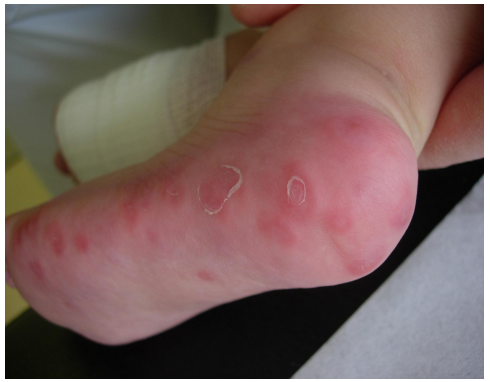

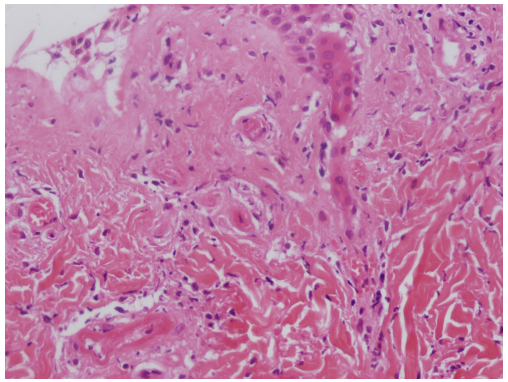

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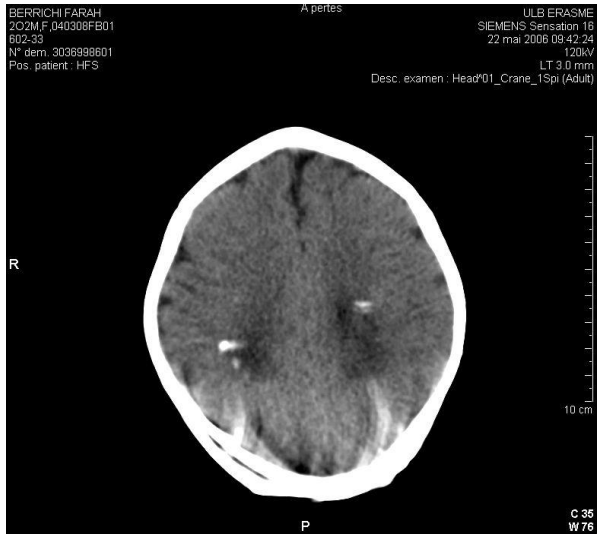

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Aicardi-Goutières syndrome

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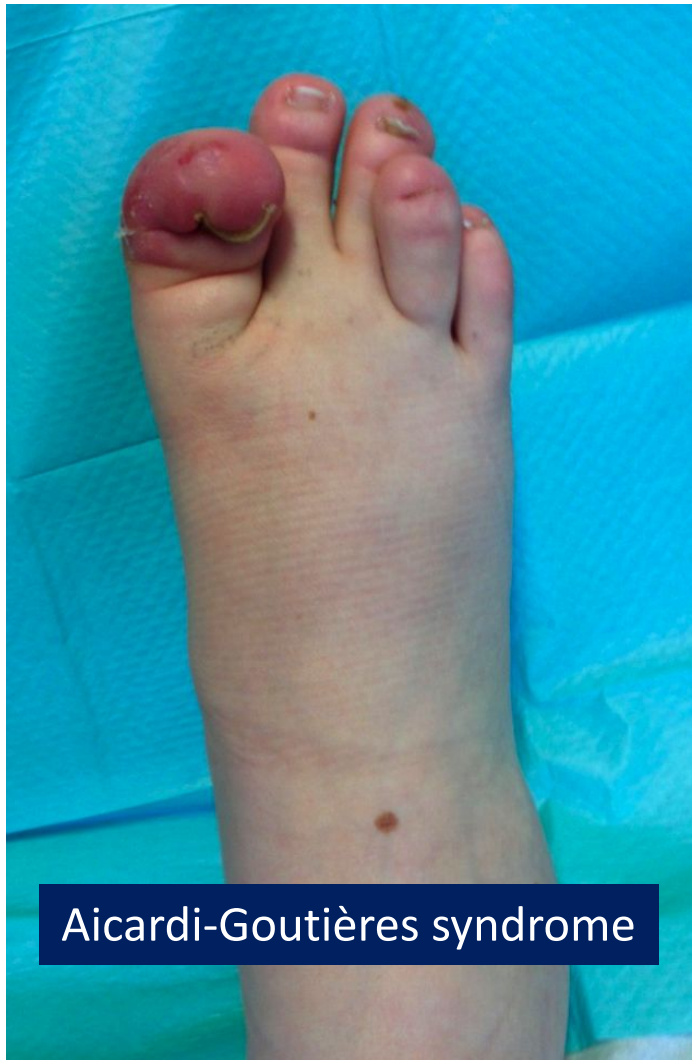
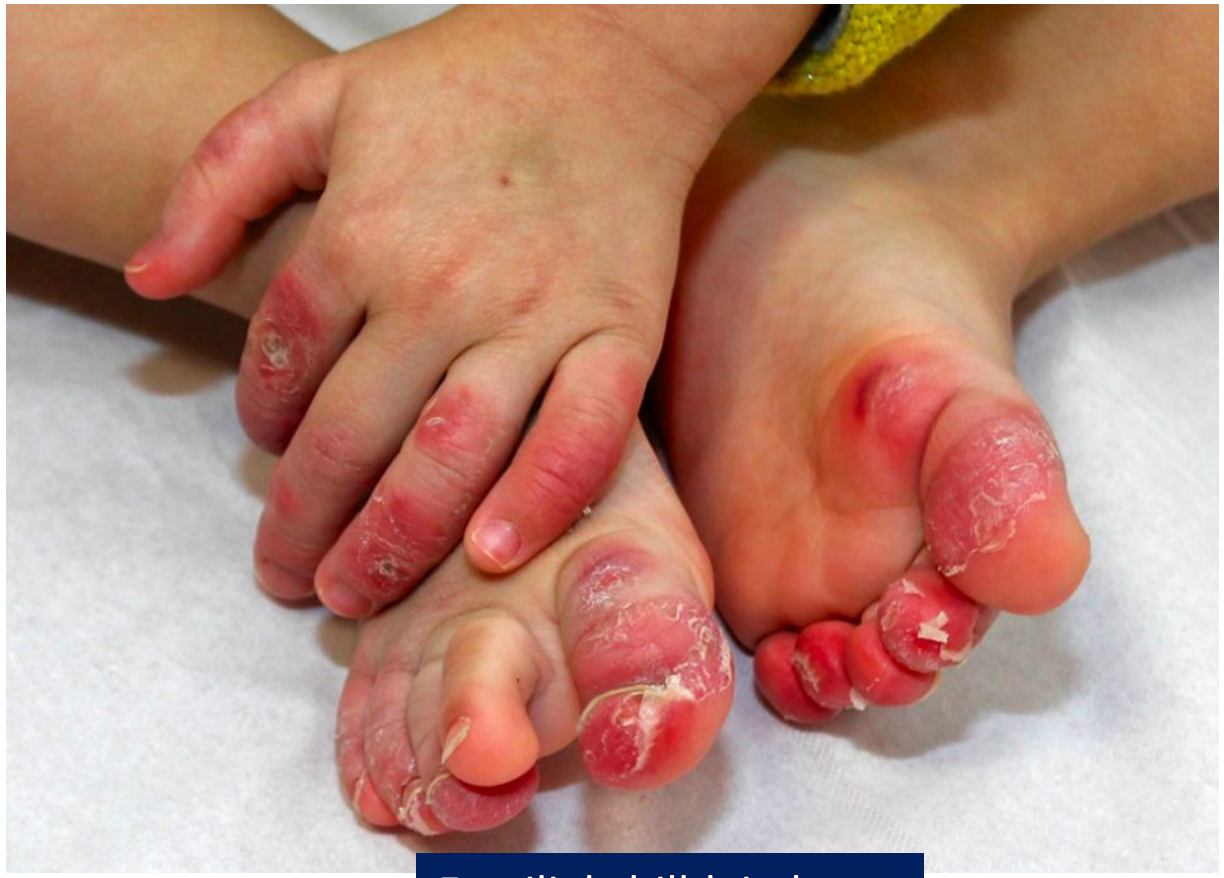
Familial chilblain lupus and Aicardi-Goutières syndrome are allelic phenotypes of the same disease



Aicardi-Goutières syndrome

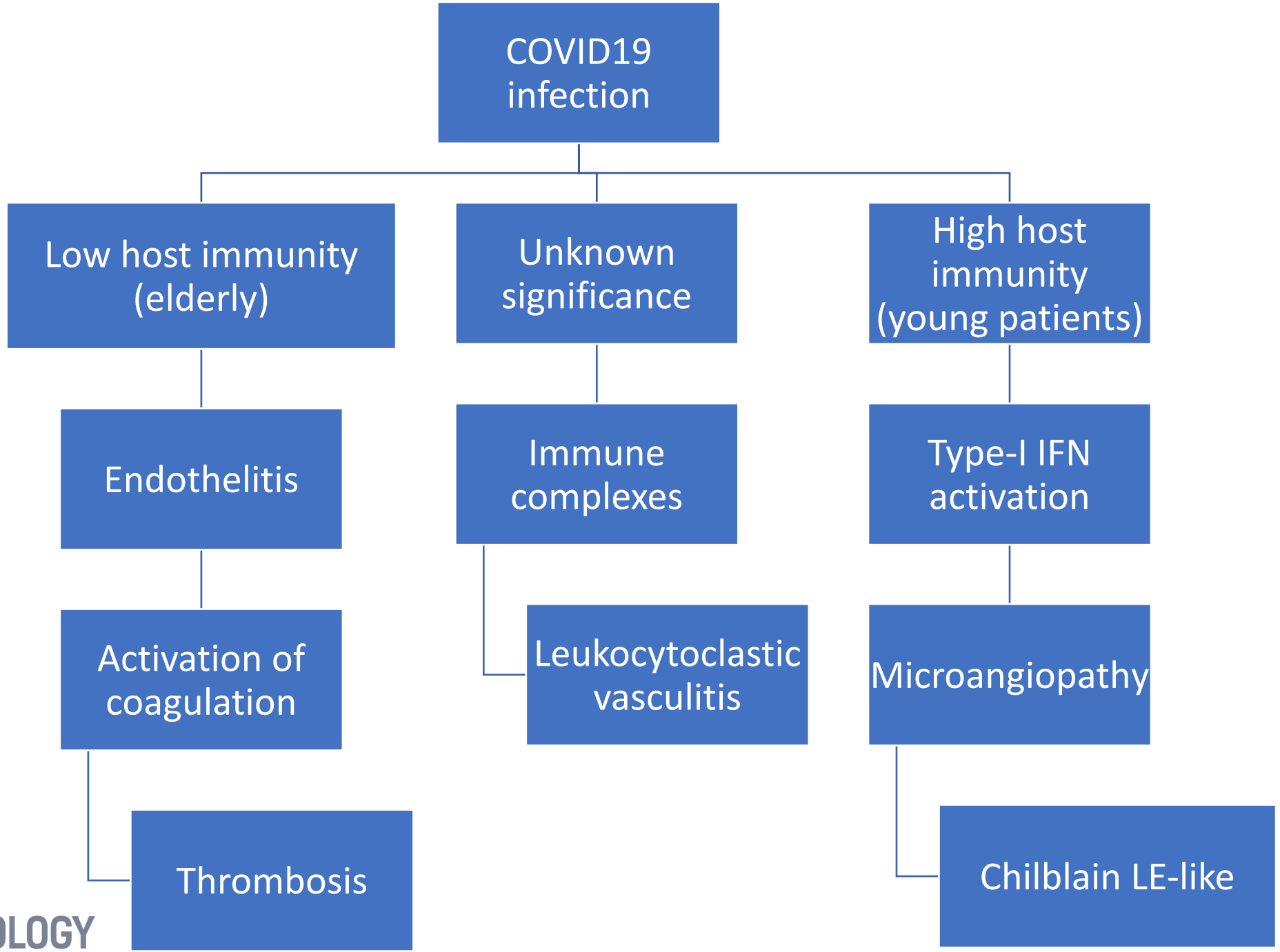


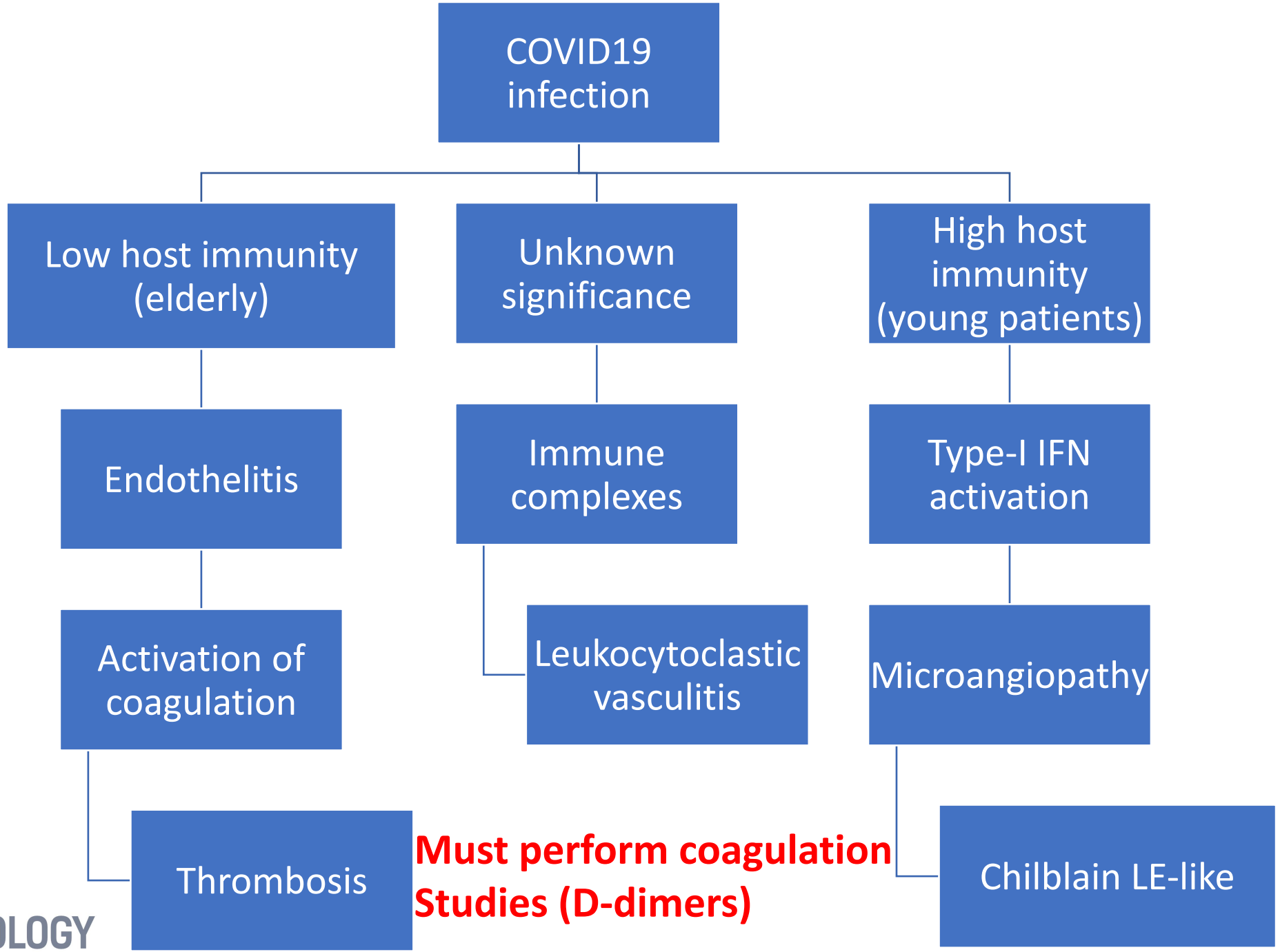
Familial chilblain lupus

Ann Dermatol Venereol 2015; 142: 653—663

Summary of COVID-19 Toes

- Stronger evidence that COVID-19 may cause chilblains, especially in young people;
- COVID-19-induced chilblains are histologically identical to chilblains resulting from the many other primary and secondary causes;
- No patients showed evidence for a systemic coagulopathy or a genetic susceptibility for a hypercoagulable state;
- Negative PCR and antibody tests do not rule-out COVID-19 causality;
- COVID-toes signal a good prognosis usually in asymptomatic patients.





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Cheers!

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CTA Lab
CURTIS THOMPSON, MD & ASSOCIATES
Skin, Hair and Nail Pathology Experts

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