# What you need to know about nail pathology

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# History

- Galen 2nd century BCE—hair shaft analogy
- 19th century—Zander/Kolliker/Unna
  - Embryology and comparative anatomy
- Early 20th nail development/anatomy
- Late 20th—Dr. Nardo Zaias—expanded concept of the nail unit

# History

- Late 20th—Zaias—expanded concept
  - Proximal NF, matrix, bed, hyponychium
  - Importance of all areas in formation and maintenance of a functional nail plate.

# Claw versus Nail

- Advantage over claw
  - Protection
  - Enhances sensation at fingertip
  - Hygiene

# Modern studies

- Chemical composition
- Genes
- Concept of Onychodermis
  - CD10+ and CD13+ cells

# Embryology

- Imaging (light, electron microscopy)

**TABLE 2.1 Stages of Nail Development of the Embryo**

| Nail Unit[a] | Embryonic/Fetal Skin[b] | Development |
|---|---|---|
| Plaque phase | Earliest recognizable digits | Day 42+ gestation |
| Fibrillar phase | Primary nail field appears | Day 70+ |
| Granular phase | Keratohyalin granules develop | Day 84+ |
| Squamous phase | Distinct keratin plate identifiable | Day 120+ |
| Definitive-nail phase | Matrix produces true nail plate | Day 150+ |

[a]Suchard R. Des modifications des cellules de la matrice et du lit de l'ongle dans quelques cas pathologiques. *Arch Physiol. (Paris)* 1882;2:445.

[b]Holbrook KA, Odland GF. The fine structure of the developing human epidermis: light, scanning, and transmission electron microscopy of the periderm. *J Invest Dermatol.* 1975;65: 16–38.

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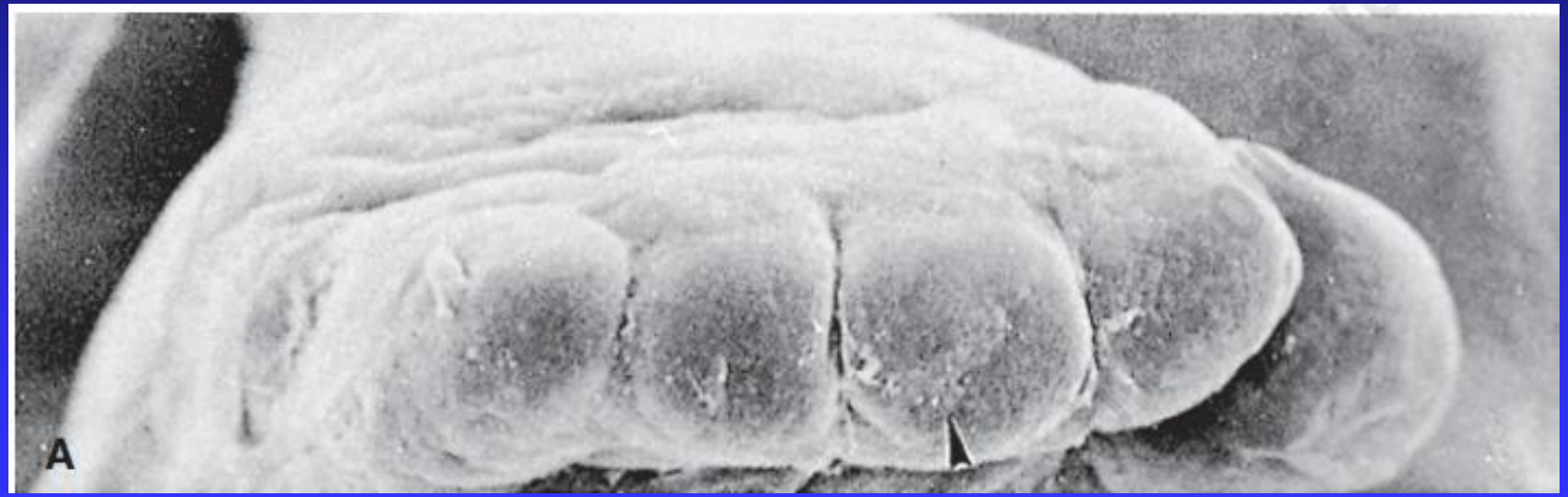
Thompson, CT. The normal nail unit, Histology for Pathologists, 6th Edition, Wolters Kluwer

# Plaque phase Day 42+

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# Fibrillar Day 70+


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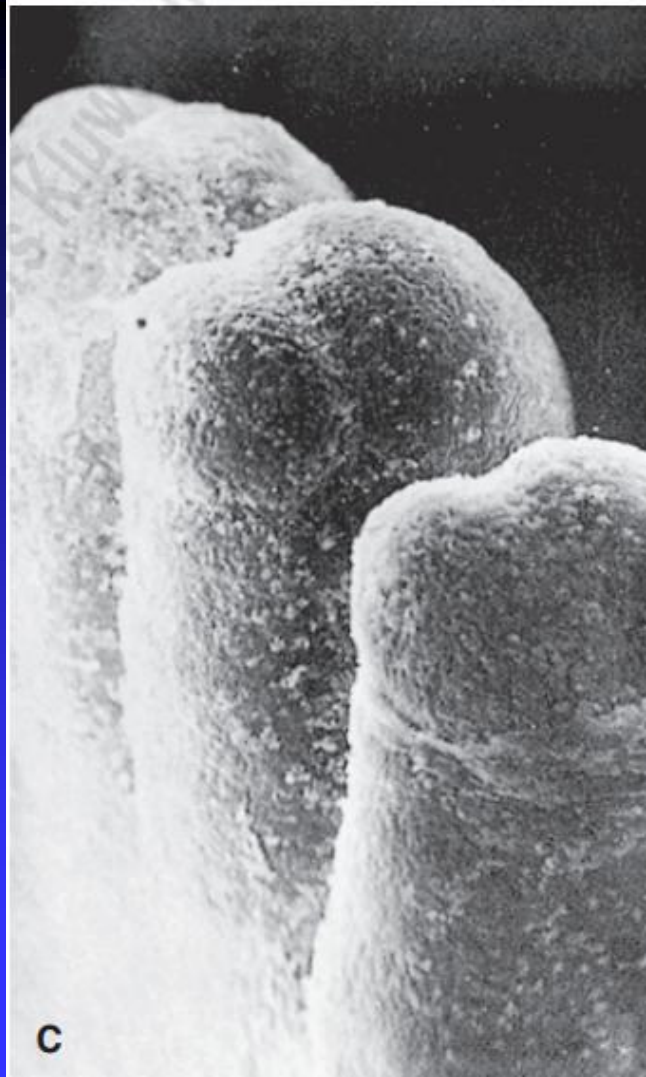
# Granular day 84+

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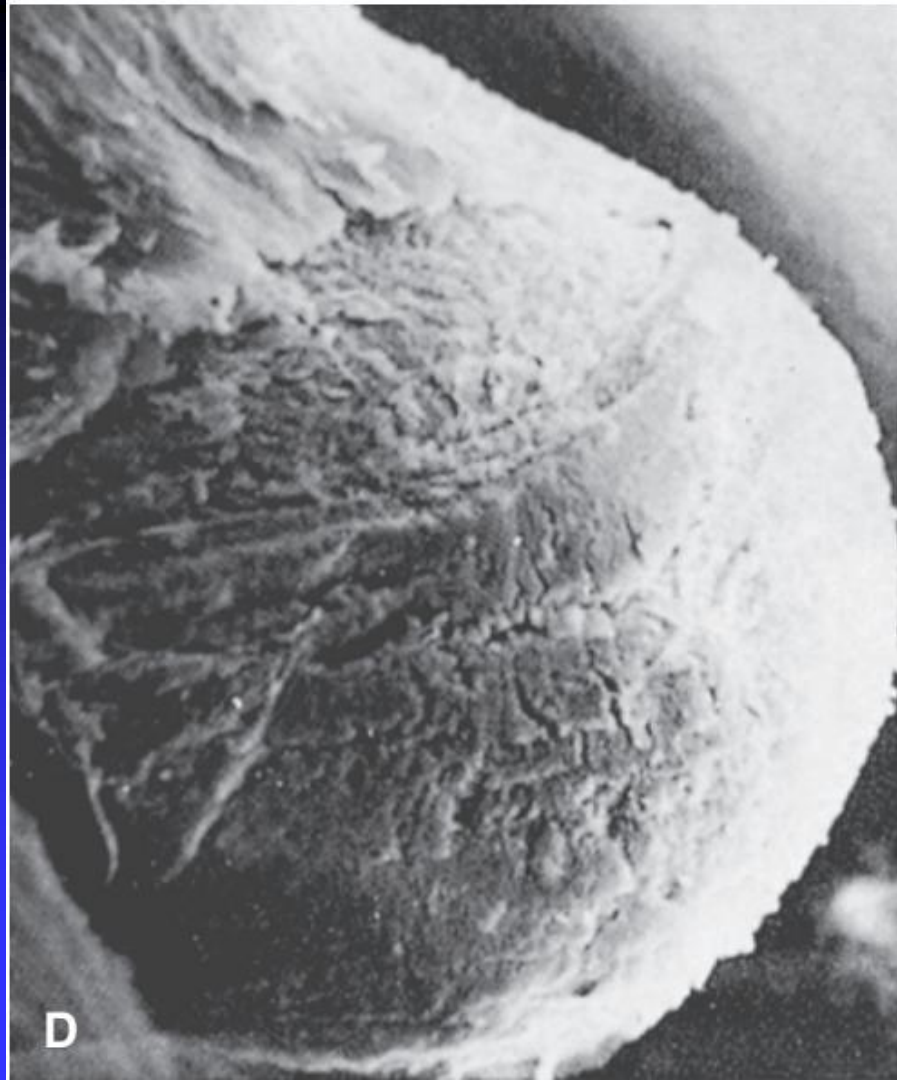
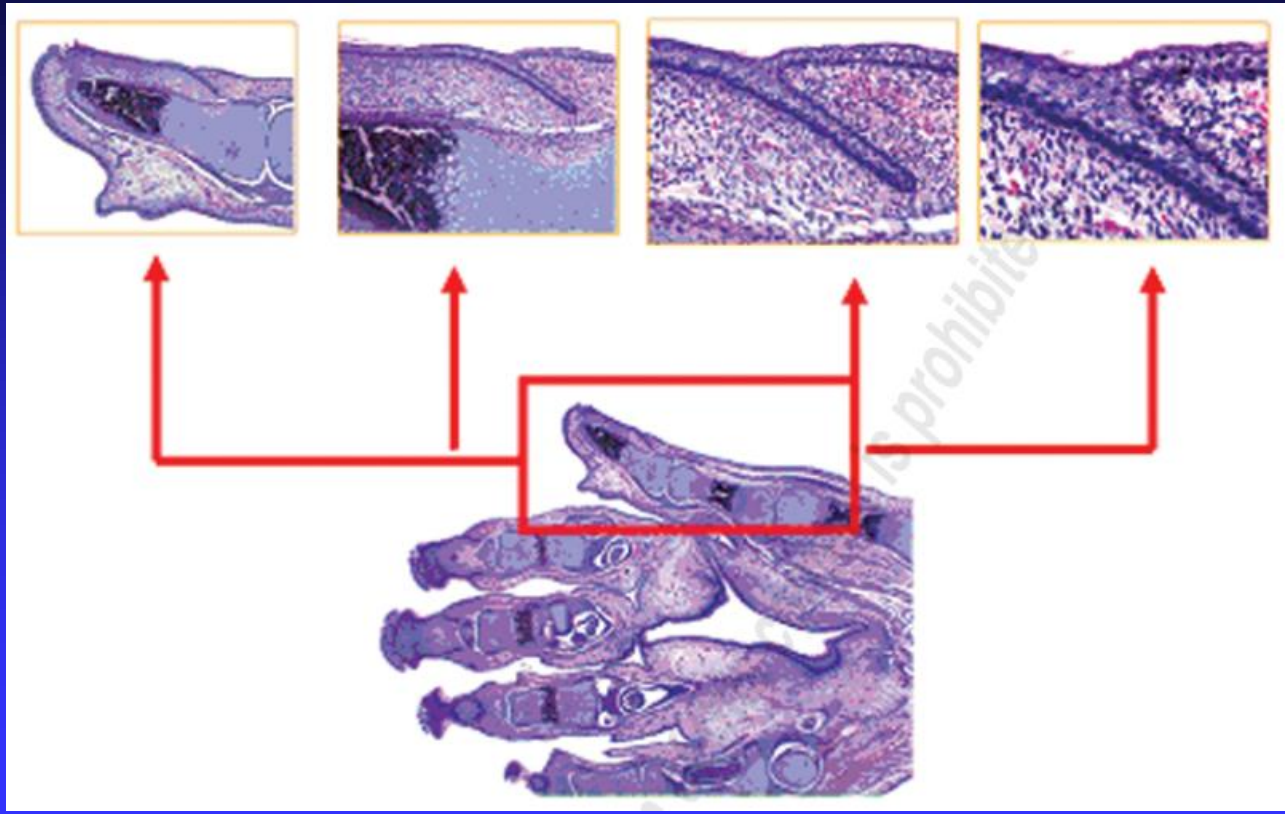
# Squamous Day 120+




Thompson, CT. (In Press, 2024). The normal nail unit, Histology for Pathologists, 6th Edition, Wolters Kluwer

# ~Day 112



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# Genetics

- Limb field  Hox transcription factors
  - (bind DNA and regular mRNA transcription)
- T-box genes—fore and hind limb
- Fibroblast GF 8—limb bud outgrowth
- Wnt7a—dorsal surface localization of unit
- Msx1/Msc2—unique nail unit

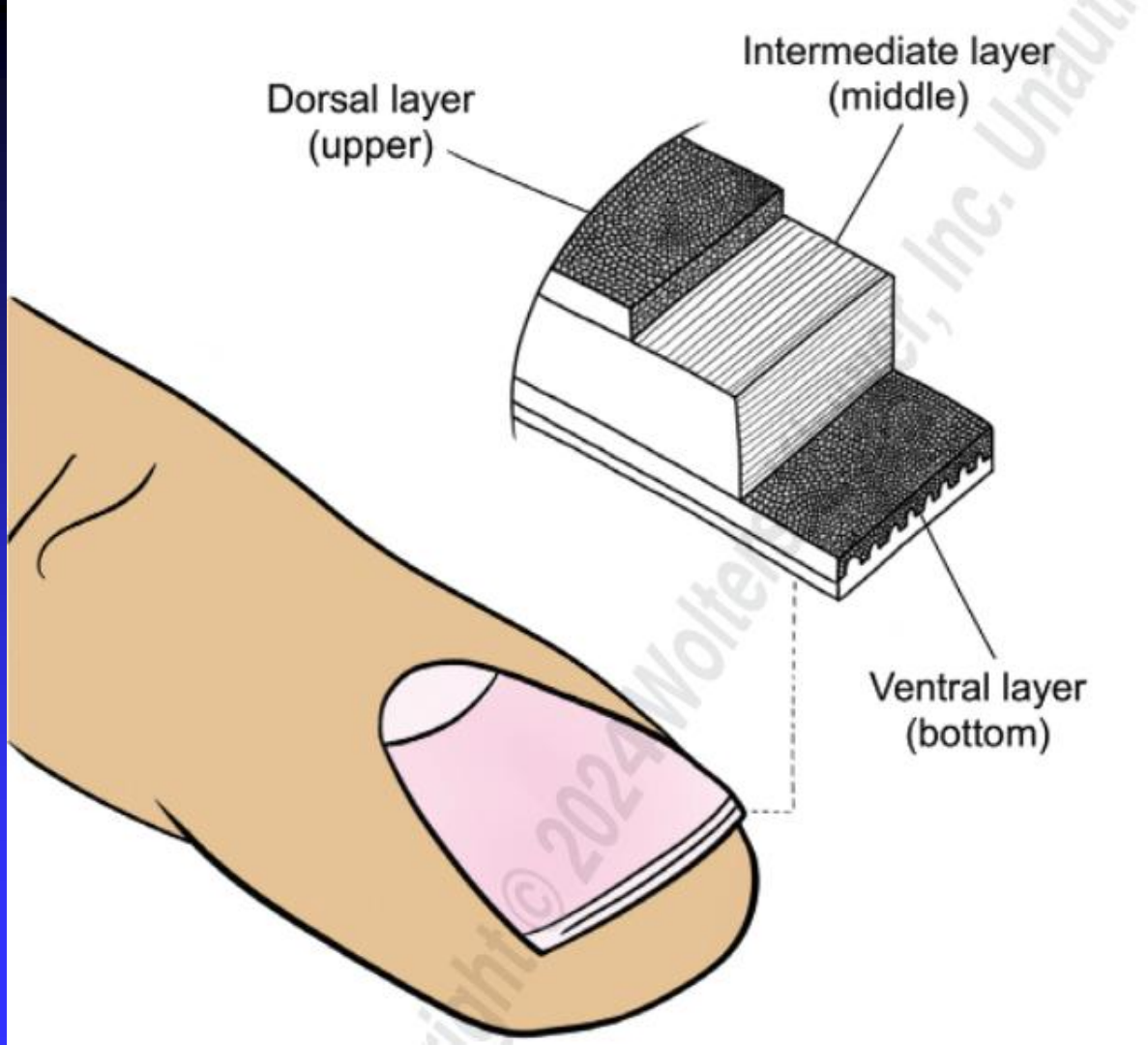
# Molecular—Primate Differences

- Major genes conserved among species (keratins)
- Regulatory mechanisms—near major genes
  - ‘cis-regulatory hypothesis’
    - Promotors, enhancers, silencers

# Keratins

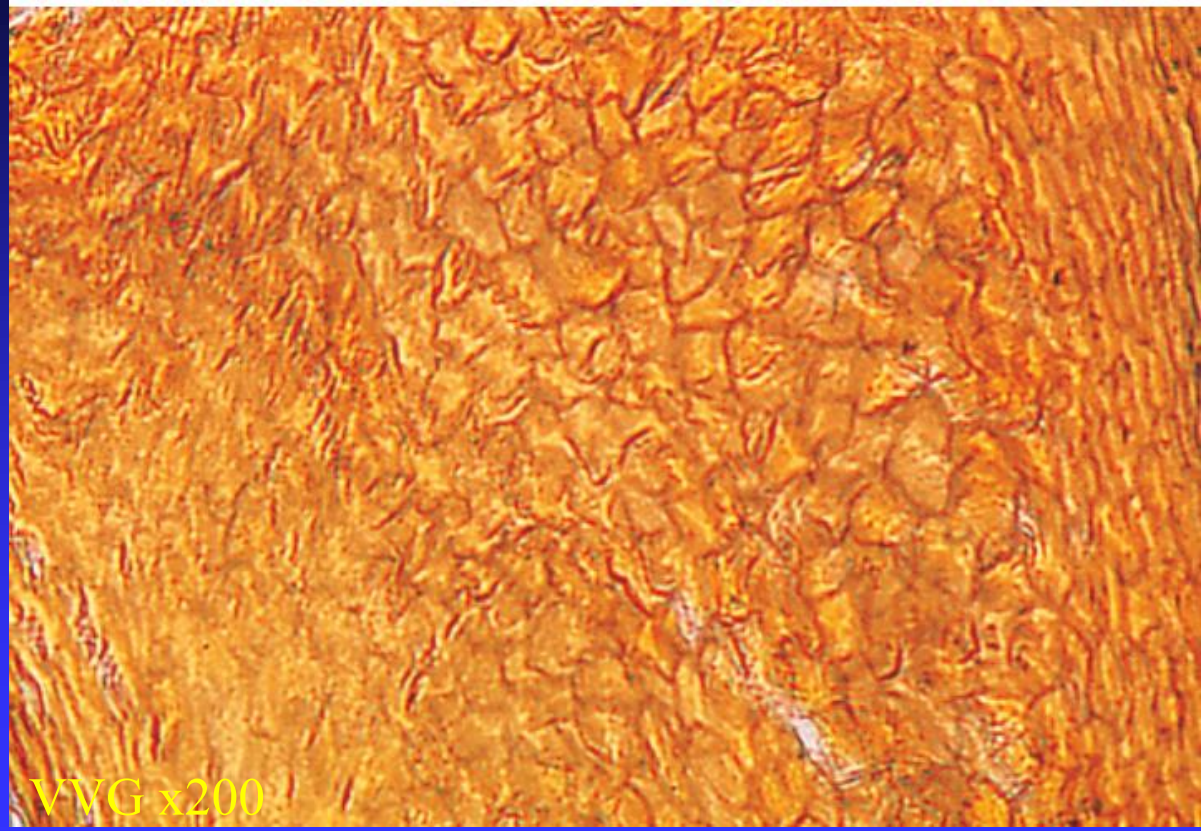
- Hard α-keratin 80%
- Soft α-keratin 20%

# Plate Architecture



# Plate layers (dorsal and ventral)

- Slanted corneocytes
- Desmosomes
- Lipid bilayer

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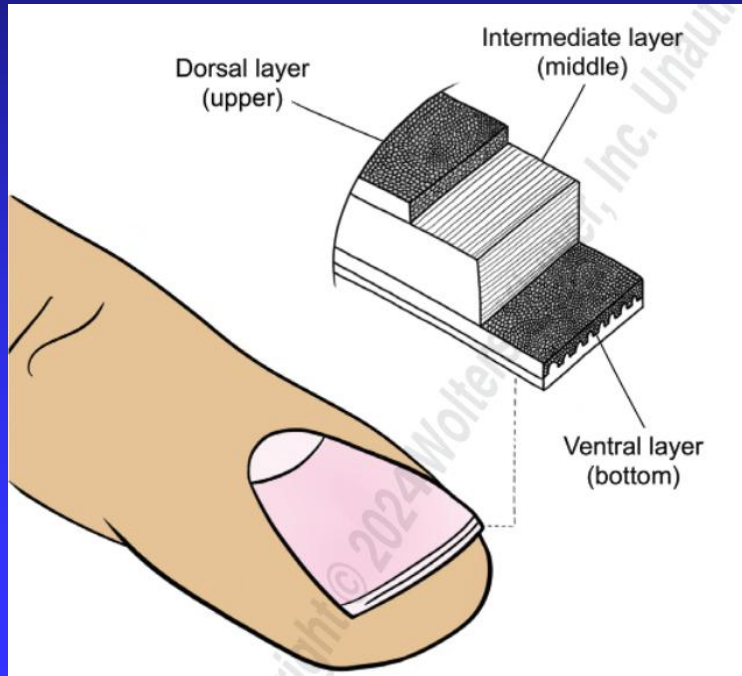
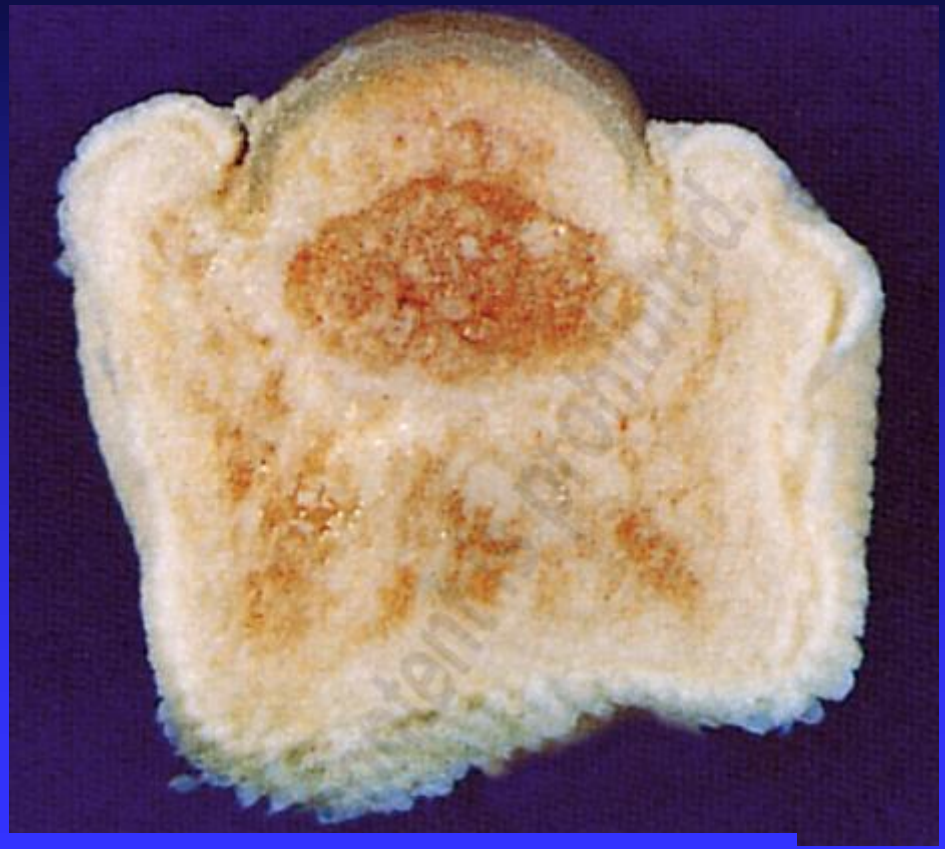
# Plate layers (intermediate)

- Corneocytes with nuclear remnants
- α-keratin
  - Transverse orientation
  - Strength




Thompson, CT. The normal nail unit.
Histology for Pathologists, 6th Edition, Wolters Kluwer

# Curvature important



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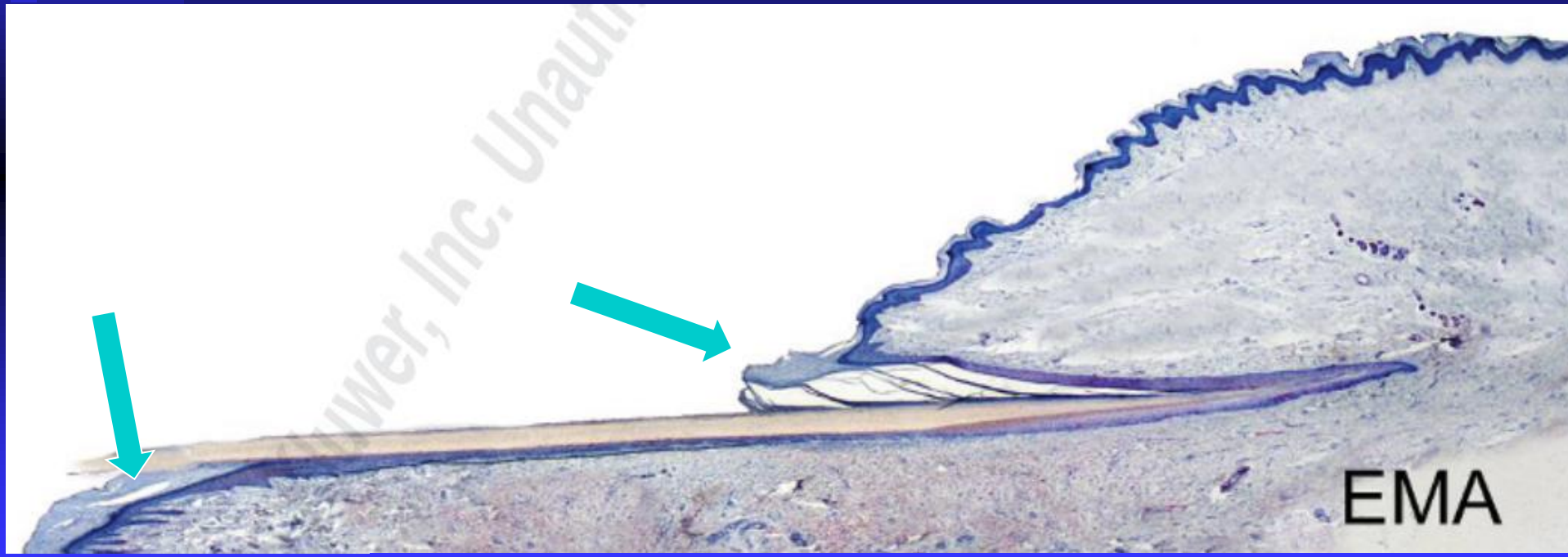
# Calcium

- 0.1% of nail weight
- 10x greater than hair shaft
- Dorsal and ventral layers

# Other minerals

- Copper, manganese, zinc, iron
  - ?Exogenous
- Utility in forensics—arsenic, drug metabolites

# Protection from environment

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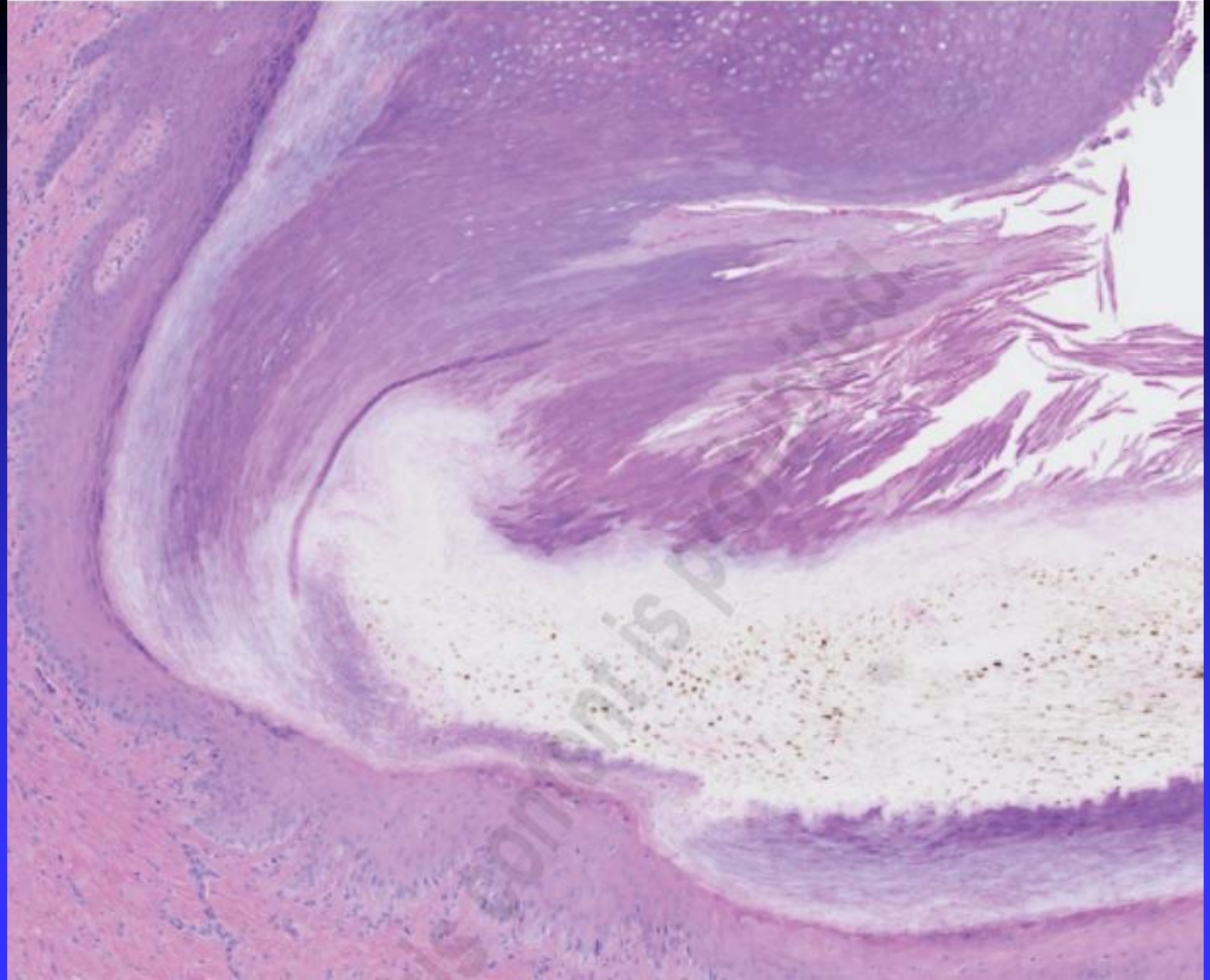
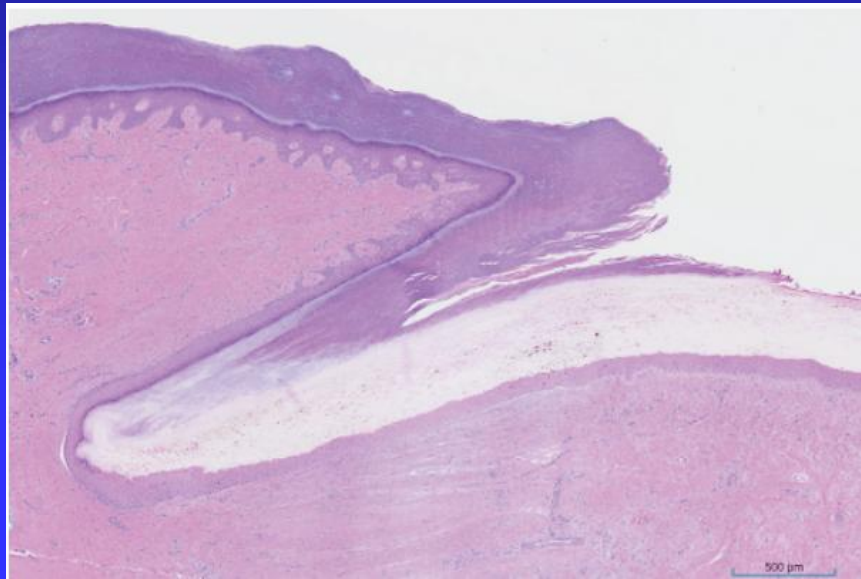


# Immune Protection (Infection)

- Proximal nail fold has a higher density CD4+ T-cells

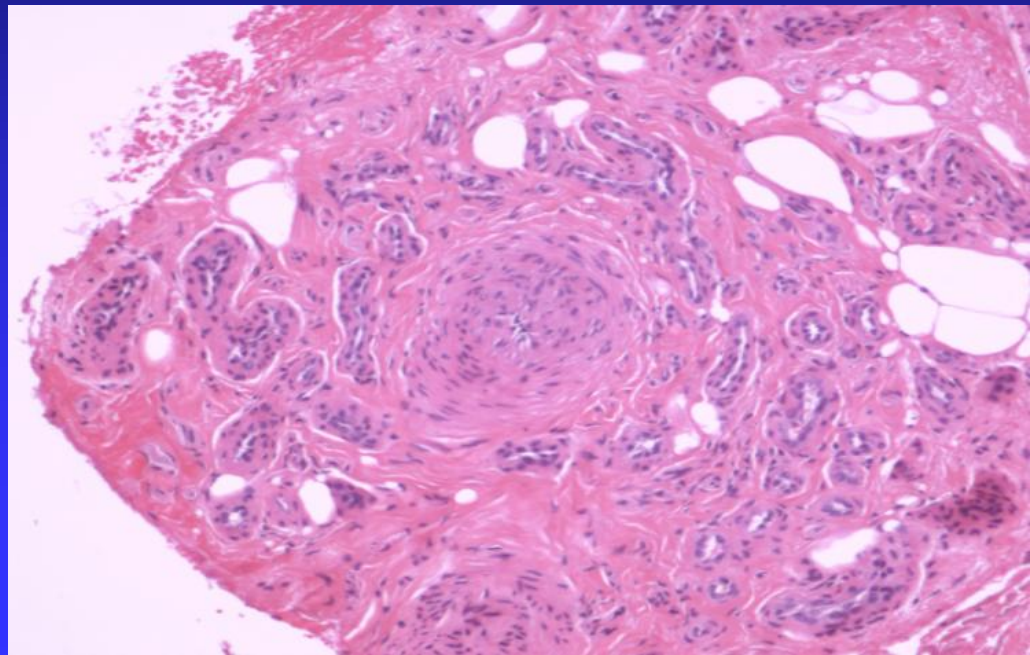


Ito T *et al*. J Invest Dermatol 125(6):1139-48, 2005.

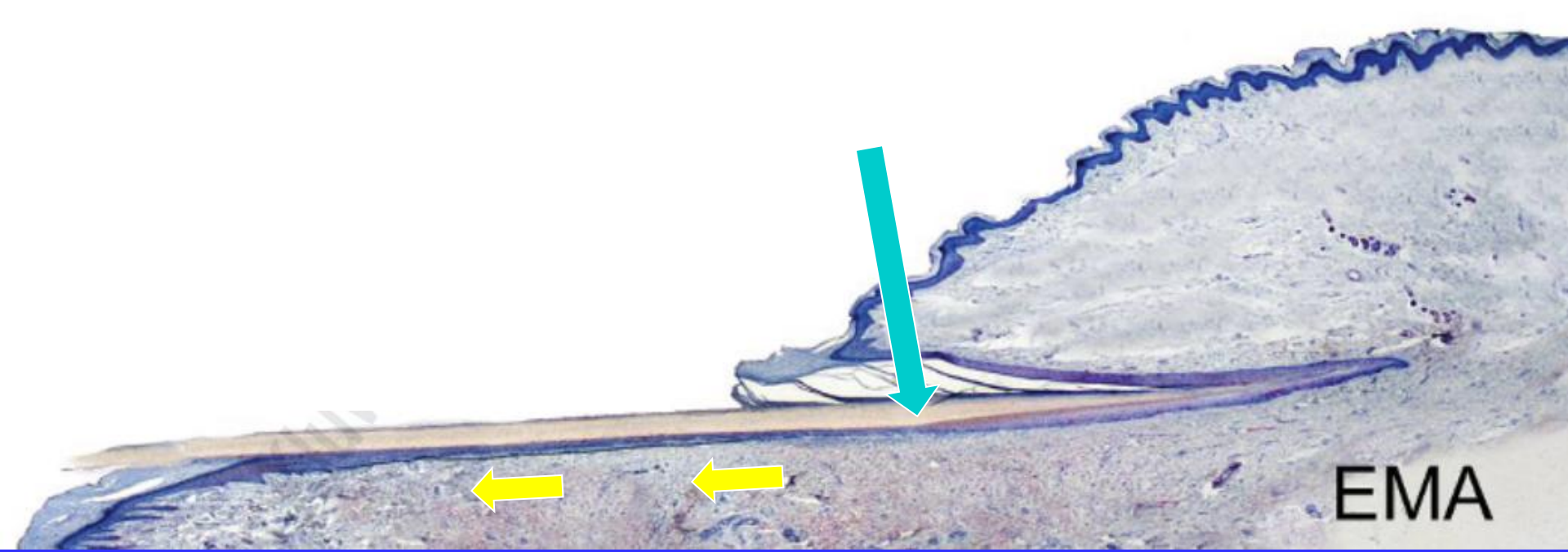
# Immune Tolerance

- Suppressed HLA in matrix  and HLA-C is suppressed in keratinocytes
- Increased Macrophage migration inhibitory factor and HLA-G is increased
  - Prevent natural killer cells and CD8+ T-cells from reacting to MHC
- Decreased CD1a-positive, CD4-positive, and CD8-positive immune cells and natural killer cells are decreased in the proximal
- Decreased expression of class II MHC and CD209 molecules by Langerhan's cells
- Increased immuno-suppressant molecules such as transforming growth factor-1, a-melanocyte stimulating hormone, insulin-like growth factor-1, and adrenocorticotropic hormone.

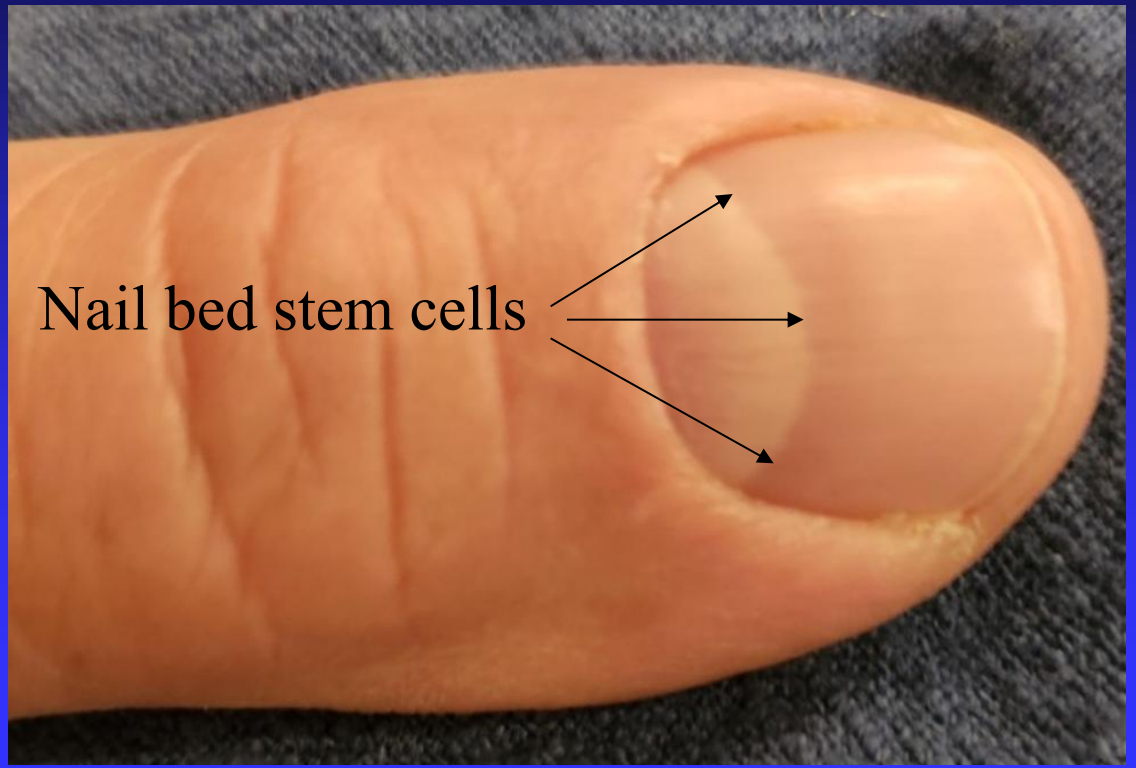
# Pitfall: Normal vasculature
# Don’t overdiagnose as hemangioma



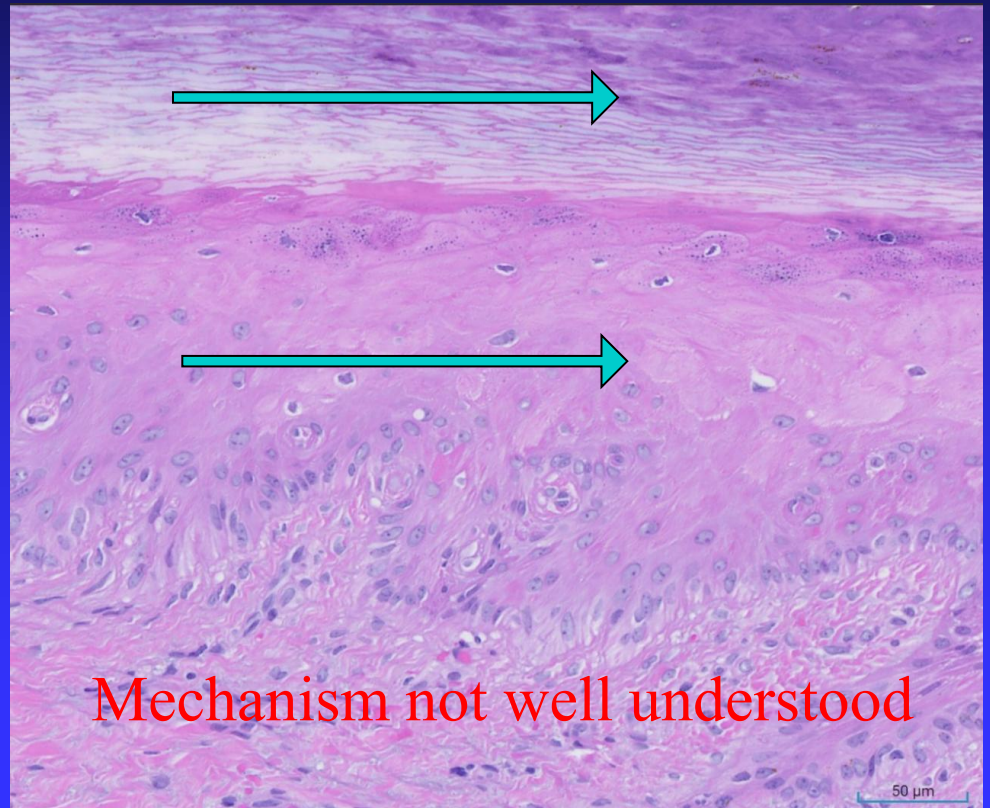
# Bed stem cells



# Continuous growth observable



# Plate and epithelium move together




Mechanism not well understood

# Onychopapilloma

- Clinical
  - Logintudinal erythronychia (redness)
  - Distal nail split

# Onychopapilloma

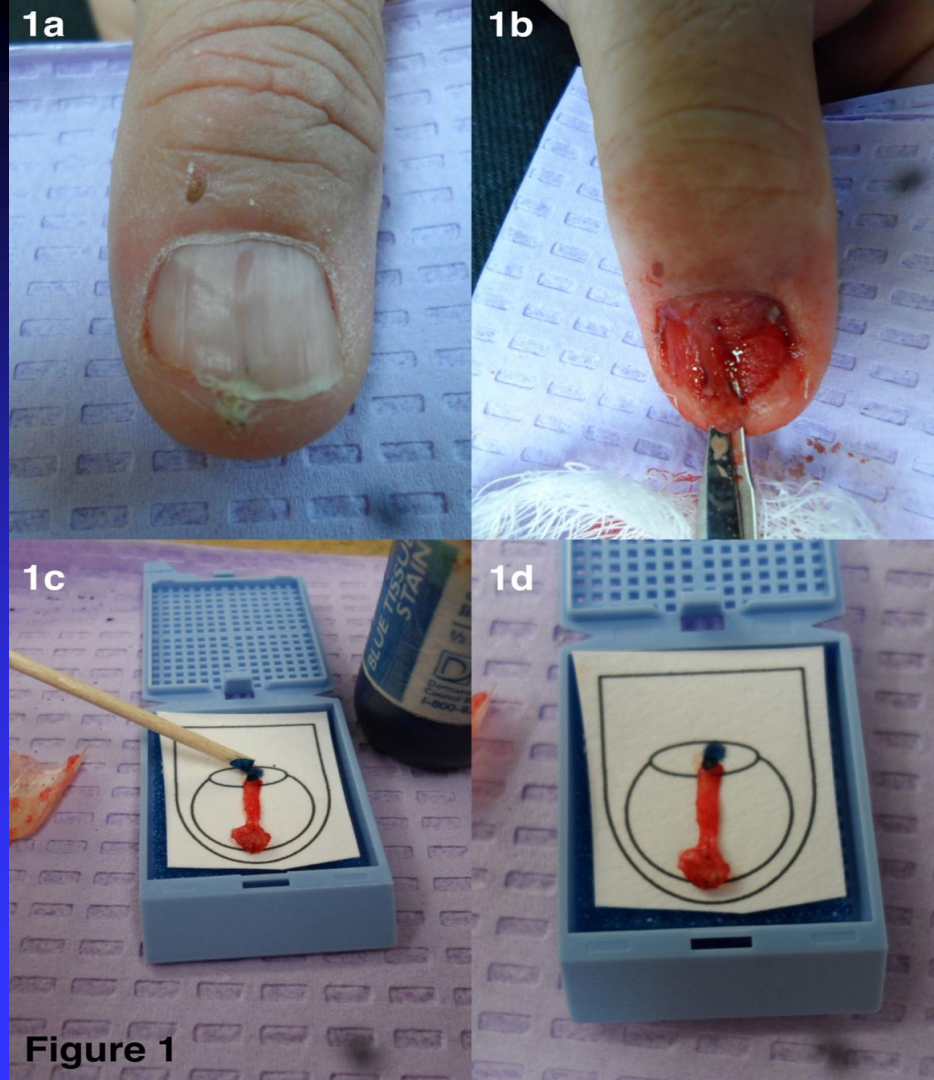
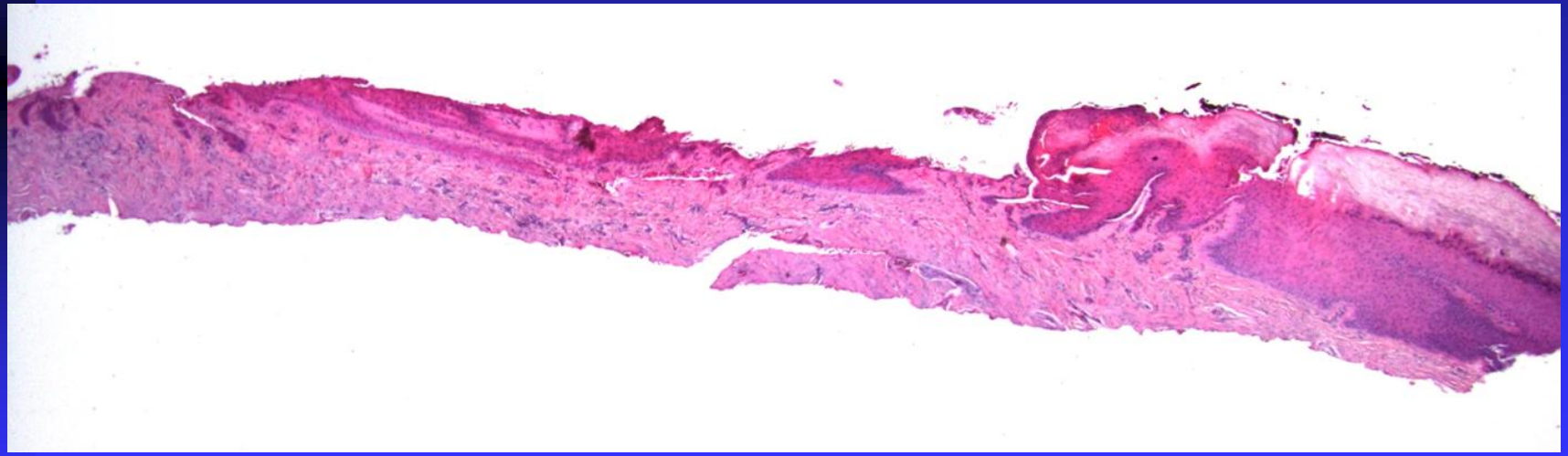



Figure 1

# Onychopapilloma—Keratin Producing



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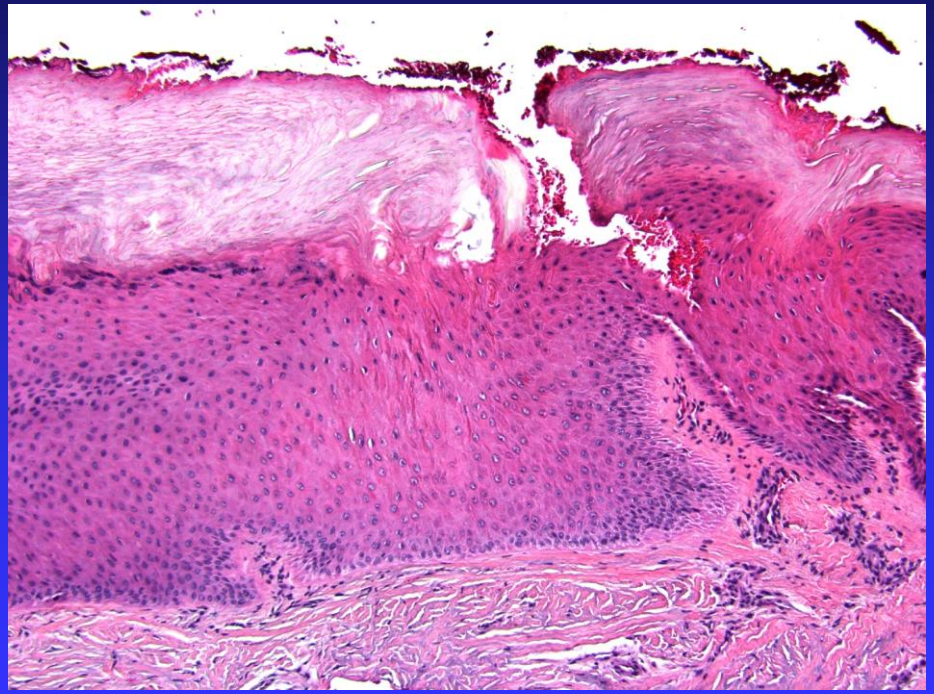
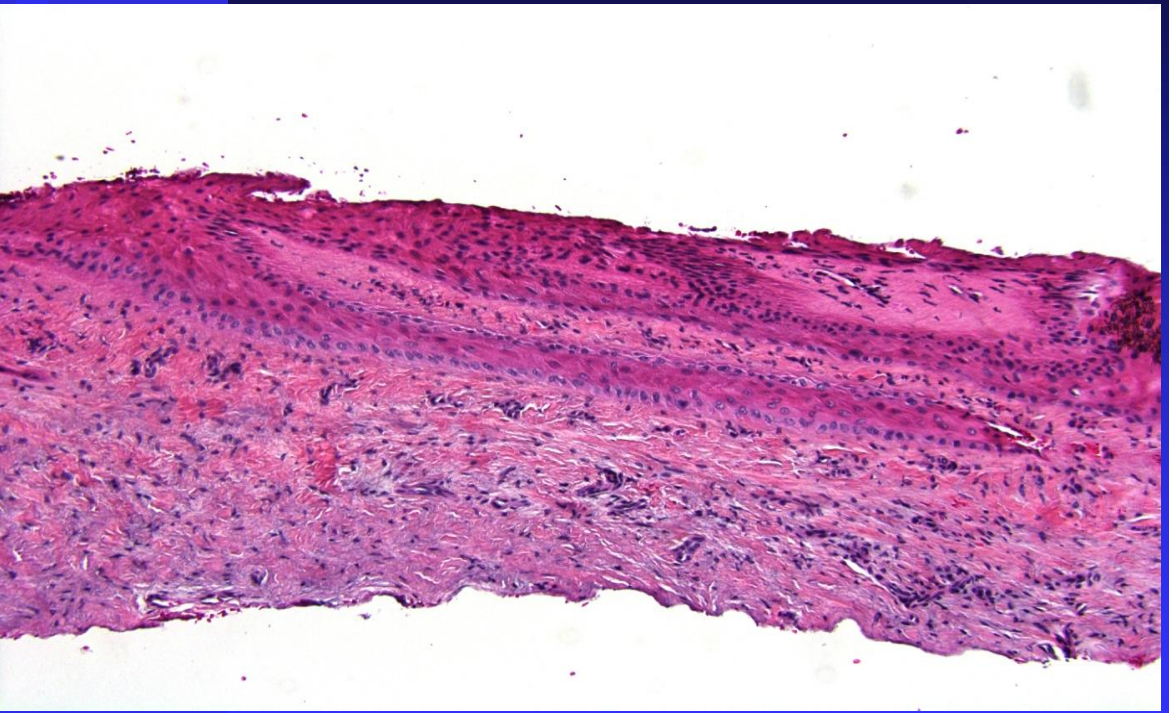
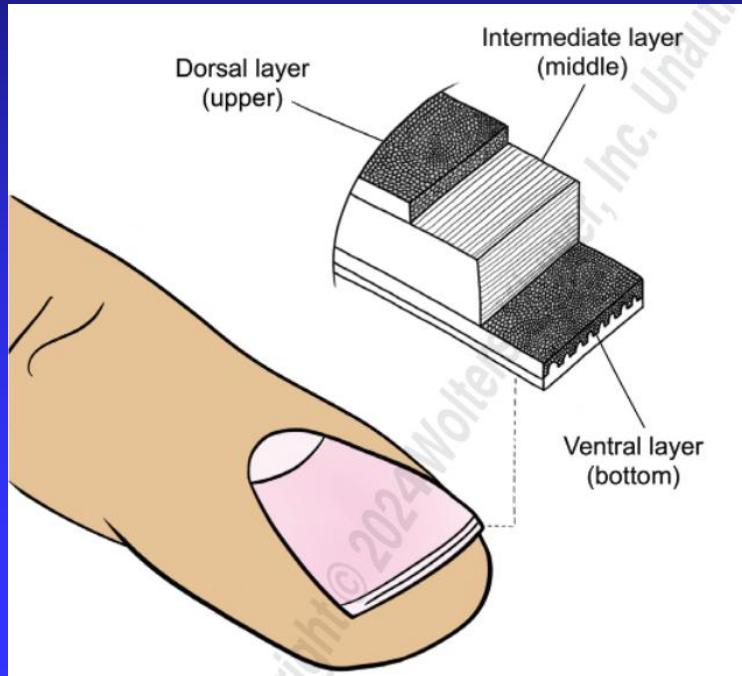
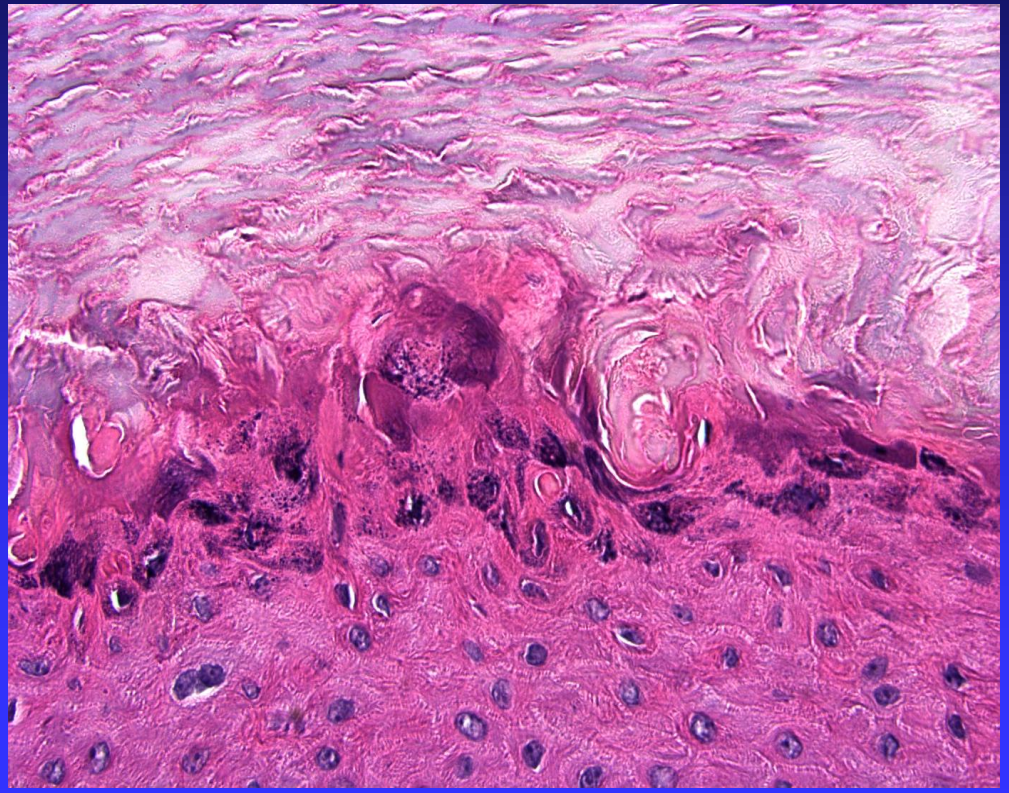


# Onychopapilloma—elongated rete





# Onychopapilloma—Not a wart



# Onychopapilloma

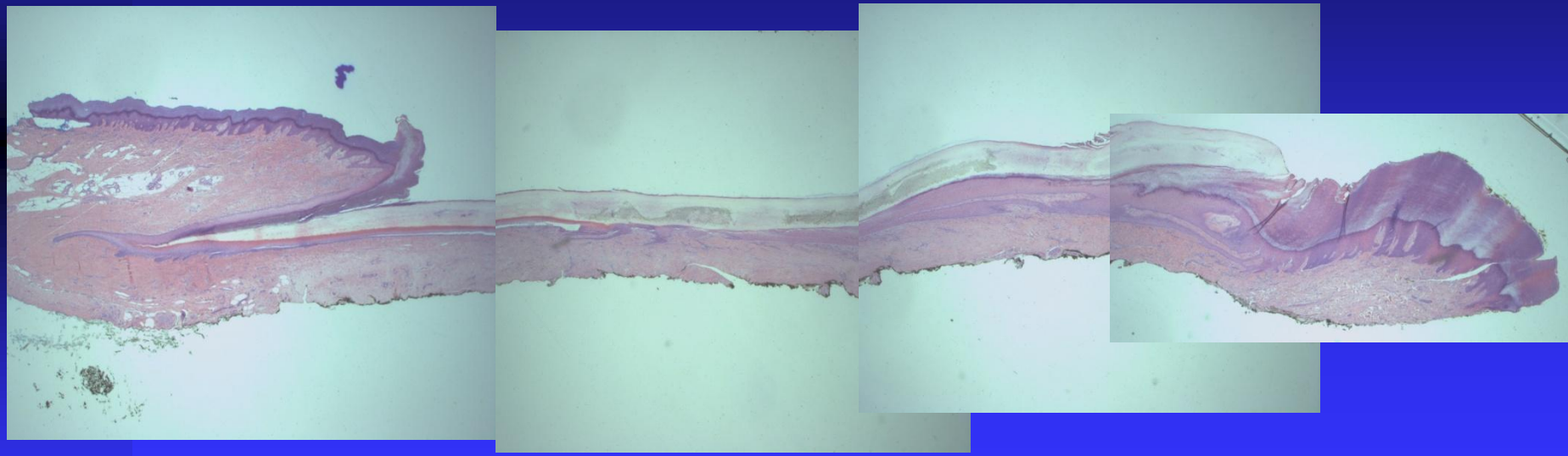
- Better termed ‘Onychohyperkeratoma’
- No specific histopathology
- No HPV

# Onychopapilloma

- Keratin-producing
- Trauma

# Hutchinson’s Sign

# Hutchinson's Sign



# Hutchinson's Sign

- J Am Acad Dermatol. 2001 Feb;44(2):305-7.
- **Two kinds of Hutchinson's sign, benign and malignant.**
- Kawabata Y, Ohara K, Hino H, Tamaki K.
- Department of Dermatology, Faculty of Medicine, University of Tokyo, Japan. KAWABATA-der@h.u-tokyo.ac.jp
- We examined 6 subungual melanomas in situ and 18 melanocytic nevi and compared pigmentation of the nail plates and hyponychium with the use of a dermatoscope. Hutchinson's sign on the hyponychium was not always evidence of subungual melanoma because it can be seen in both diseases. However, there was a wide difference in their dermatoscopic features. We believe that observation of pigmentation on the hyponychium with the use of a dermatoscope contributes to the precise diagnosis of subungual melanoma.

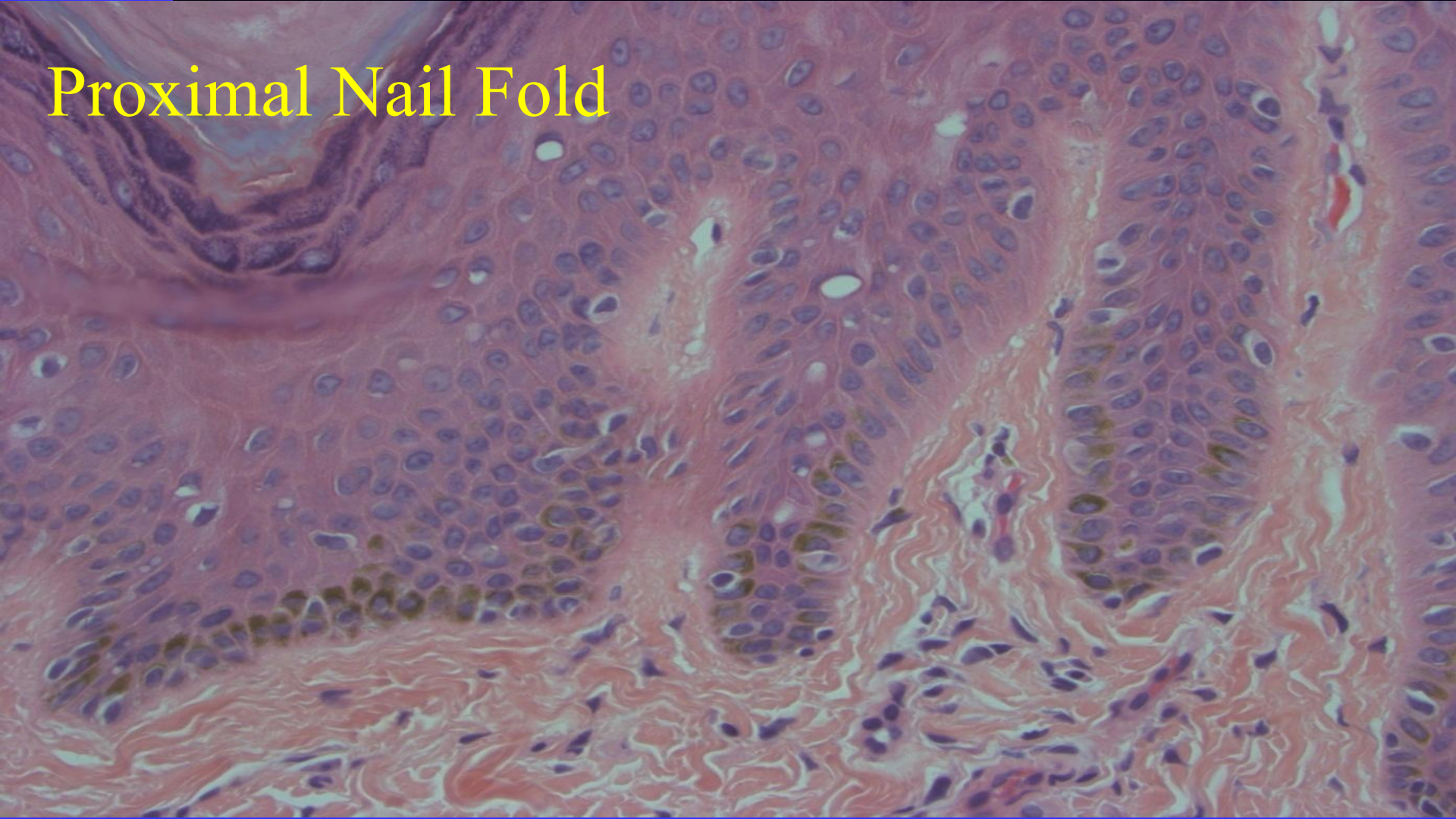
# Biopsy

- Matrix sampled
- Proximal nail fold sampled

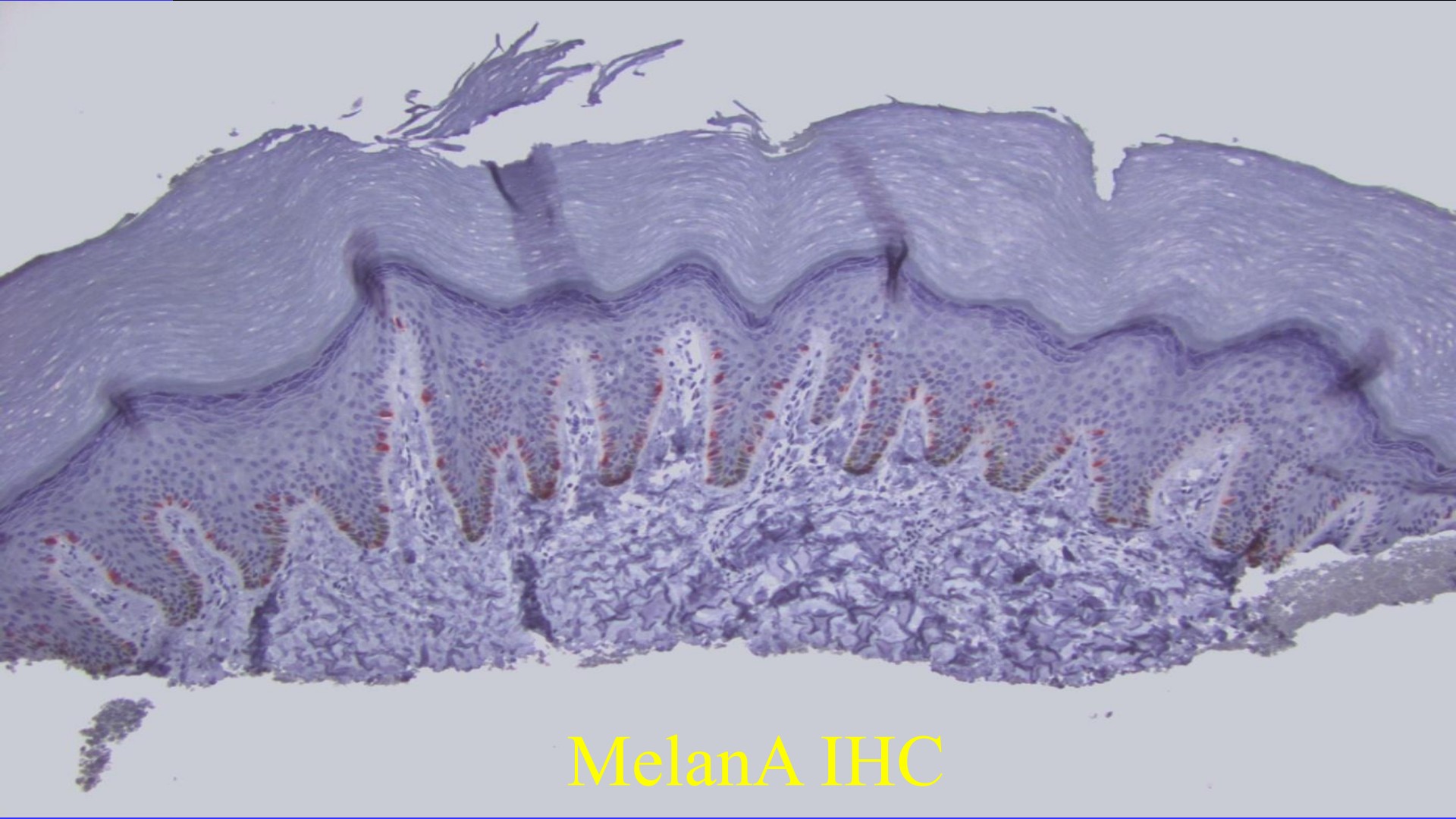
# Dr. Rich's Differential Diagnosis

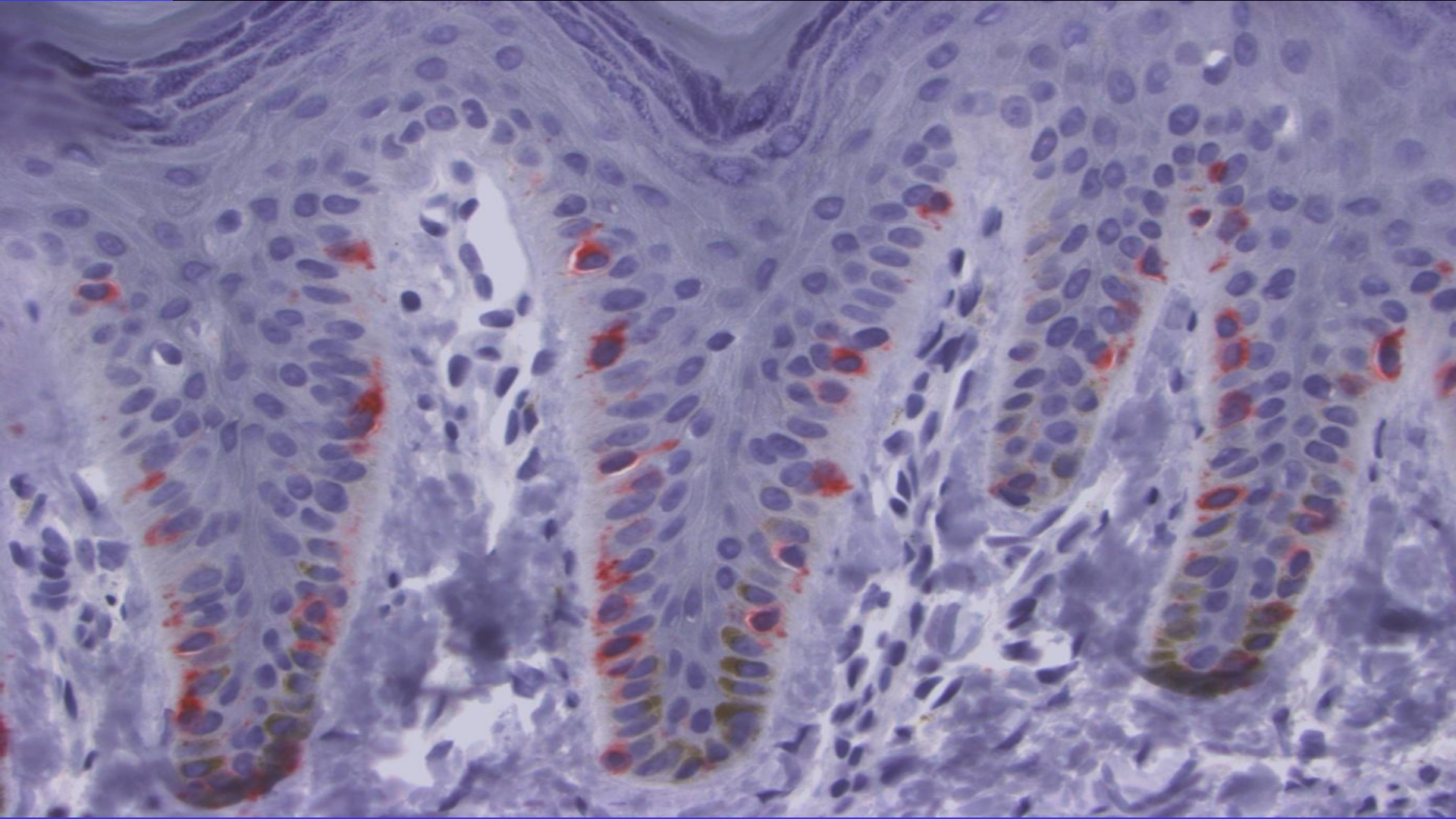
- Trauma pigment
- Nevus
- Lentigo
- R/O Melanoma

# Proximal Nail Fold

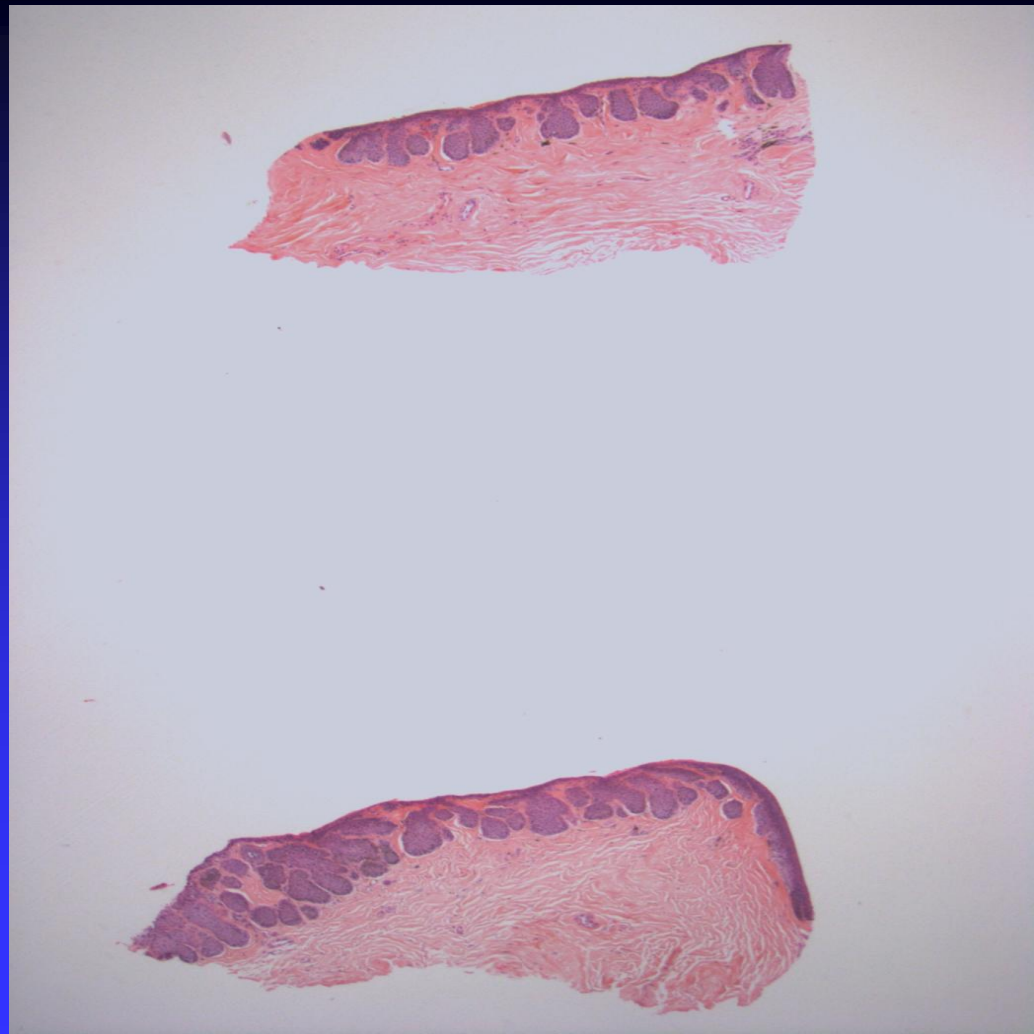

Proximal Nail Fold

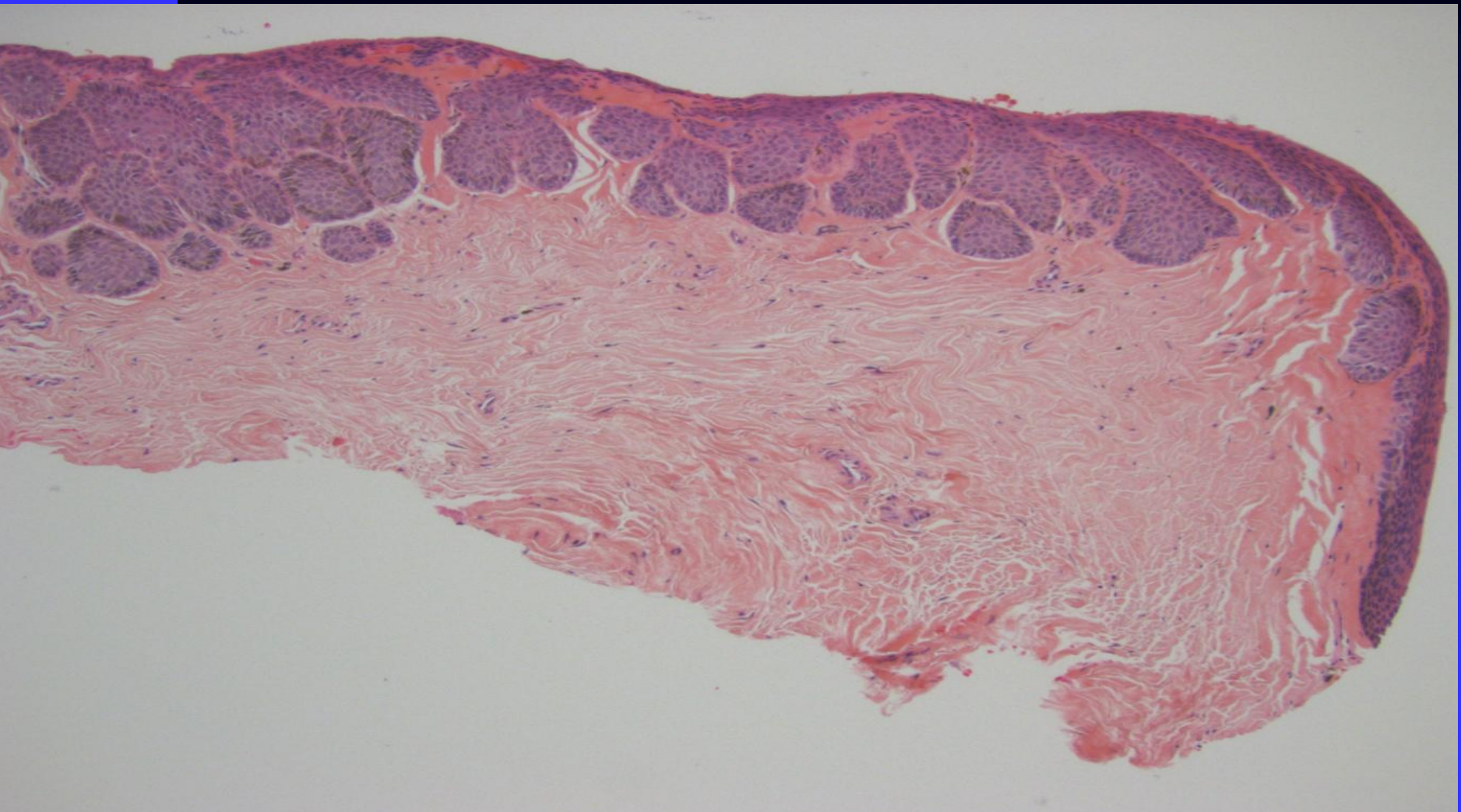

Fontana-Masson Stain

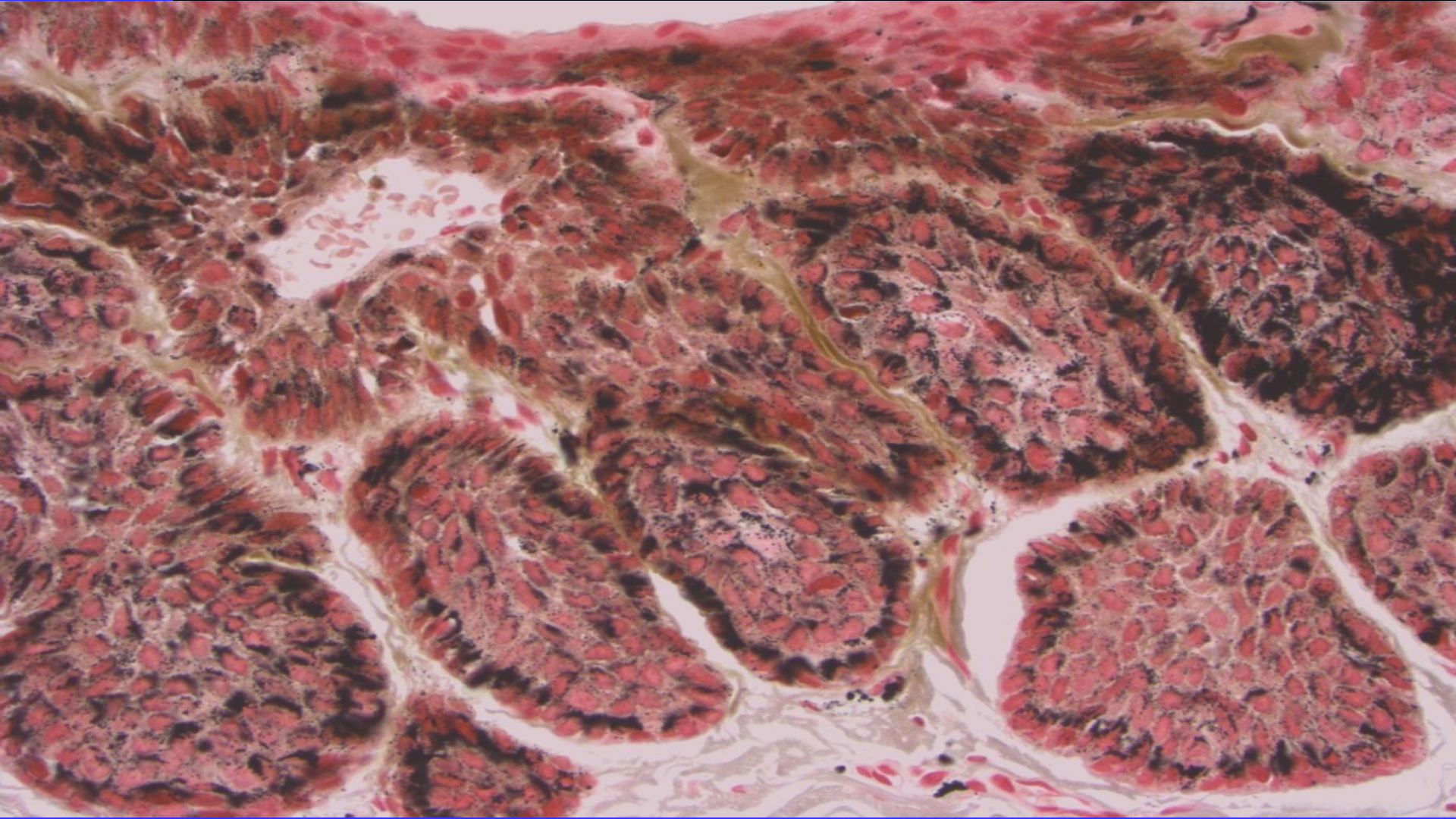

MelanA IHC

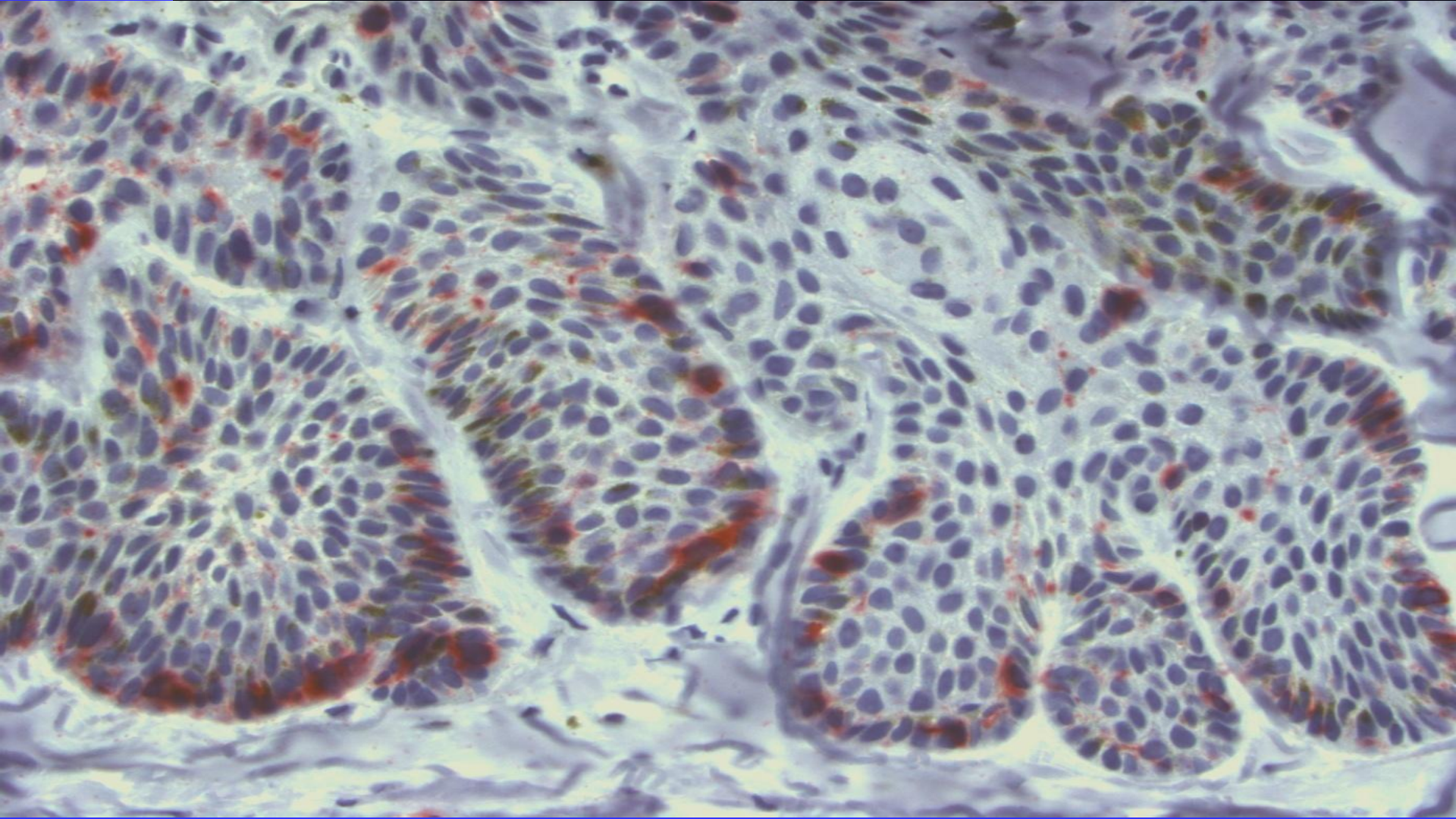


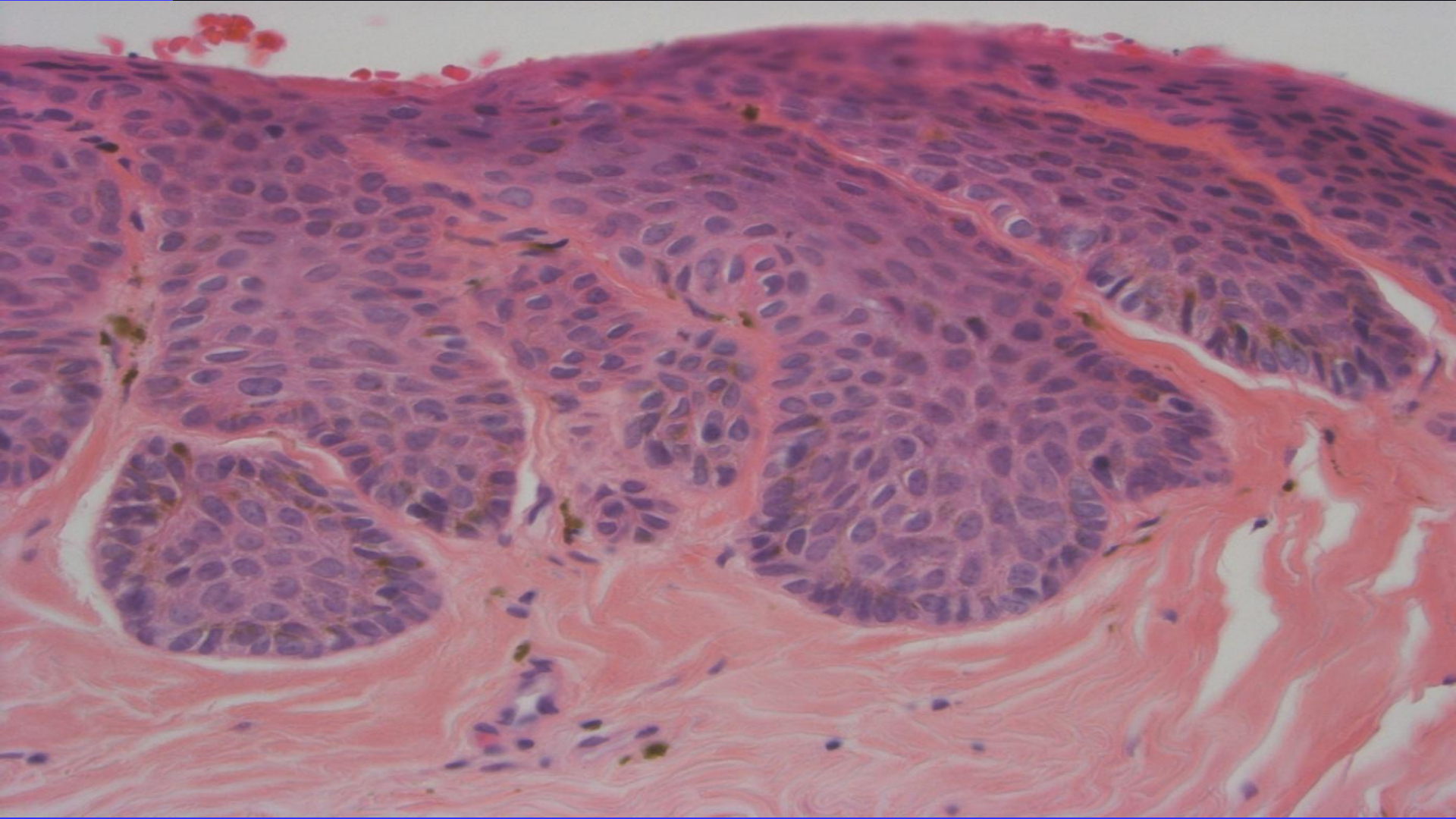
# Nail Bed/Matrix



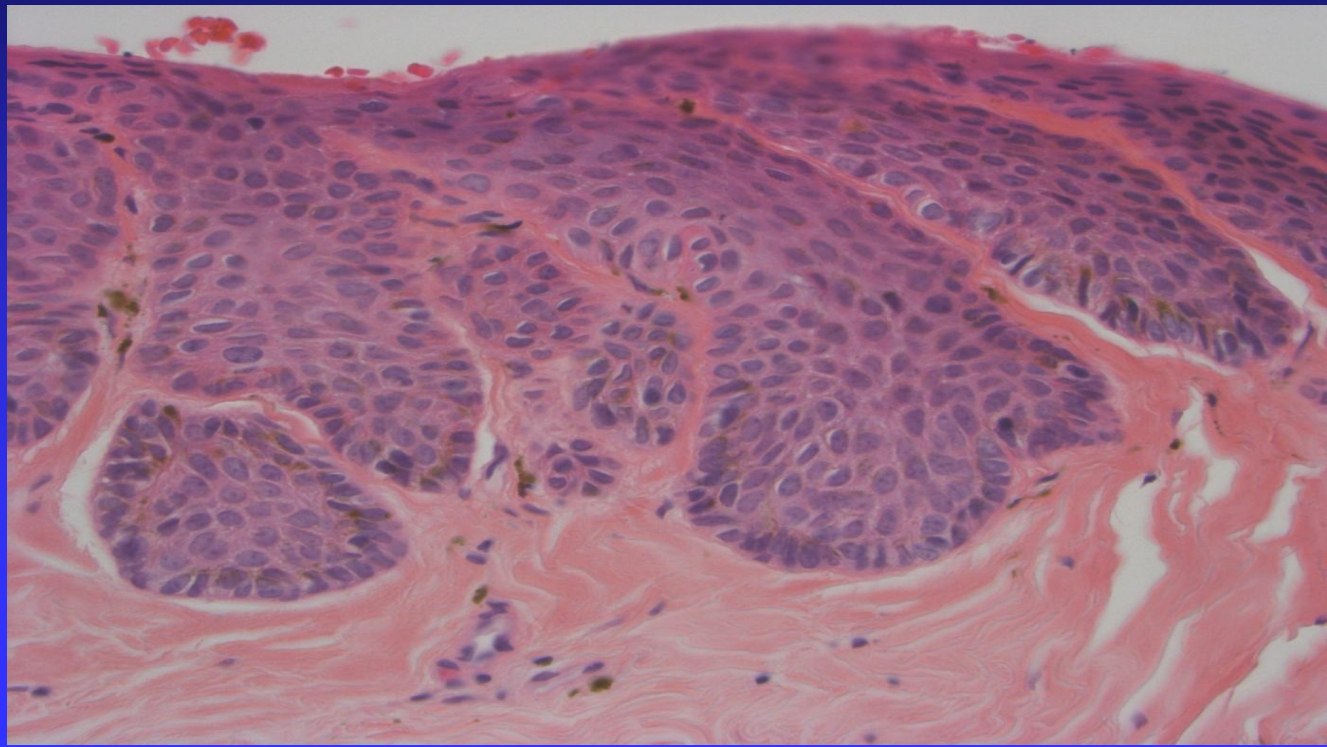








# Onychocytic matricoma with a Hutchinson's sign



# Onychocytic Matricoma

Am J Dermatopathol. 2012 Feb;34(1):54-9. doi: 10.1097/DAD.0b013e31822c3d8b.

**Onychocytic matricoma presenting as pachymelanonychia longitudinal. A new entity (report of five cases).**

Perrin C[1], Cannata GE, Bossard C, Grill JM, Ambrossetti D, Michiels JF.

**Author information**

**Abstract**

Among the tumors of the epidermal appendages, only rare tumors have been proved as differentiating in the direction of the nail. Beside onychomatricoma, we report a new matrical tumor of the nail: onychocytic matricoma (acanthoma of the nail matrix producing onychocytes). The main differential diagnosis of onychocytic matricoma is seborrheic keratosis. However, if attention is paid to the nature of the different layers of the tumor and the peculiar microanatomy of the nail matrix, the differentiation is not difficult. Onychocytic matricoma is a localized (monodactylous) longitudinal melanonychia which is slightly raised. The term pachymelanonychia is used to define the 2 clinical features of the tumor. Pachyonychia indicate a localized thickening of the nail plate, and melanonychia indicate its longitudinal pigmented band. Onychocytic matricoma is composed of a basal compartment with a varying admixture of prekeratogenous cells and keratogenous cells. Endokeratinization originating in the deep portion of the tumor and nests of prekeratogenous and keratogenous cells in concentric arrangement are a characteristic feature. Three major patterns can be identified as follows: acanthotic, papillomatous, keratogenous type with retarded maturation. Given the peculiar thickening of the nail plate observed both in pigmented onychomatricoma and onychocytic matricoma, the term pachymelanonychia longitudinal could be proposed to specify clinically these 2 lesions, which the clinician sometimes mistakes for melanoma.

# Onychocytic matricoma
# vs
# Nail unit seborrheic keratosis
# vs
# Benign acanthoma

- Semantic difference?
- Seborrheic keratosis is very common
- More important is to make sure this is not subtle, pigmented squamous cell carcinoma
- Onychocytic matricoma is a difficult name

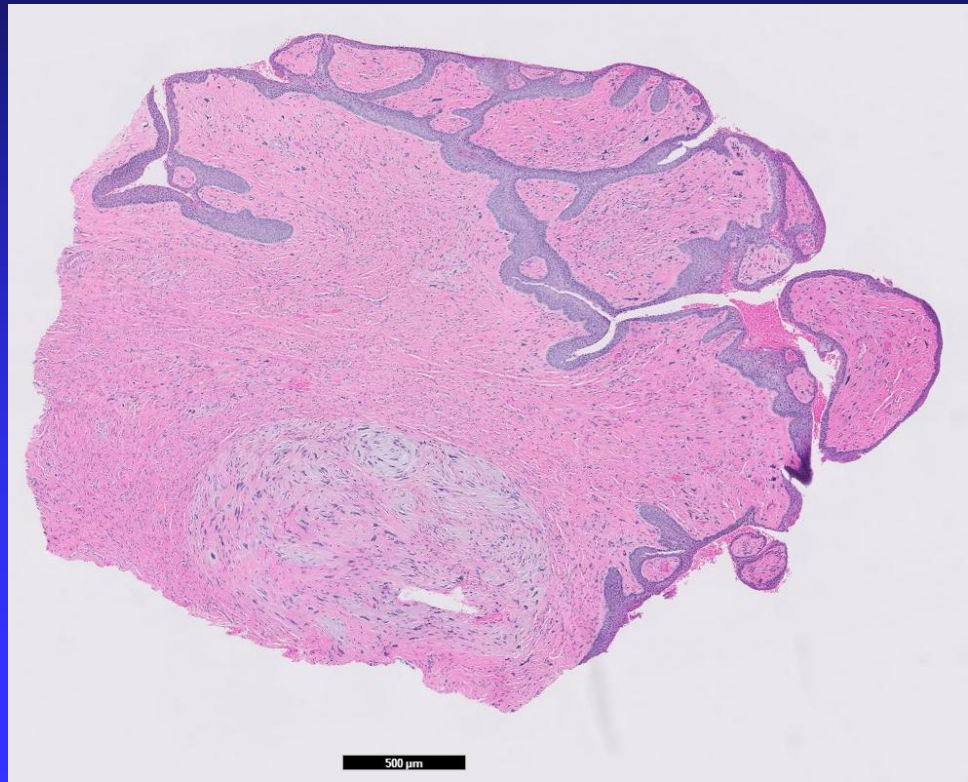
# Onycomatricoma

# Onycomatricoma

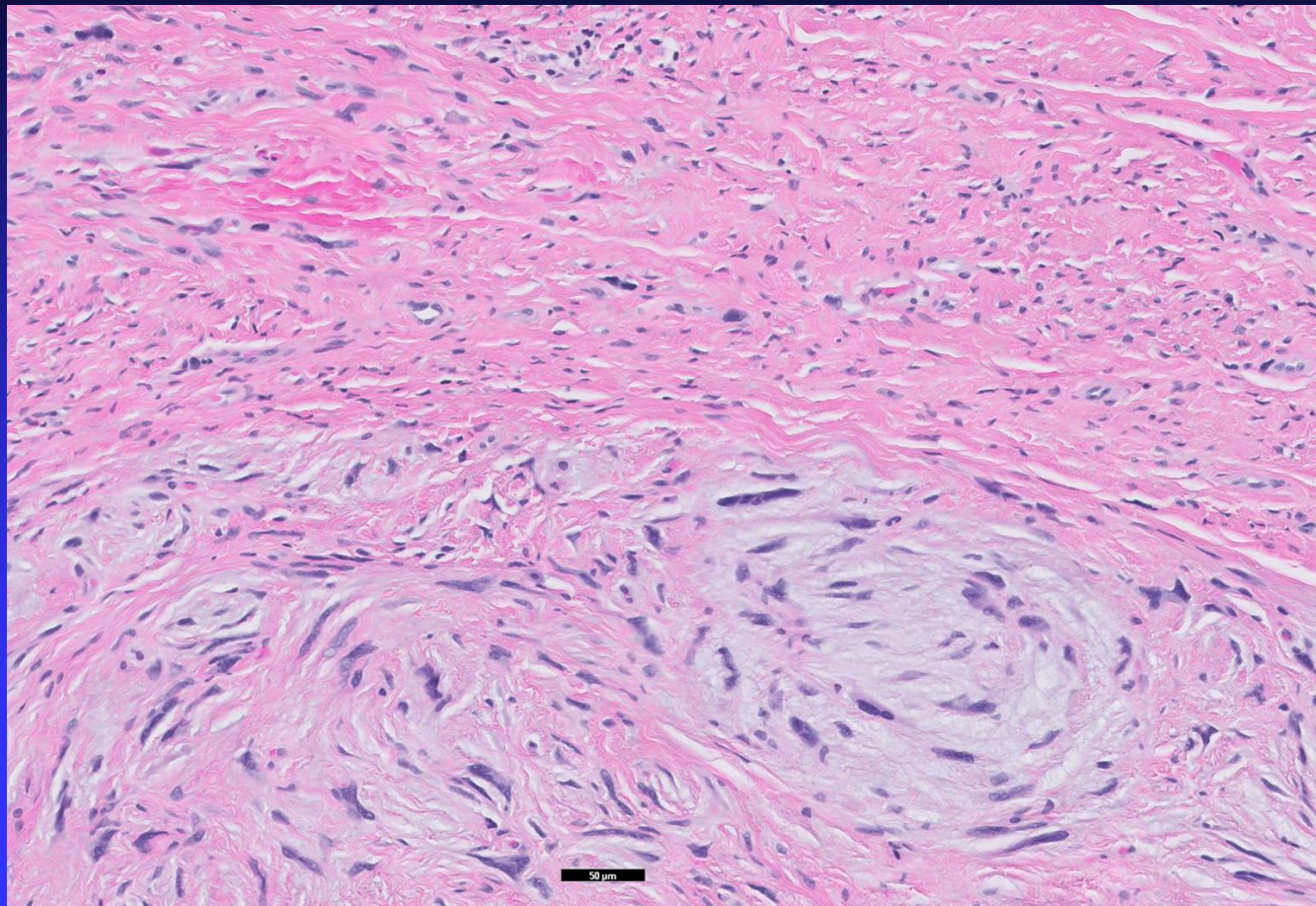
# Onycomatricoma

# Onycomatricoma

- Reactive epithelial component?



# Onycomatricoma



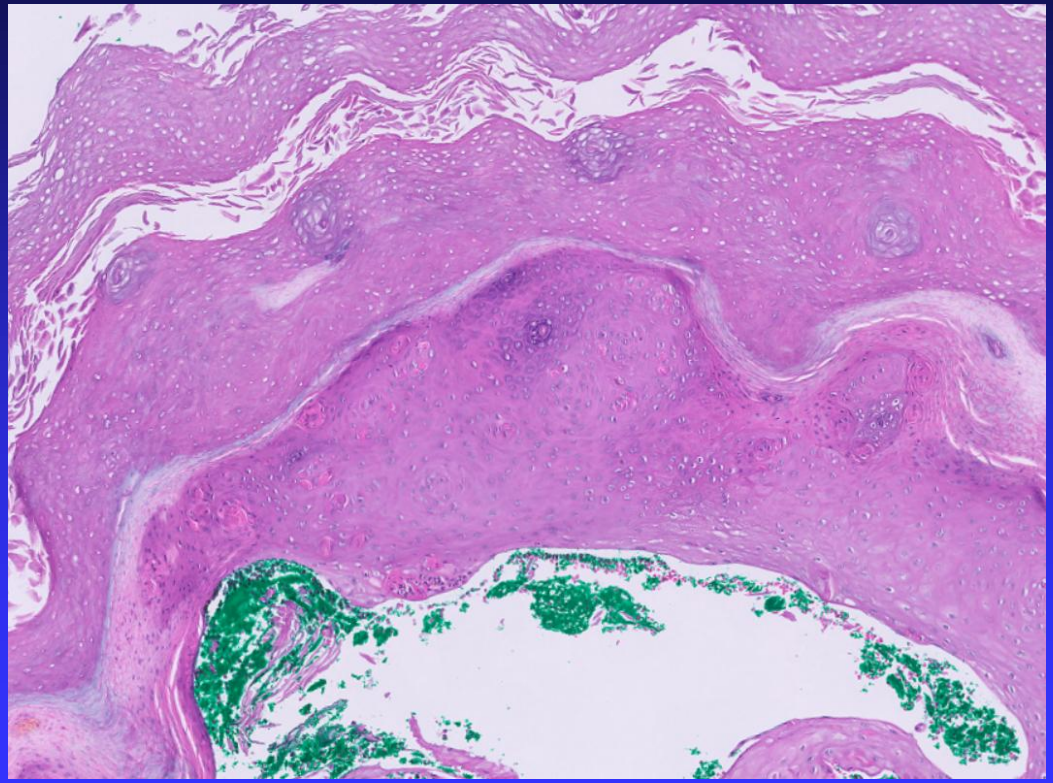
# Death by ‘Onycho’pathology

Onychocytic acanthoma, onychopapilloma, onycholemmal horn, proliferating onycholemmal tumor, proliferating oncholemmal cyst, onychomatricoma, onychocytic carcinoma, onycholemmal carcinoma, onychocytic matricoma

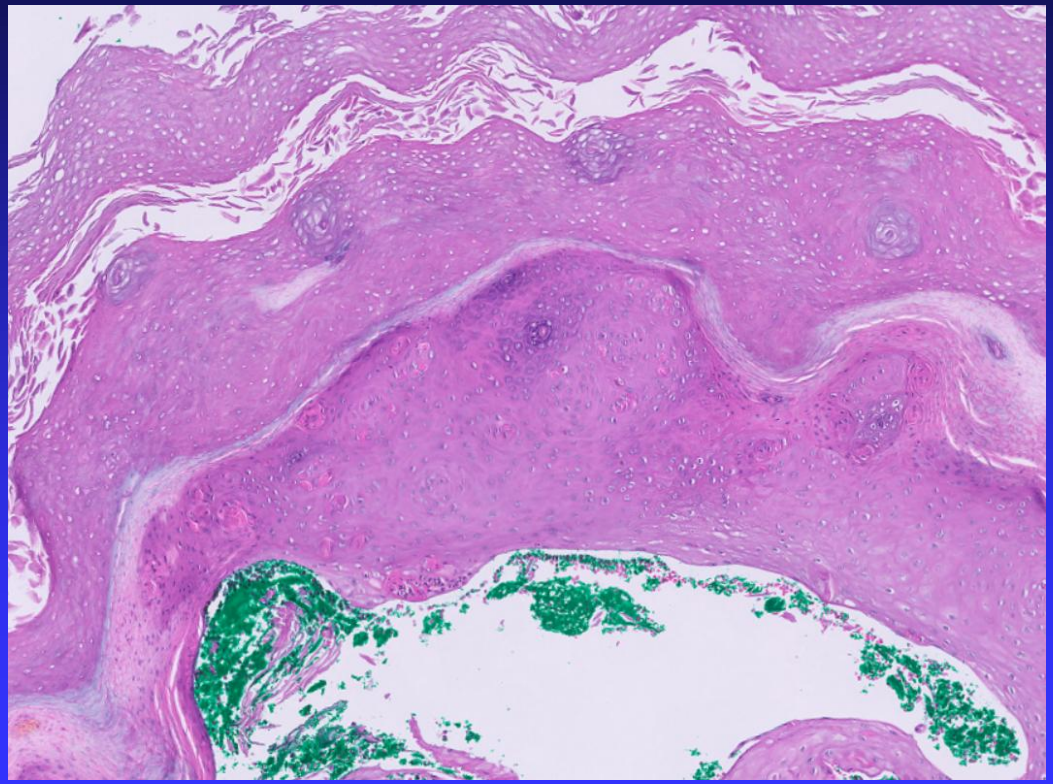
# Neoplasms

- Squamous
  - HPV-related
  - Benign and malignant “Onycho”
- Melanocytic
  - Nevus, MIS, MM
  - Lentigo/SK
- Soft tissue
  - Vascular
  - Spindle cell neoplasm—benign and malignant

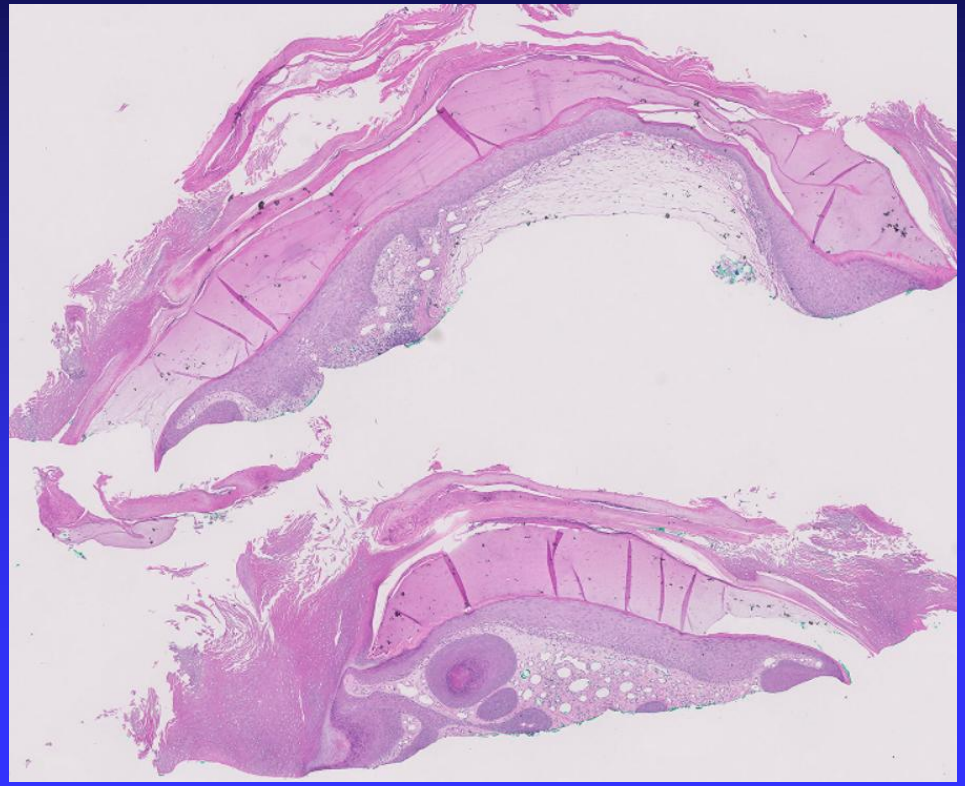
# 73y/o F great toe—”keratotic papule”



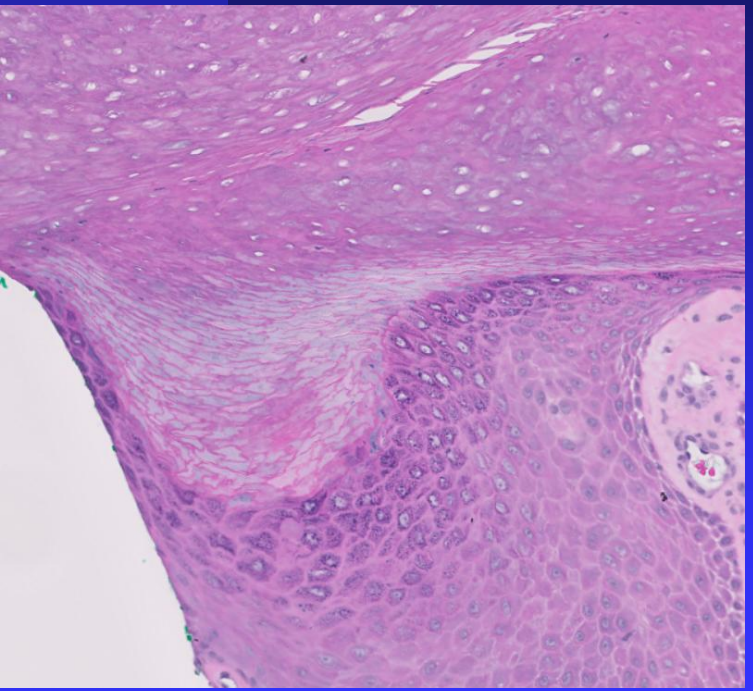
# Dx:  Verruca (Wart)



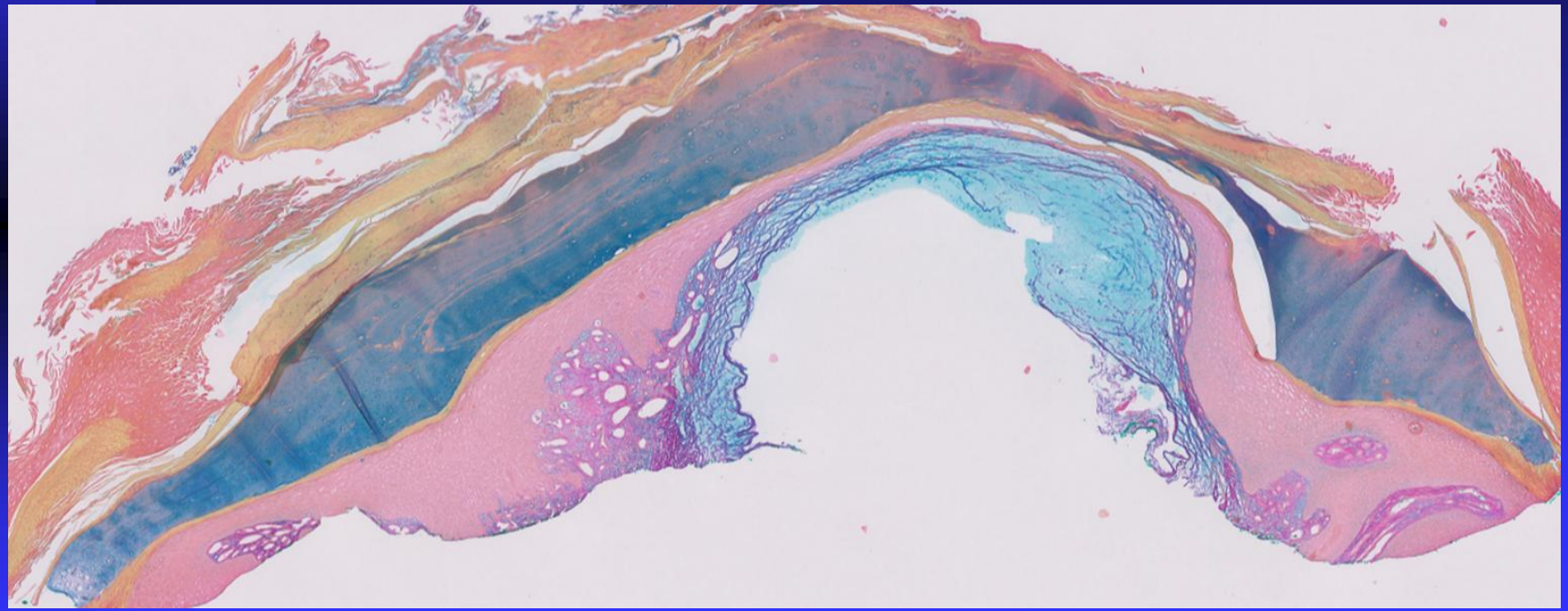
# Lesion persists—rebiopsy



# Lesion persists—rebiopsy

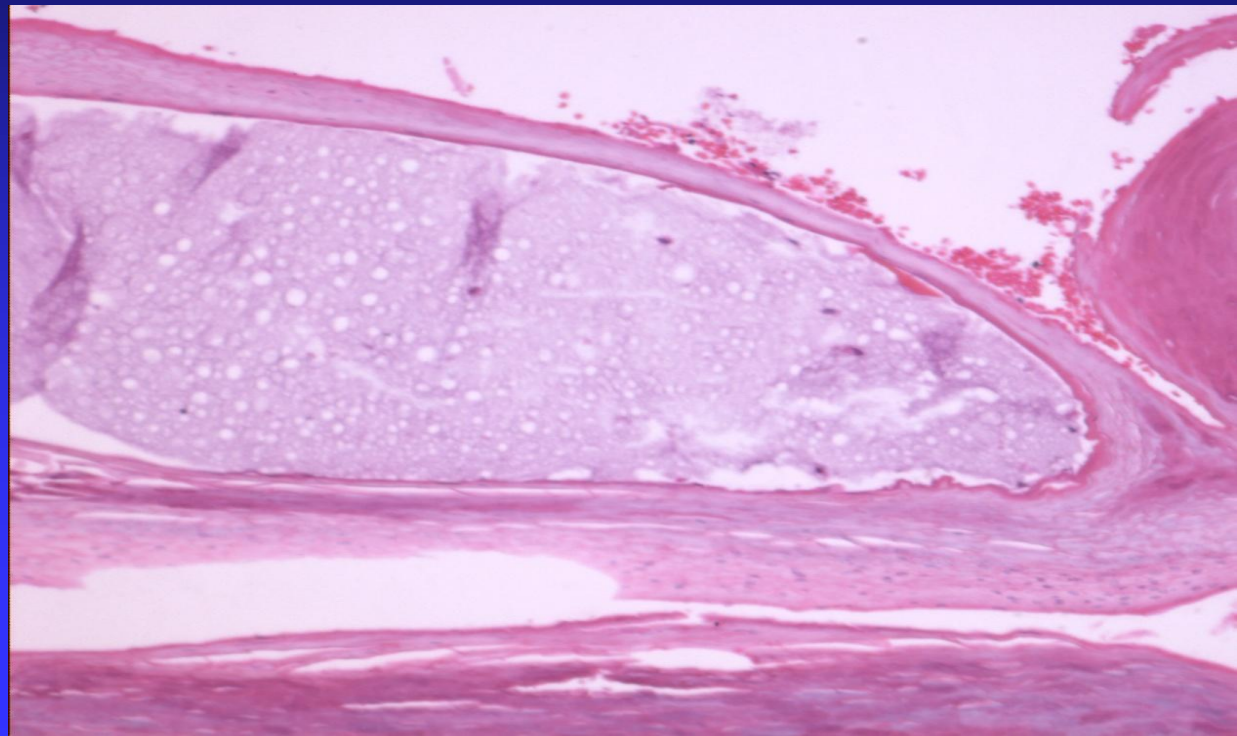


# Dx: Digital mucous/myxoid cyst



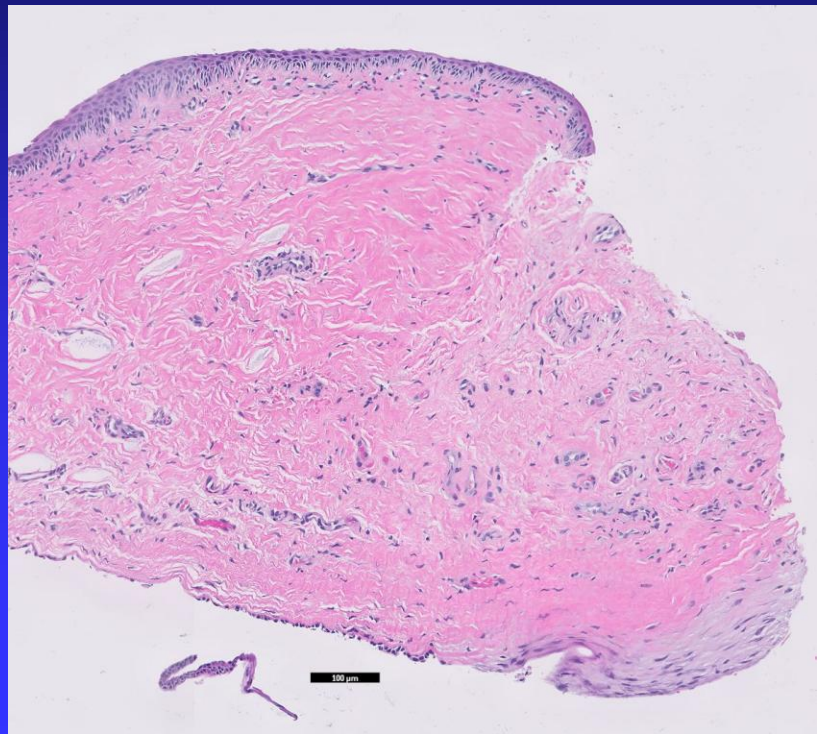
# Digital Myxoid/Mucous Cyst

- Mucin may be anywhere

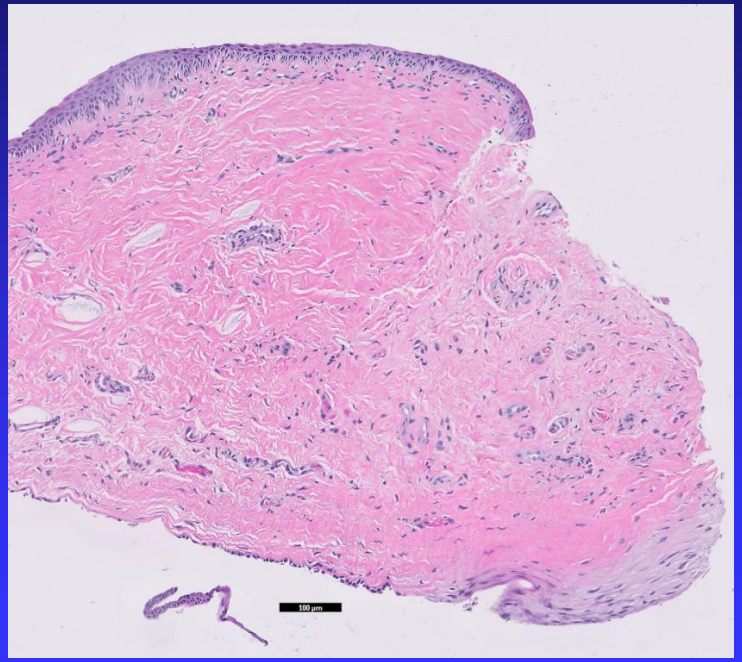


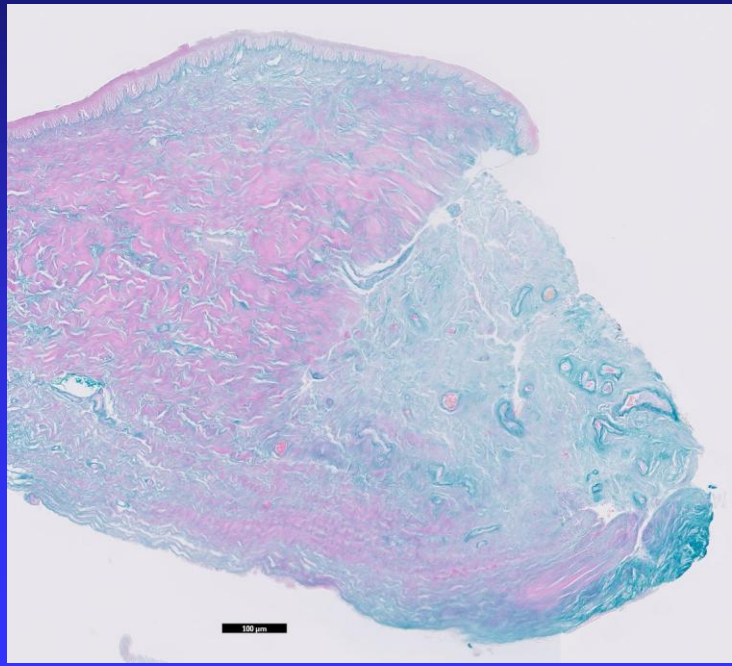
# Digital Myxoid Cyst

- Often don’t see mucin
  - Scar
  - Reactive changes

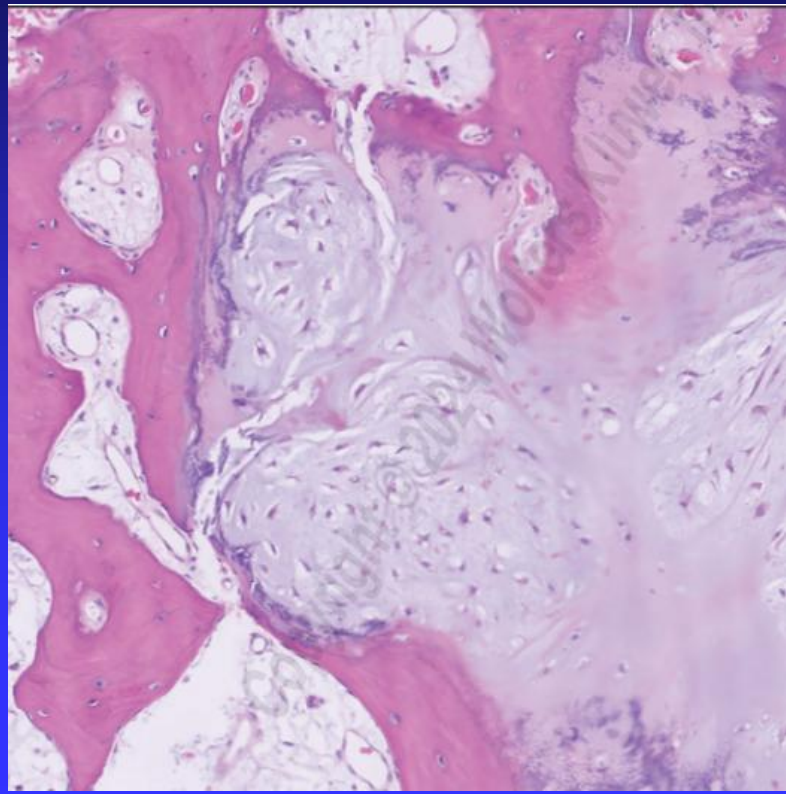


# Mucin stain often required

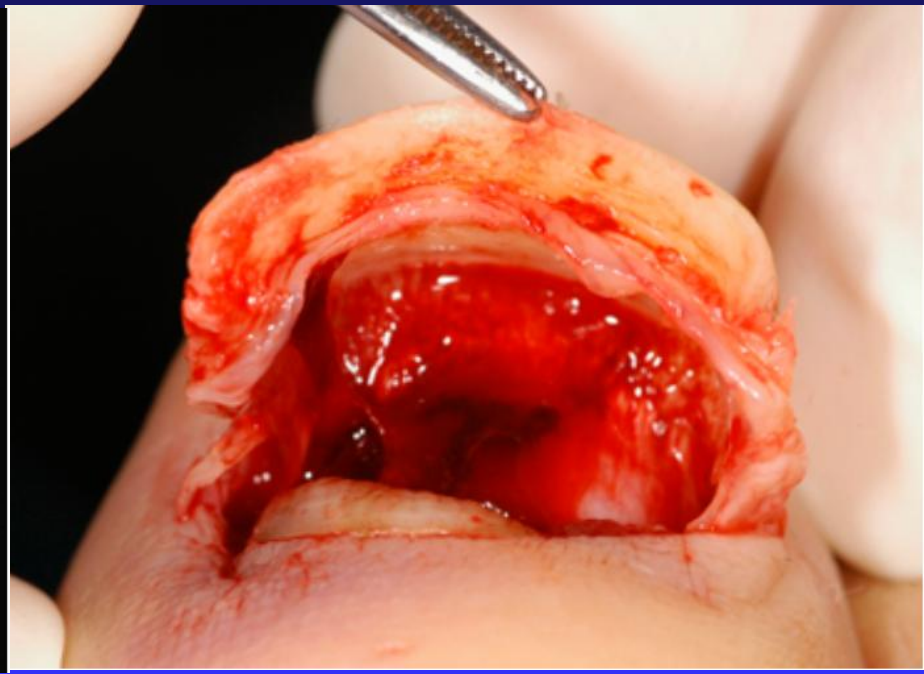




# What lies beneath . . .



# Retronychia



Baumgartner M and Haneke E. Retronychia: Diagnosis and Treatment. Dermatologic Surgery 36(10):1610-4, 2010

# Why is the nail unit so daunting to dermatologist and dermatopathologists?

https://www.katiemoorevisualartist.com/the-louisiana-museum-of-modern-art-copenhagen/

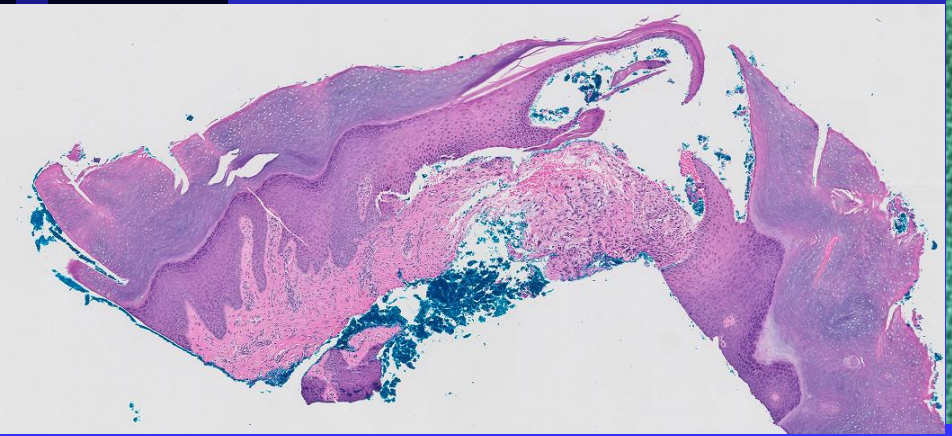
# Why are nails so difficult?

- Poor sample
- Insufficient biopsies

https://collection.waikatomuseum.org.nz/objects/4306/bomb-fragments

# Why are nails so difficult?

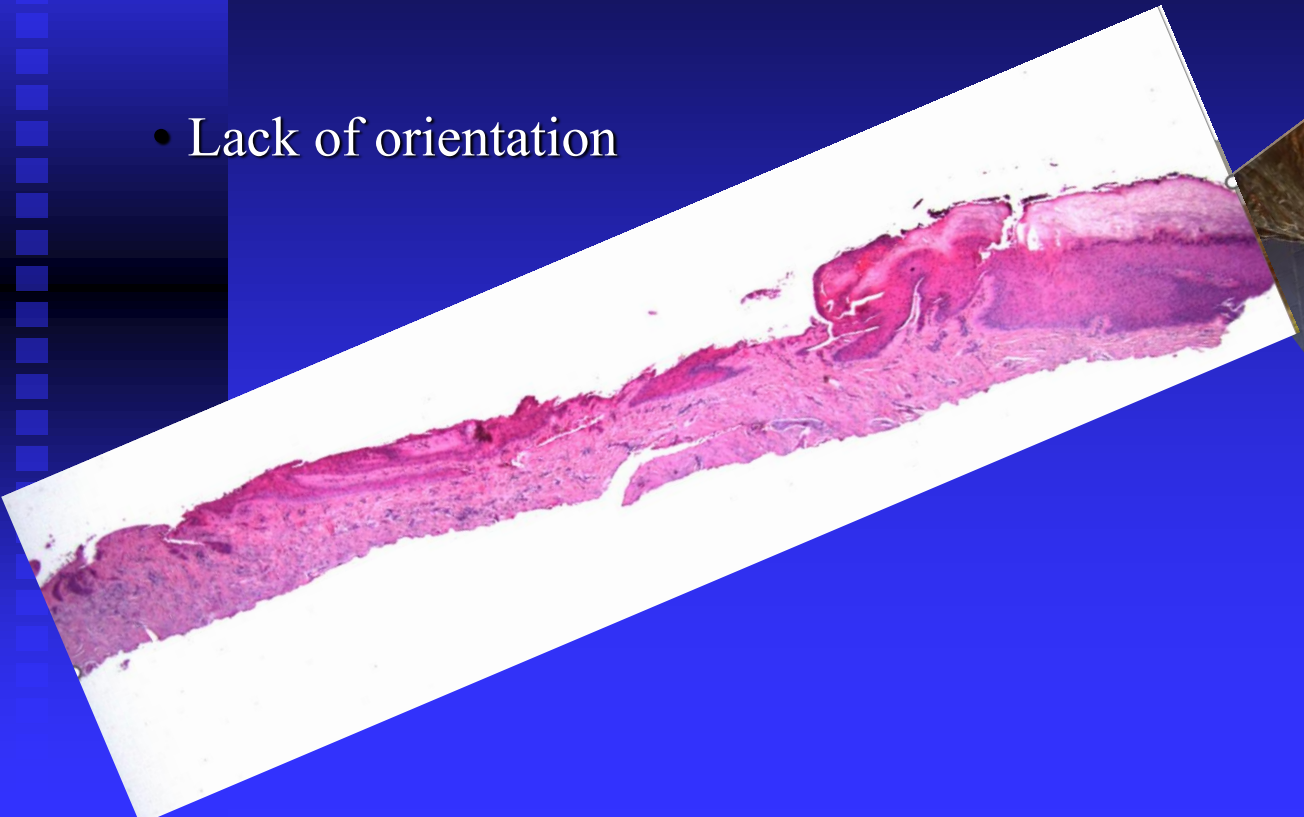
- Never see normal



https://cdn.ymaws.com/www.aocd.org/resource/resmgr/ddb_high/lichen_planus_3_high.jpg

# Why are nails so difficult?

- Lack of orientation



# Why are nails so difficult?

- Rare sample—little experience

**`i`iwi**

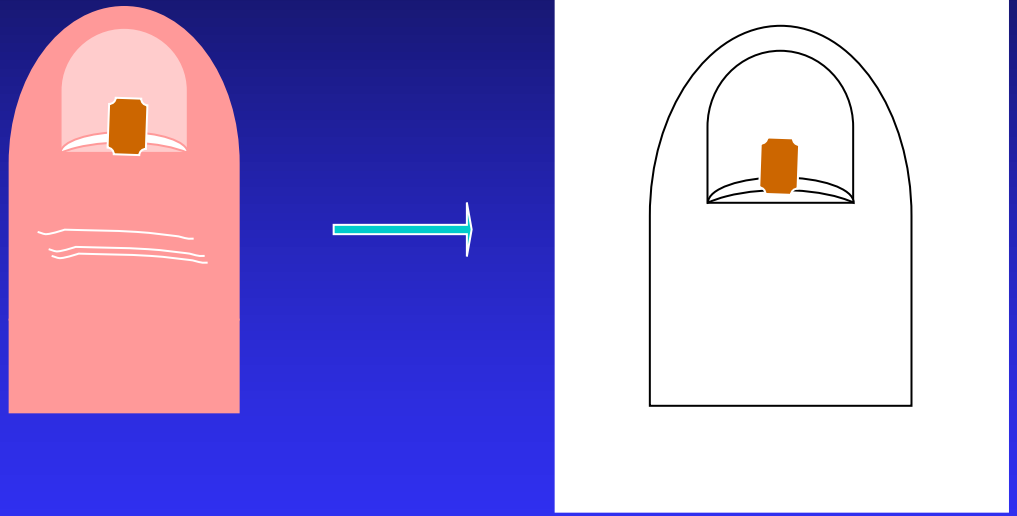
Main pollinator
of lobelia

https://blog.nwf.org/2018/05/will-this-rare-hawaiian-forest-bird-go-extinct/

What can the nail surgeon do to submit a bed/matrix specimen for appropriate interpretation?

# Need concise and clear guidelines for specimen submission:

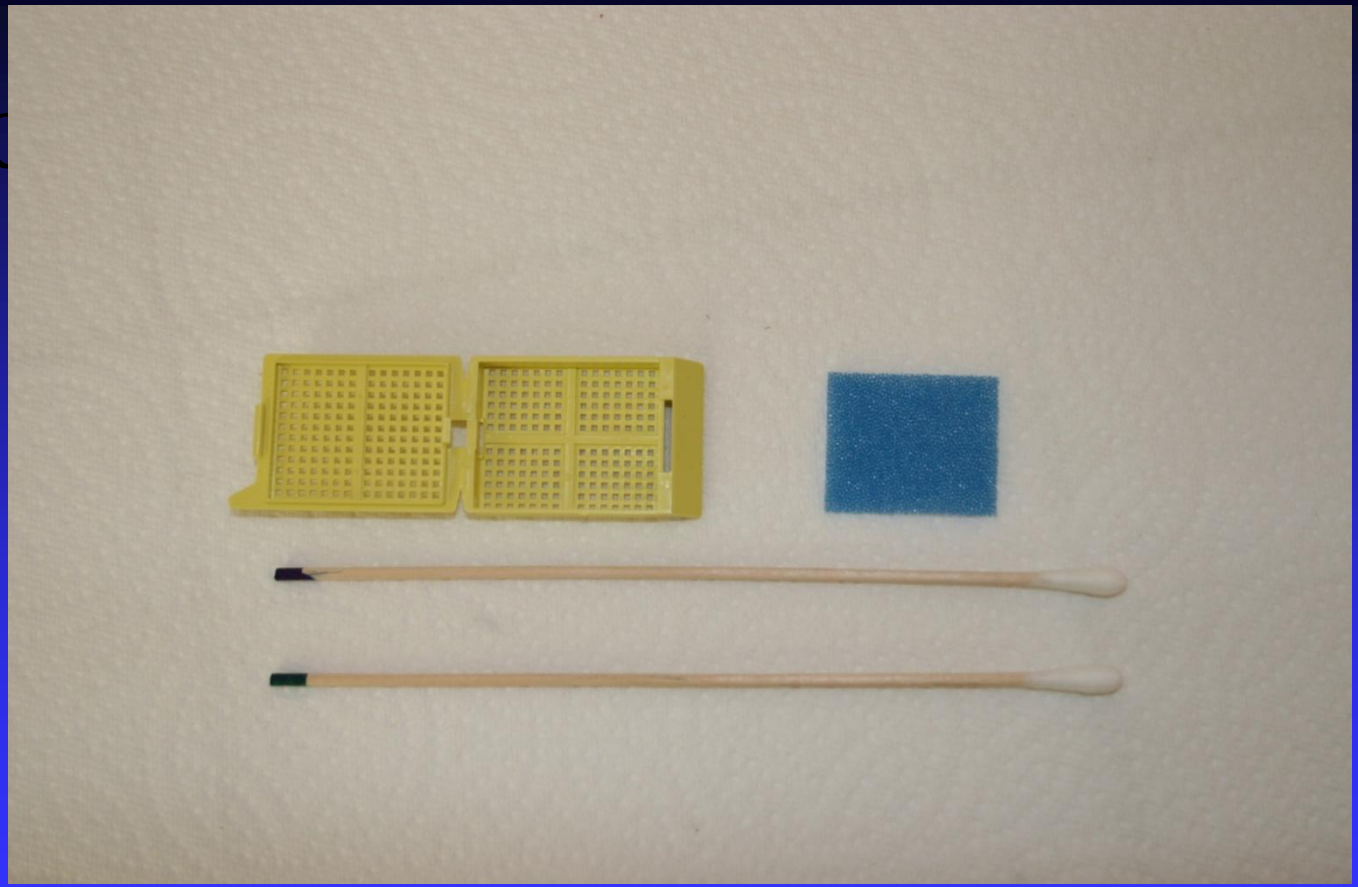
- Orientation of tissue
- Clear information to histotechnicians
- Reproducible among different laboratories




Courtesy of Dr. Phoebe Rich

Print template at www.ctapathology.com

# Histolo



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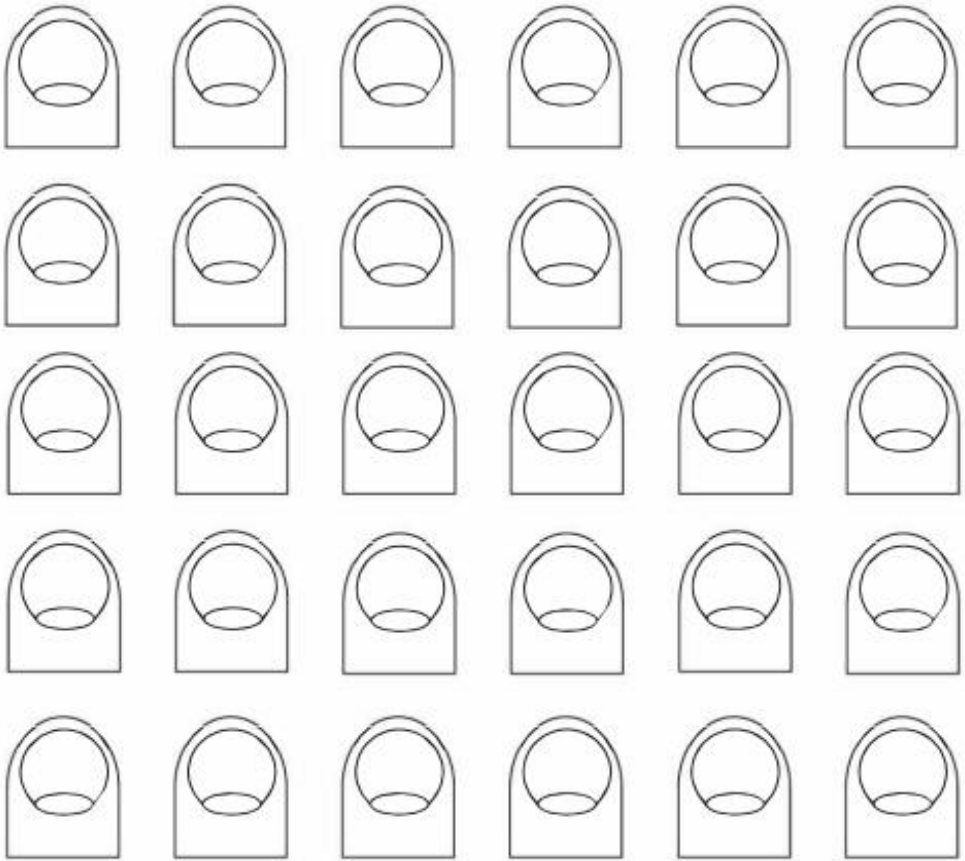
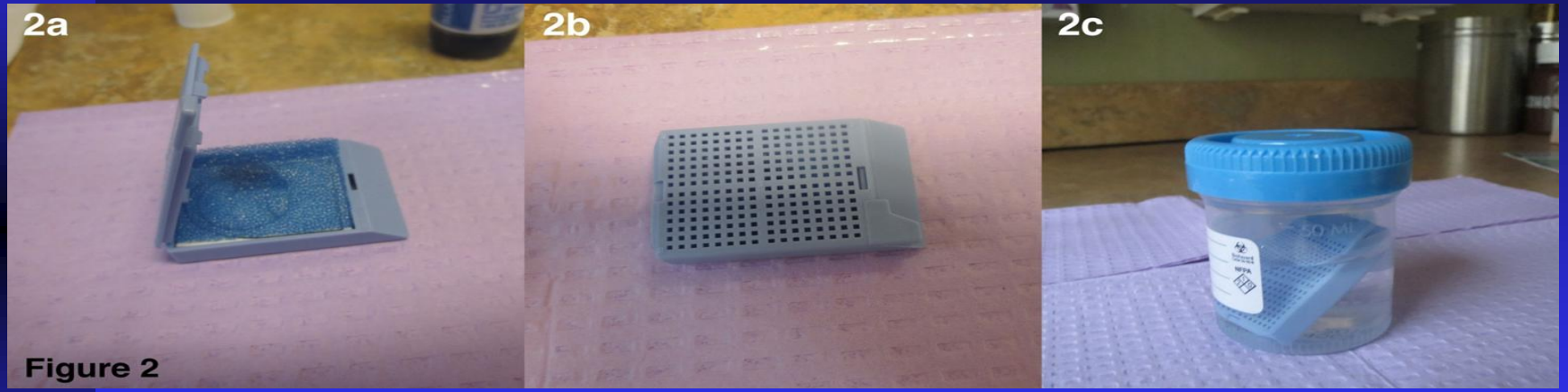
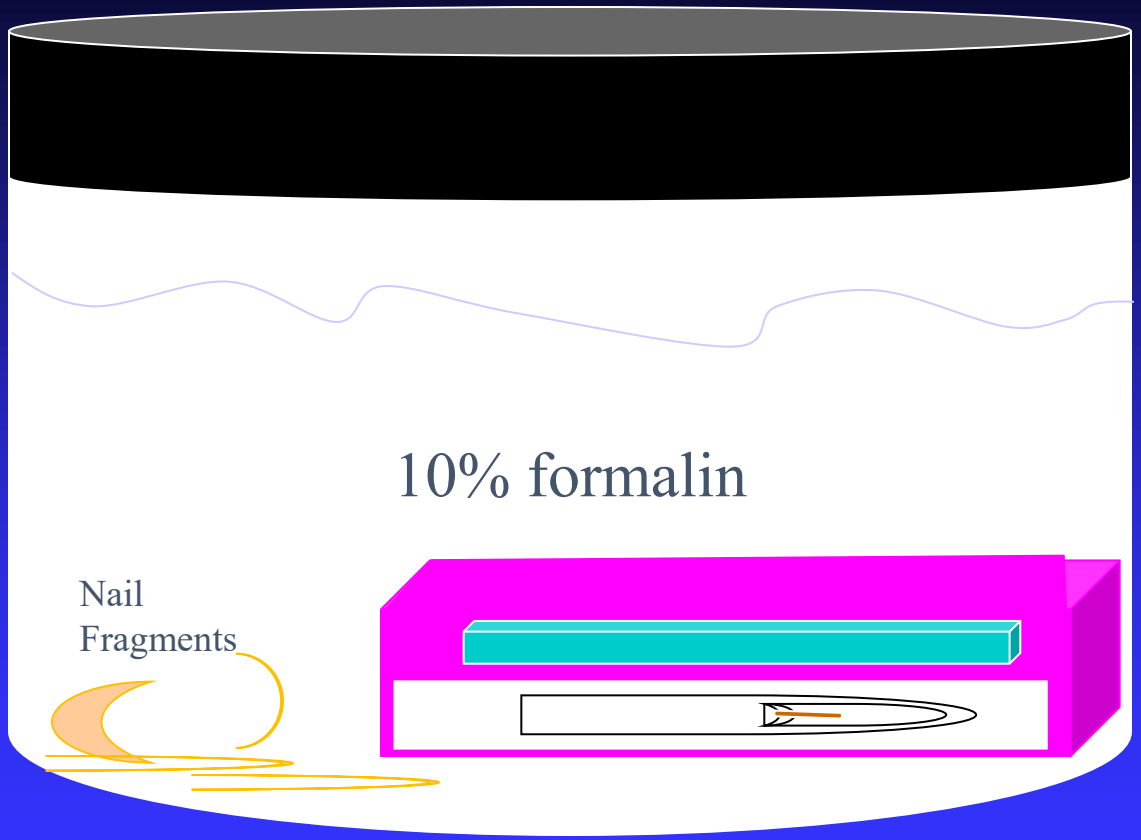
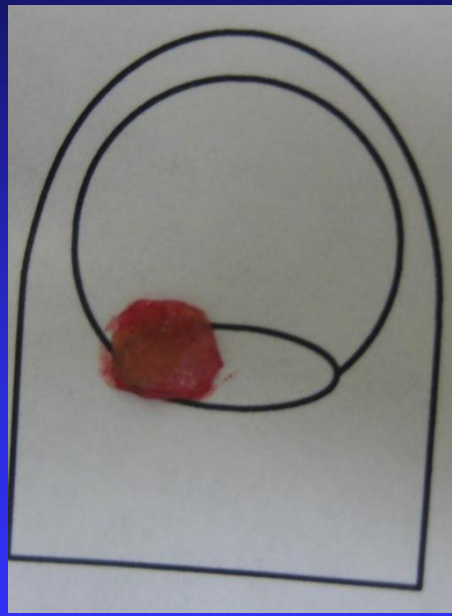



Courtesy of Dr. Phoebe Rich

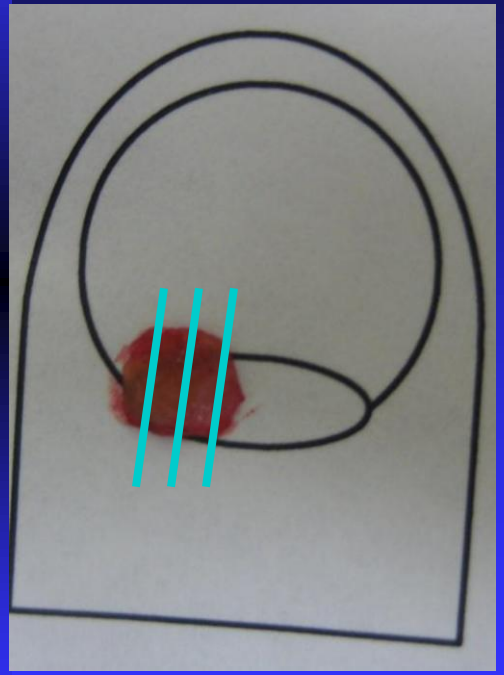
Print template at www.ctapathology.com


2a
2b
2c
Figure 2


10% formalin
Nail
Fragments



# Shave biopsy



- Section after overnight fixation
- Preorders
  - Levels and unstained
  - MelanA, Fontana-Masson
  - PAS

# Nail adherence to glass slide

## Periodic Acid-Schiff's Stain (P.A.S.) Stain for Nails

**Procedure:**

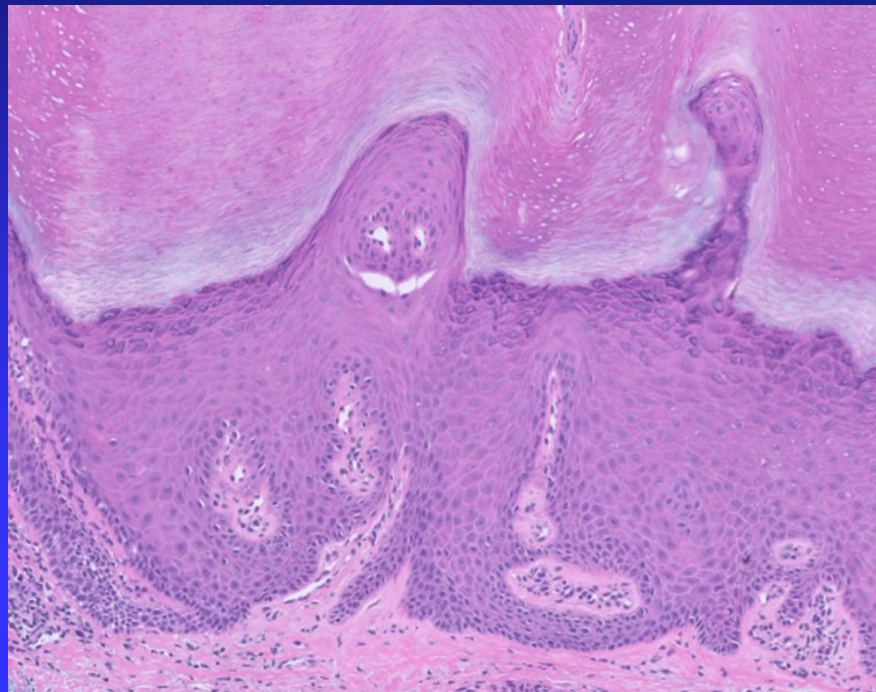
1. Place a small amount of Gelatin in water bath
2. Cut ribbon at 4um and float onto gelatin water bath
3. Using positively charged slide, pick up desired sections for PAS & H&E slides.
4. Place in 65 deg. C oven for 45 minutes. (More time for "difficult" specimens)
5. Deparaffinize slides using Xylene or Xylene substitutes and hydrate through alcohols (or place PAS slides on programmed de-paraffin run and H&E slides on H&E program on stainer).
6. Gently rinse slide in running tap water.
7. Rinse slide in distilled water.
8. **DO NOT "DIGEST" SLIDES!!!**
9. Place slide in 1% Periodic Acid for 10 minutes.
10. Gently rinse slide quickly in distilled water.
11. Place slide in Schiff's Solution for 10 minutes.
12. Gently rinse slides in warm- hot tap water for 5 minutes.
13. Place slide in Light Green Stain as needed to reach desired background intensity. (Approx. 30 seconds)
14. Dehydrate slide through 3 changes of Absolute Alcohol.
15. Clear slide through 3 changes of Xylene or Xylene substitute.
16. Coverslip using permanent mounting media.

**Results:**

Basement membrane, Fungi, Glycogen and Mucin: PINK TO RED
Other tissue: Green

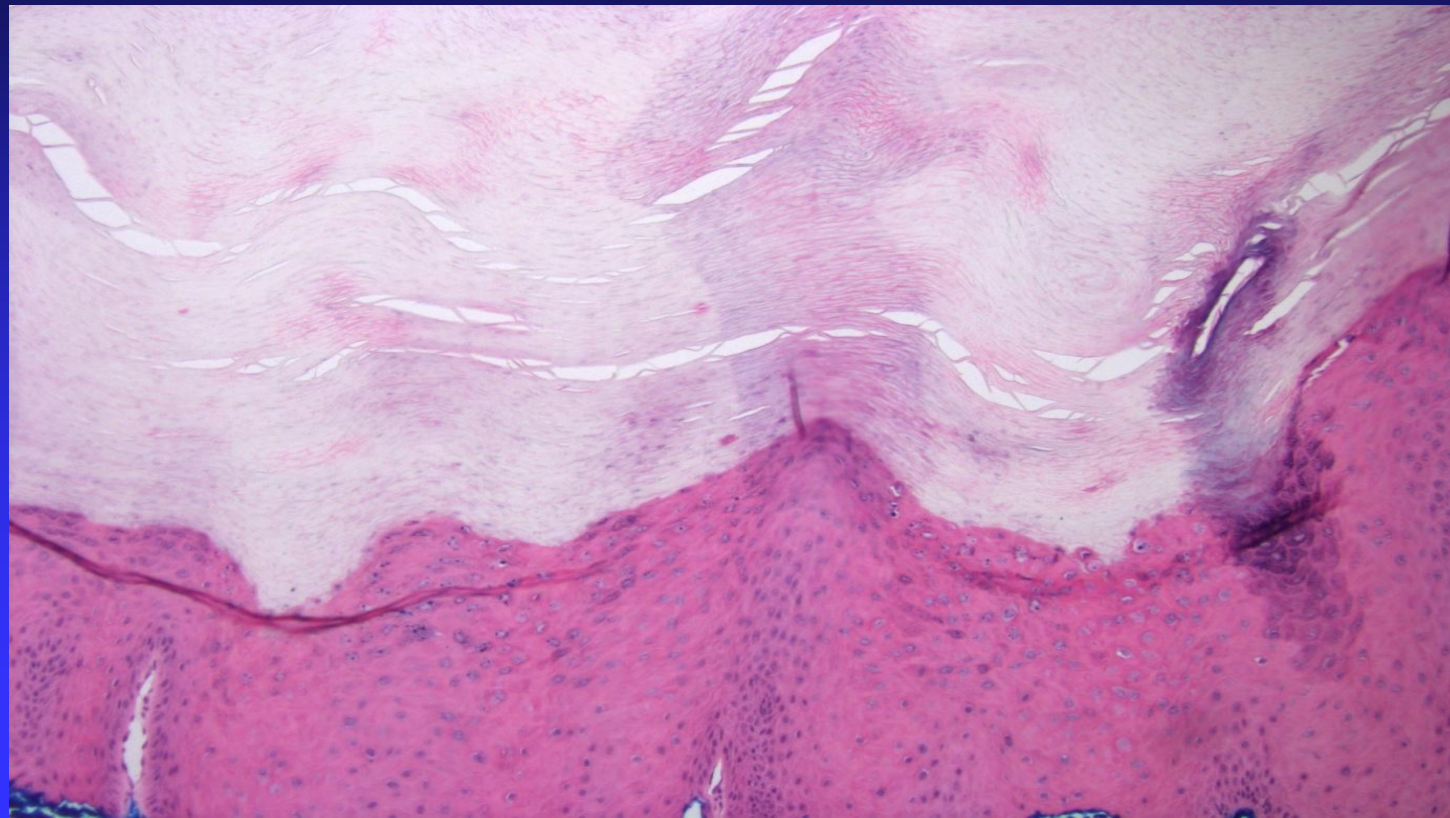
**Reference**: American Master Tech Scientific, Inc. "PAS Kit Procedure."

# Squamous neoplasms
# HPV benign and malignant

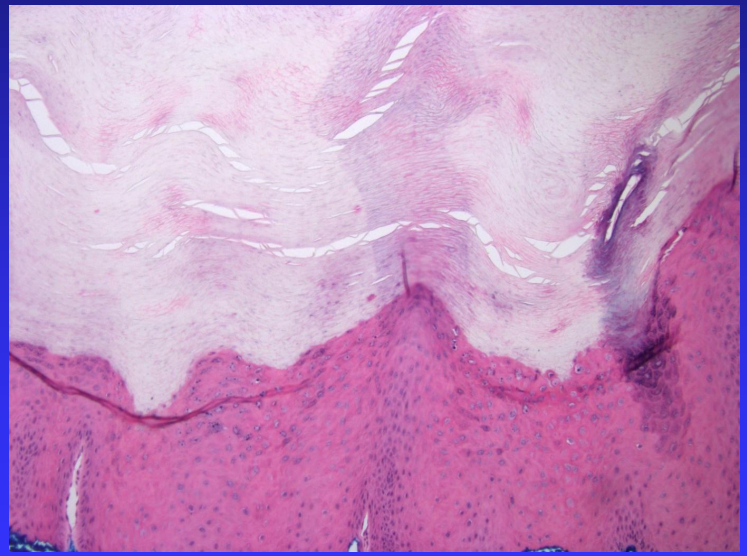



# Squamous cell carcinoma

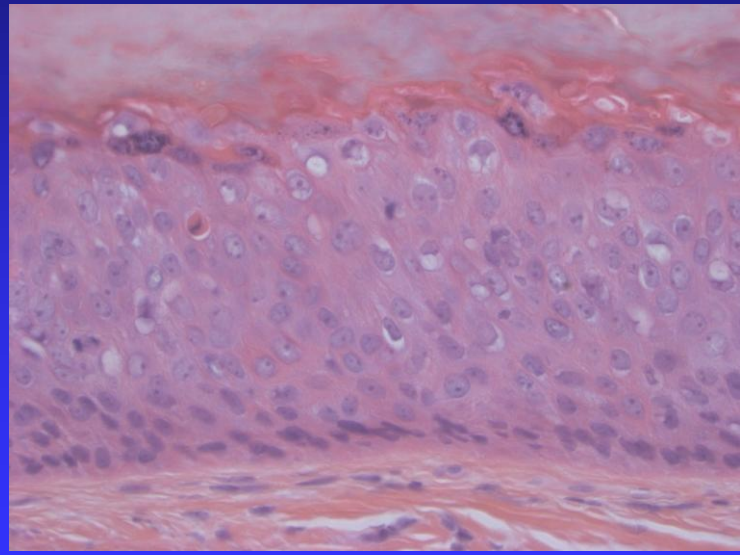
# SCC versus Wart/Verruca



# Squamous neoplasms
# HPV benign and malignant



Verruca



SCC

# SCC versus Wart/Verruca

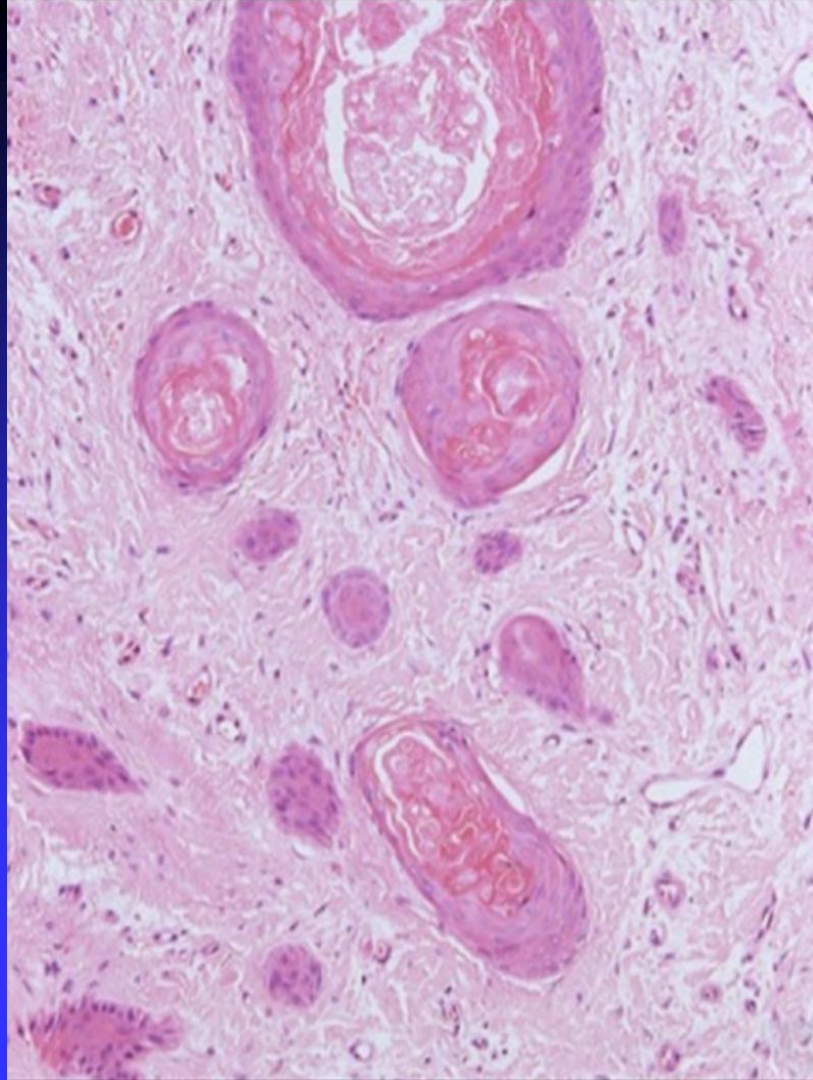
- Clinical correlation often necessary
  - Immunosuppression (esp HIV)
  - If it is destroying bone, it is not benign!
  - Sample more if suspicious

# HPV In-situ Hybridization (ISH)

- HPV Subtypes—same as cervical SCC
  - Low risk--Verruca
  - High risk—Squamous cell carcinoma
  - Pan HPV test—Benign and malignant

# Benign squamous inclusions/cyst

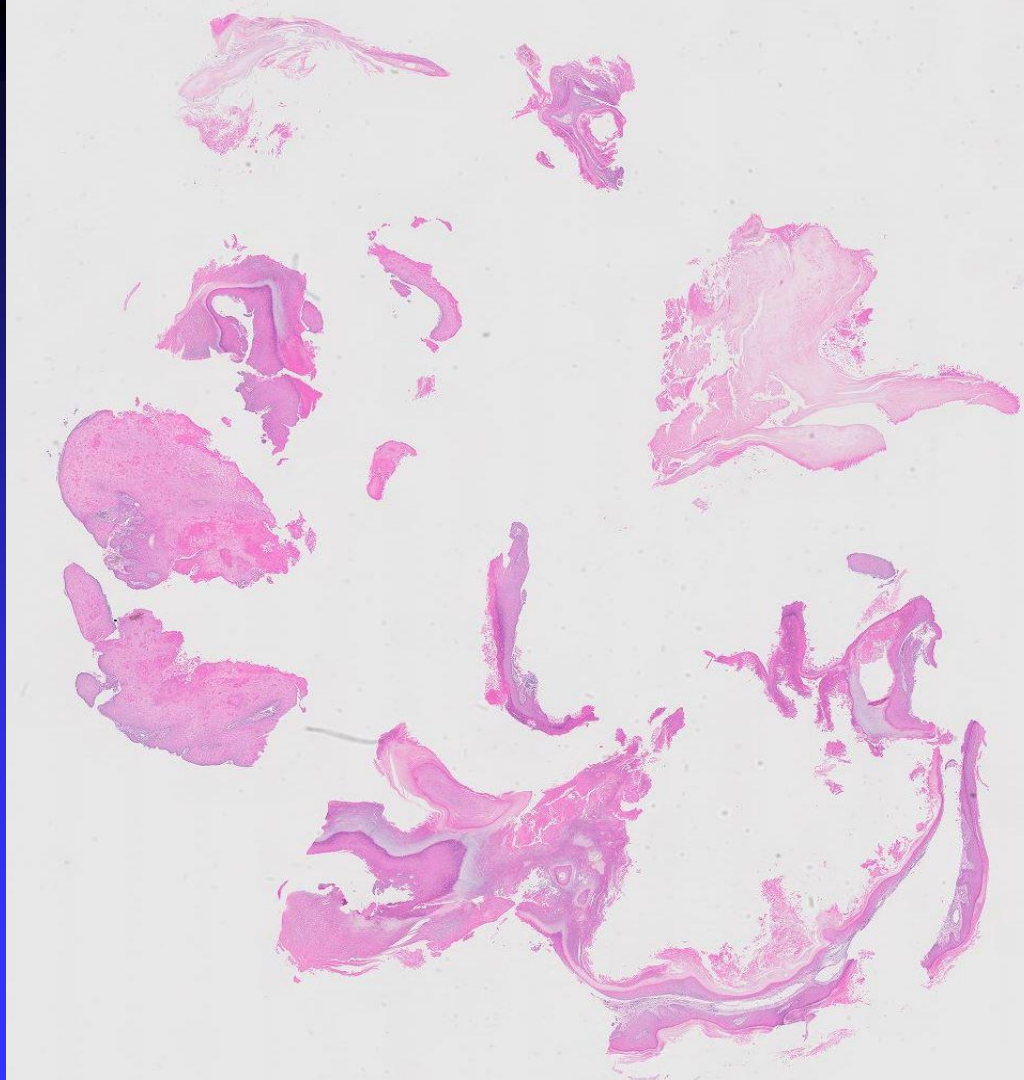
Not squamous cell carcinoma

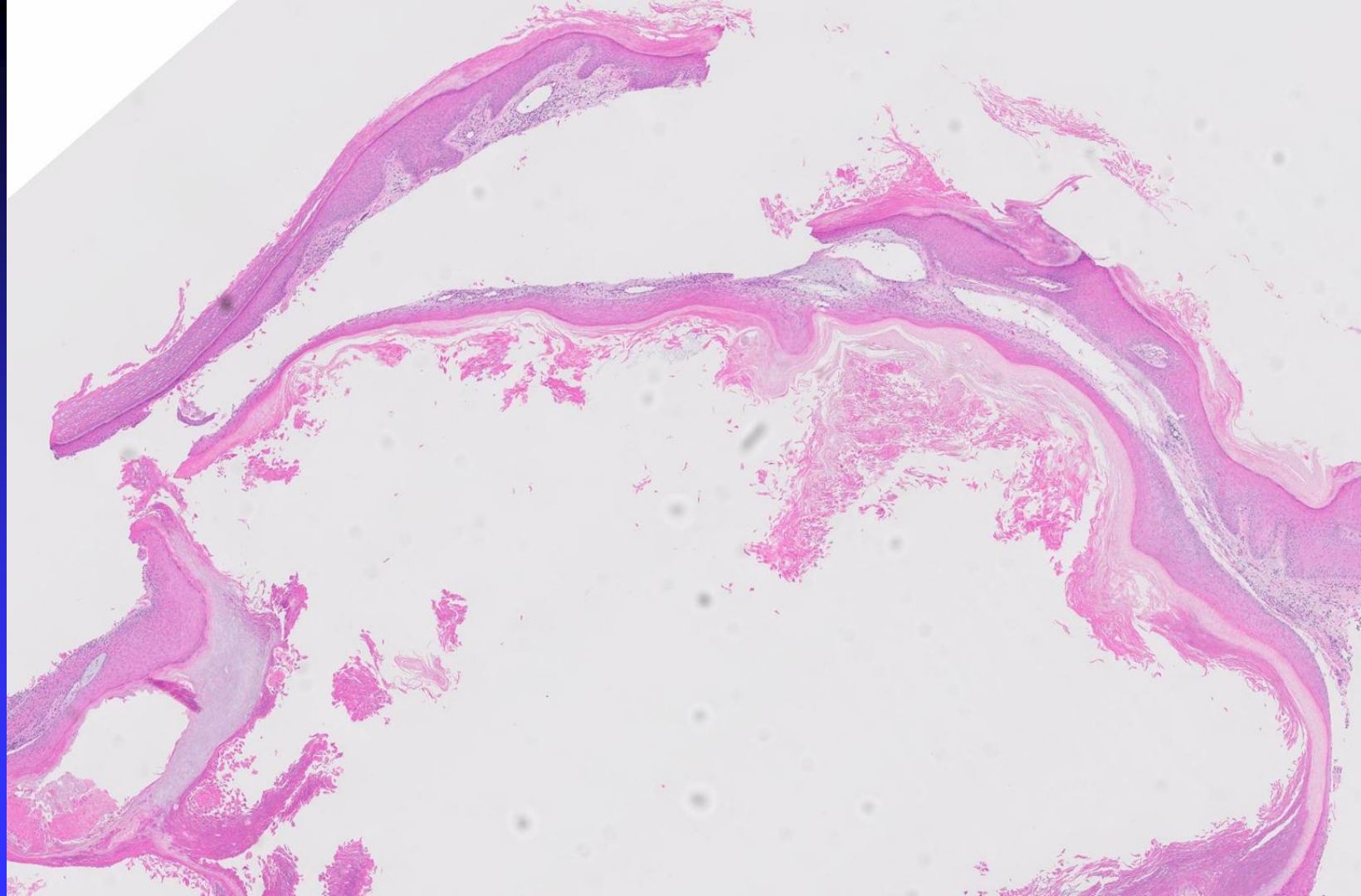


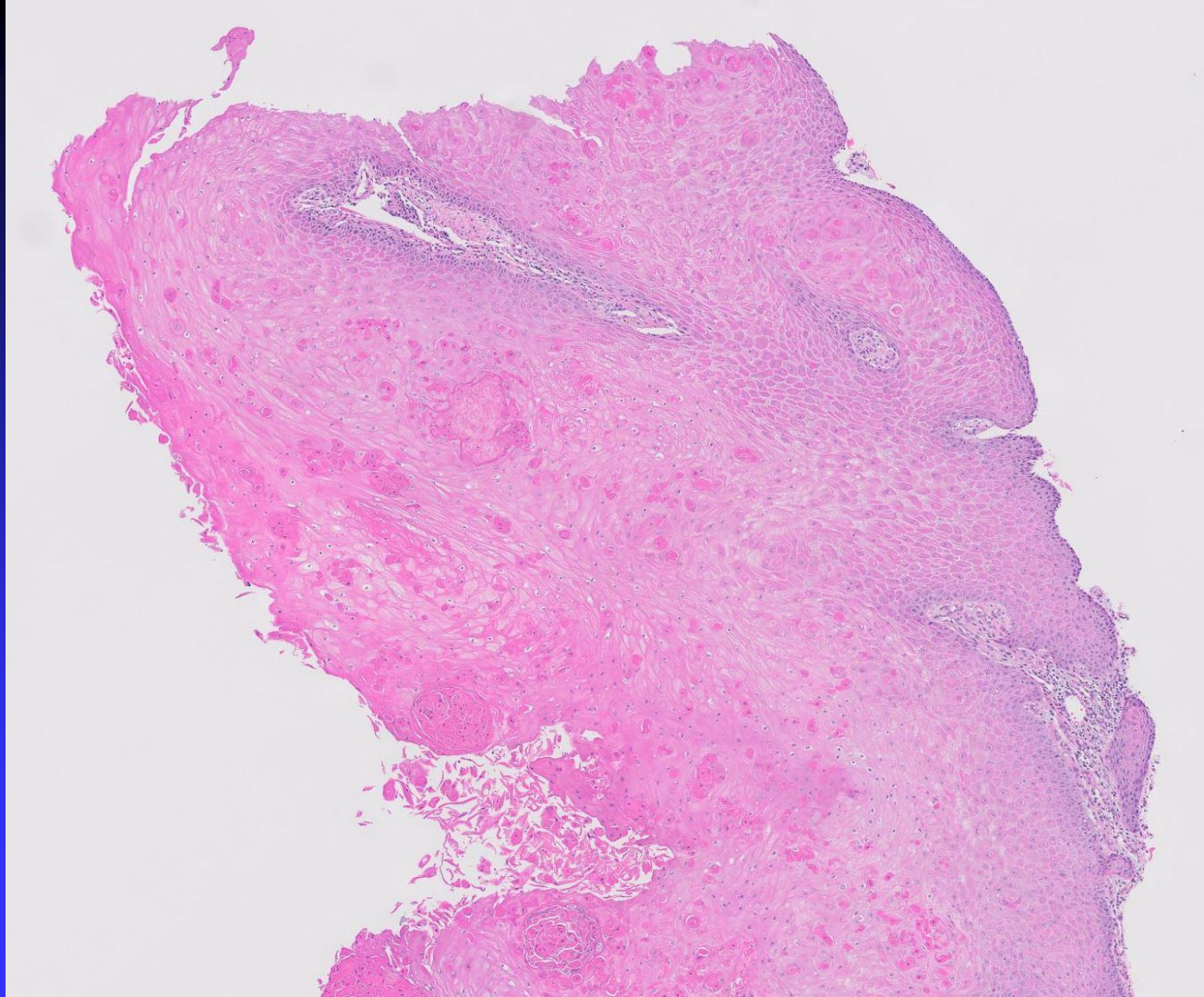
# Case: 64 y/o male

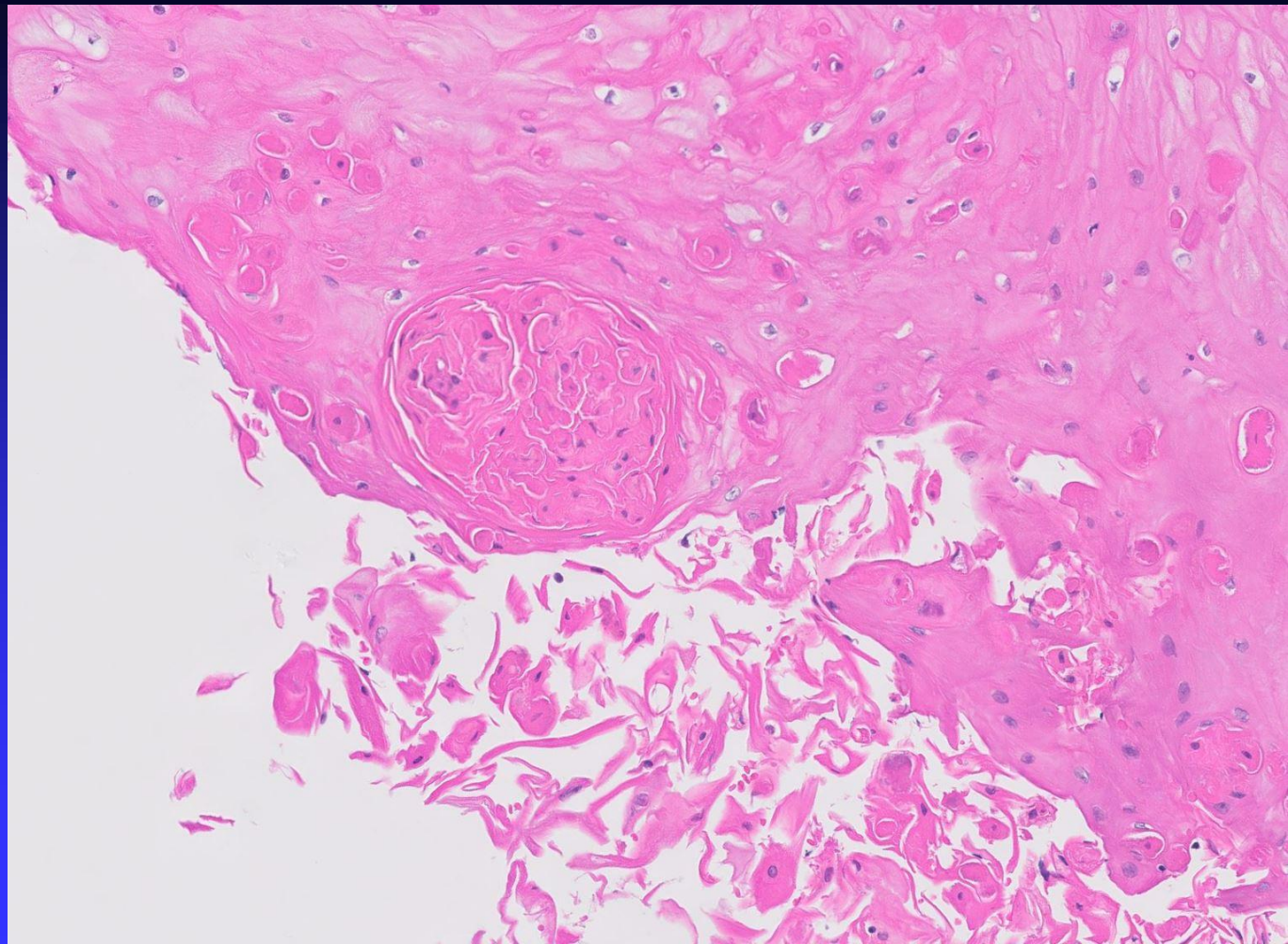
- Rapidly enlarging nodule in fingernail for one month
- All other nails normal

64 y/o male









# Subungual Keratoacanthoma

- Similar to the keratoacanthoma-type of SCC elsewhere
- Destroys bone and does not regress but otherwise not aggressive
- Biopsy often curative

# Cutaneous diseases also present in nails.

- Dermatitides
  - Psoriasis, lichen (planus, aureus, niditus, striatus), PRP, eczema, AA, EM, KLC, GA, EED, DM, LE, PV, PF, BP, scleroderma, vasculitis, PG, ILVEN . . .
  - Infection (viral, bacteria, myco, treponeme, mycosis, protozoa, leishmaniasis, scabies, parasite)

# Thanks!

Mahalo!

curtisinportland@gmail.com

Gracias!

Mālō 'aupito